CHAPTER 1

Integration of Gastrointestinal Function

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Integration of Function

The digestive system includes the primary gastrointestinal (GI) tract (oropharynx, esophagus, stomach, intestine, and colon), exocrine pancreas, liver, and biliary tract. The role of the digestive system is to provide for nutrition, energy balance, intermediary metabolism, and a mechanism for excretion. To fulfill this role, the digestive system has evolved six major functions: (a) *Motility*—Motility permits the prehension of food and its transit from mouth to anus, while at the same time mixing and reducing the size of the food content. The rate at which food moves through the GI tract is regulated to optimize time for secretion, digestion, and absorption. (b) *Secretion*—Secretions from the salivary glands, stomach, intestine, pancreas, liver, and biliary tract add fluid, electrolytes, acid, bicarbonate, mucus, bile salts, and enzymes to the GI tract lumen. These serve to aid in the digestion and absorption of ingested nutrients. (c) *Digestion*—Ingested nutrients are progressively reduced in size primarily by luminal hydrolytic digestion with some fermentative digestion contributed by colonic bacteria. (d) *Absorption*—The intestine has a highly specialized epithelium, which mediates the absorption of nutrients, electrolytes, minerals, vitamins, and water. (e) *Blood flow*—The major function of the splanchnic circulation is to support the broad range of metabolic activities described above. The splanchnic circulation also serves as a storage site for a large volume of blood that can be mobilized during exercise. (f) *Metabolism*—The liver has a wide range of metabolic functions, including carbohydrate, protein, lipid, and nucleic acid metabolism; coagulation factor synthesis; bile secretion; porphyrin, metal, vitamin, glutathione, hormonal, and xenobiotic metabolism; and immune surveillance. The elements of this highly integrated model are outlined in Figure 1-1. Neural, endocrine, and paracrine control mechanisms serve to regulate and integrate these various functions.

Structural Organization

Primary Gastrointestinal Tract

The structural organization of the primary GI tract consists of a luminally oriented mucosa, submucosa, muscularis externa, and serosa (Fig. 1-2).[1] The *mucosa* consists of a superficial epithelium, lamina propria, and muscularis mucosae. Epithelial cells carry out digestive, secretory, and absorptive functions, as well as immune surveillance. The lamina propria consists of connective tissue, blood, and lymphatic vasculature. The muscularis mucosae is made up of smooth muscle cells that function primarily to change the shape and surface area of the epithelial cell layer in response to luminal distention. The *submucosa* consists of collagen, elastin, secretory glands, and major blood vessels. Motility of the GI tract is provided by circular and longitudinal layers of smooth muscle, interposed between the submucosa and serosa. Two nerve plexuses, the submucosal plexus and myenteric plexus, contain the intrinsic nervous system of the GI tract. The *submucosal plexus* (Meissner's plexus) lies between the submucosa and the circular smooth muscle, and regulates the overlying epithelium. The *myenteric plexus* lies between the circular and longitudinal muscle layers, and regulates their contraction. The *serosa* is a thin external membrane consisting of a layer of serous fluid-secreting cells. Serous secretions serve to reduce friction from the muscular motion of the GI tract. Each segment of the primary GI tract has unique features that promote one or more of the GI functions (Fig. 1-3A to 1-3D).

Pancreas

The pancreas contains exocrine and endocrine elements, which serve to regulate digestion and metabolism, respectively. The exocrine pancreas is a mixed tubuloalveolar or tubuloacinar gland. Acinar cells synthesize and secrete digestive enzyme into a ductal system for transport to the small intestine (Fig. 1-3E).[2,3] Islet cells of the endocrine pancreas are interspersed between the acinar and duct cells. The exocrine pancreas has four major physiologic functions: (a) *acinar cell* secretion of digestive zymogens, which initiate protein, carbohydrate, and lipid digestion; (b) *acinar cell* secretion of antibacterial proteins, which serve to regulate the small intestinal bacterial flora; (c) *ductal cell* secretion of bicarbonate and water, which serves to hydrate and neutralize the duodenal pH; and (d) *ductal cell* secretion of pancreatic intrinsic factor, which facilitates cobalamin (vitamin B_{12}) binding and absorption in the distal ileum.[2,3] The exocrine pancreas does not have a direct arterial blood supply. Acinar cells are instead perfused by venous blood emanating from islet vasa efferentia via an islet–acinar portal system.[4] Arterial blood first perfuses the islets, which secrete their hormones (e.g., insulin, glucagon) into the postcapillary venules and veins that then perfuse the acinar cells. The endocrine pancreas thereby autoregulates exocrine secretions and pancreatic growth. The efferent nerve supply to the pancreas includes both sympathetic and parasympathetic fibers. Sympathetic postganglionic fibers arise from the celiac and cranial mesenteric plexuses and accompany the arteries to the exocrine pancreas. Parasympathetic preganglionic fibers are

distributed by branches of the vagi traversing the stomach and duodenum and terminate at the acini, islets, or intrinsic cholinergic nerves of the pancreas. In general, parasympathetic nerve fibers stimulate exocrine pancreatic secretion, and sympathetic nerve fibers inhibit exocrine pancreatic secretion.[5]

Liver

The *hepatic lobule* is the *anatomic* unit of the liver. In the anatomic model, liver lobules are organized into irregular polygons demarcated by connective tissue and composed of plates of hepatocytes radiating outward from the central vein to the portal triads (Fig. 1-3F). The *hepatic acinus* is the *functional* unit of the liver. In the functional model, hepatocytes are instead oriented around the afferent vascular system (portal veins and hepatic arteries) just as they anastomose into sinusoids (Fig. 1-3F), and the central vein is at the periphery of the acinus instead of centrally located as in the anatomic model. The acinus is divided into three contiguous zones (1-3) that correspond to distance from the arterial blood supply. Hepatocytes closest to the arterioles (zone 1) receive the greatest oxygen content, but are also the first to be affected by toxins transported from the gut to the portal vein. Zone 3 hepatocytes reside at the periphery of the acinus near the central vein, and zone 2 hepatocytes are interspersed between zones 1 and 3. The anatomic model is perhaps easier to understand, but the functional model serves as a better foundation for understanding liver pathology.[6,7]

In either model, portal venous and arterial blood flows centripetally, that is, toward the central vein, whereas bile flows centrifugally, that is, away from the central vein. Hepatocytes extract nutrients and oxygen from portal and arterial perfusion, respectively, and produce bile acids and other bile constituents that are transported from hepatocytes into bile canaliculi, ductules, and ducts.[8] Hepatocytes account for 60% of the liver cell mass and contribute to the wide range of metabolic activities described in the preceding section. Hepatocytes are supported by other cell types, which account for 40% of the liver cell mass.

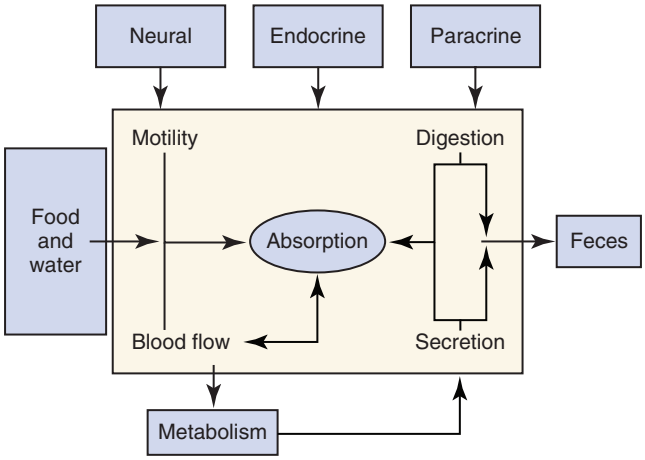


Figure 1-1 Model for the integration of the major functions of the digestive system.

Biliary Epithelial Cells (Cholangiocytes)

These represent 7% to 10% of liver cell mass.[9,10] They secrete water, bicarbonate, and cations into the bile in the physiologic state, but in some diseases they may participate in the immune response as antigen-presenting cells (APCs).

Kupffer Cells

These represent 2% to 5% of the liver cell mass, and serve as resident macrophages lining the sinusoids. Kupffer cells are phagocytic and may contribute to pathology through production of inflammatory mediators, activation of Toll-like receptors (TLRs), and

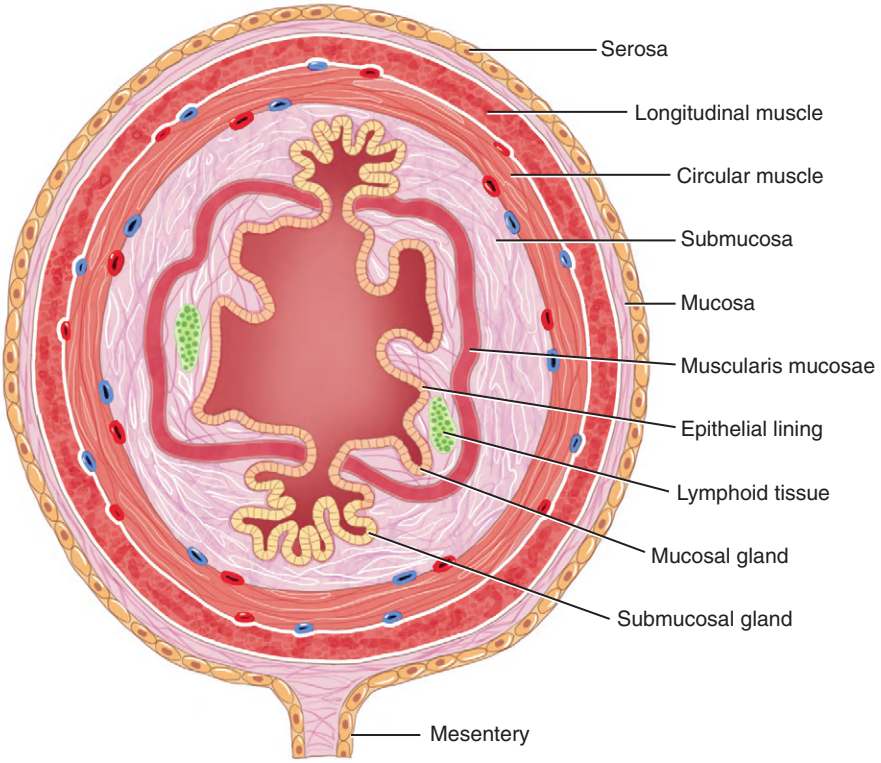


Figure 1-2 General organizational structure of the primary gastrointestinal tract.

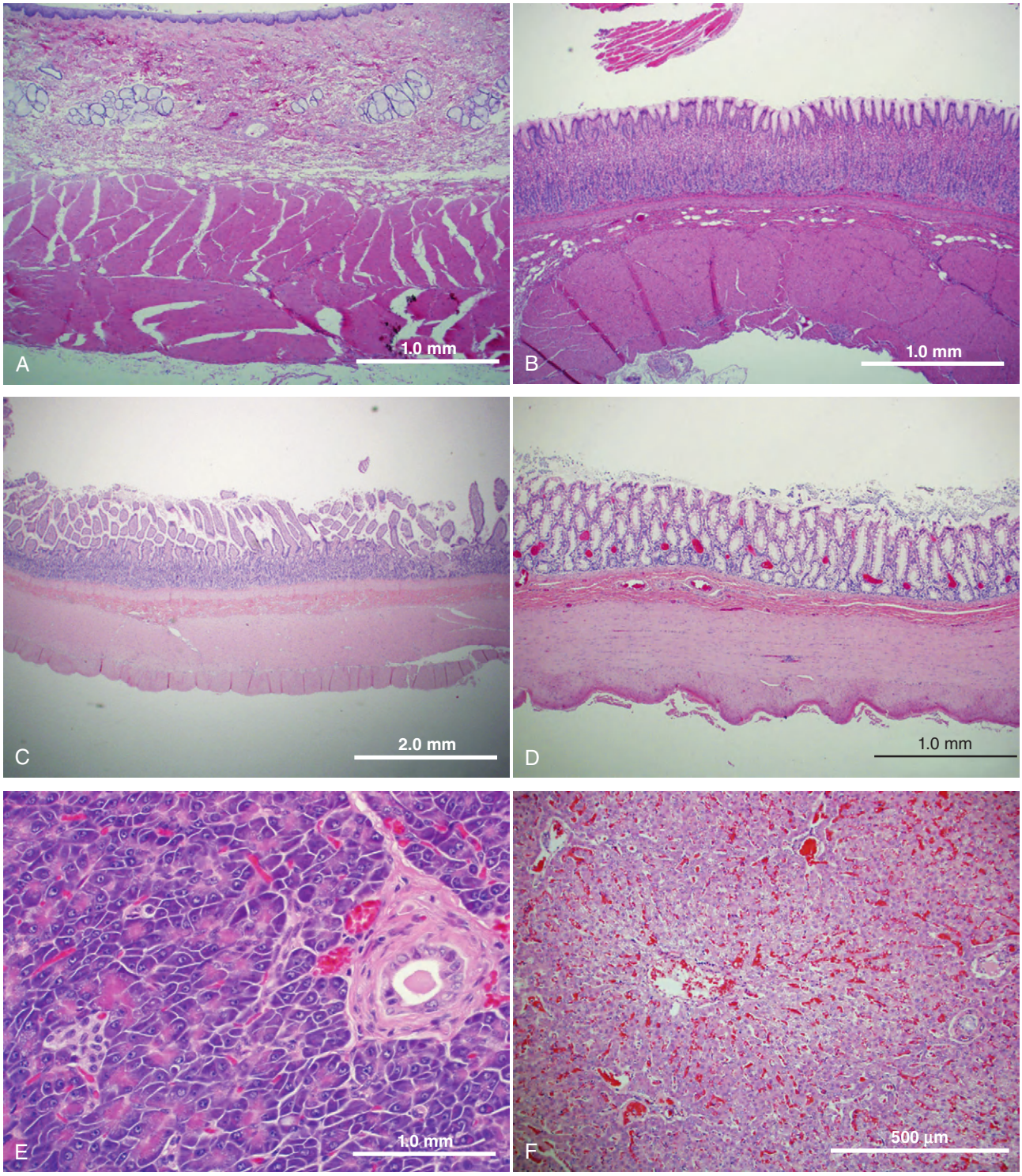


Figure 1-3 **A,** Microscopic structure of the esophagus (×400). **B,** Microscopic structure of the stomach (×400). **C,** Microscopic structure of the intestine (×400). **D,** Microscopic structure of the colon (×400). **E,** Microscopic structure of the pancreas (×400). **F,** Microscopic structure of the liver (×400). (Courtesy of Dr. Arno Wuenschmann of the University of Minnesota.)

elaboration of proinflammatory cytokines such as tumor necrosis factor (TNF)-α.[7]

Hepatic Stellate Cells

Formerly known as Ito cells, stellate cells represent 3% to 5% of liver cell mass and store lipid and vitamin A in the healthy liver. When activated in liver damage, stellate cells produce collagen, causing hepatic fibrosis that can progress to end-stage cirrhosis.[11]

Natural Killer Cells

Also known as *pit cells*, these represent 1% of liver cell mass, and serve as part of the immune surveillance in the hepatic sinusoids. Natural killer (NK) cells are cytotoxic in function.

Hepatic Endothelial Cells

Hepatic sinusoidal endothelial cells represent 20% of the liver cell mass and act as resident APCs in health, although they contribute to a heightened immune response in disease conditions.[12]

Smooth Muscle

Representing 2% to 5% of the liver cell mass, smooth muscle cells are located primarily in the hepatic artery and portal vein and their tributaries.

Hepatic Stem Cells

Also known as hepatic progenitor cells, stem cells represent 1% of the liver cell mass, and are capable of regenerating the liver tissue postinjury.[13]

Innervation of the Gastrointestinal Tract

The autonomic nervous system (ANS) innervation of the GI tract has both extrinsic and intrinsic components (Fig. 1-4). The extrinsic component consists of the parasympathetic and sympathetic branches. The intrinsic component is the enteric nervous system that is contained within the submucosal and myenteric plexuses (Fig. 1-5).[14] The enteric nervous system communicates extensively with the parasympathetic and sympathetic nervous systems.

Parasympathetic Innervation

Parasympathetic innervation is supplied by the vagus and pelvic nerves. The vagus innervates the upper GI tract, and the pelvic nerve innervates the lower GI tract. Parasympathetic neurons have long preganglionic fibers that synapse in ganglia in or near the target organs. Postganglionic neurons of the parasympathetic nervous system are classified as either cholinergic or peptidergic. Cholinergic neurons release acetylcholine (ACh) as the neurotransmitter, whereas peptidergic neurons release one or more enteric neuropeptides, including substance P (SP), vasoactive intestinal peptide (VIP), neuropeptide Y (NPY), and gastrin-releasing peptide (GRP). The vagus nerve is a mixed nerve in which 75% of the fibers are afferent and 25% are efferent. Afferent fibers transmit sensory information from mechanoreceptors and chemoreceptors in the wall of the GI tract to the central nervous system (CNS). Efferent fibers deliver motor information from the CNS back to cells in the periphery, for example, smooth muscle, secretory, and endocrine cells. Thus, mechanoreceptors and chemoreceptors in the GI mucosa

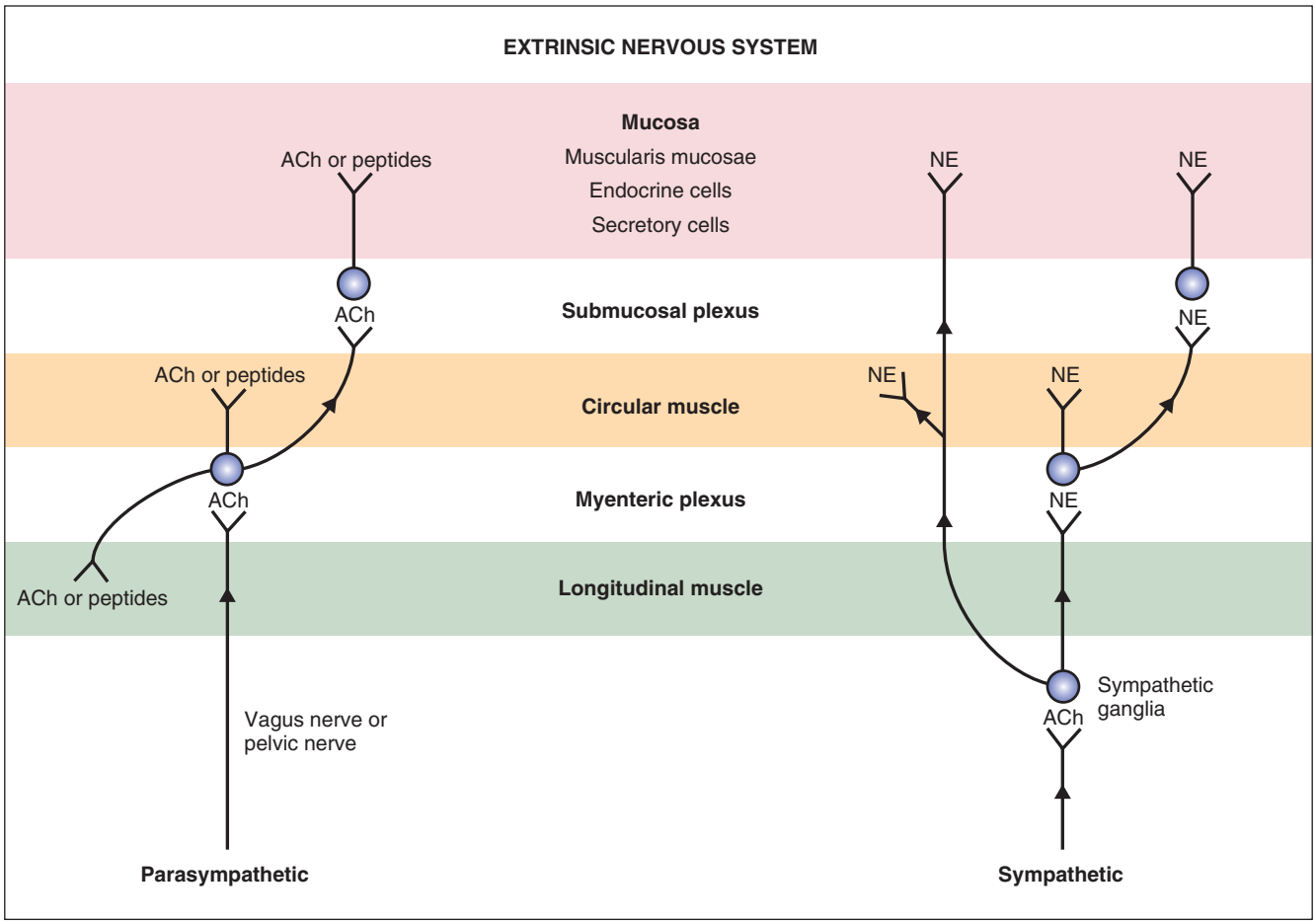


Figure 1-4 Extrinsic nervous system of the gastrointestinal tract. ACh, acetylcholine; NE, norepinephrine. (From Costanzo L [ed]: *Physiology*, 4th ed. Philadelphia: Saunders, 2010.)

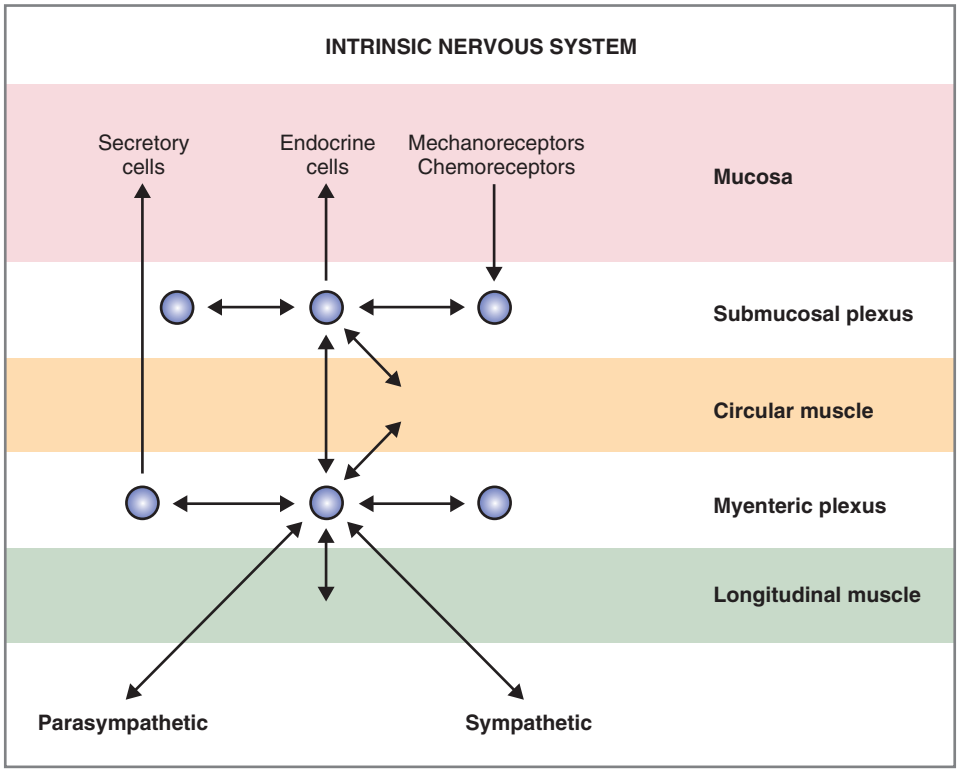


Figure 1-5 Intrinsic nervous system of the gastrointestinal tract. (From Costanzo L (ed): *Physiology*, 4th ed. Philadelphia: Saunders, 2010.)

relay afferent information to the CNS via the vagus nerve, which triggers reflexes whose efferent limb is also in the vagus nerve.

Sympathetic Innervation

Sympathetic innervation is supplied by spinal segments T1 to L3 of the thoracolumbar spinal cord. As part of the "fight-versus-flight" response, the sympathetic nerves innervate the heart, blood vessels, bronchi, and GI tract. Sympathetic neurons have short preganglionic fibers that synapse at ganglia (celiac, superior mesenteric, inferior mesenteric, and hypogastric) outside the GI tract. Postganglionic neurons of the sympathetic nervous system are adrenergic and release norepinephrine as the neurotransmitter. Approximately 50% of the sympathetic nerve fibers are afferent and 50% are efferent. As with parasympathetic innervation, sensory and motor information is relayed between the GI tract and the CNS, and is coordinated by the submucosal and myenteric plexuses.

Intrinsic Innervation

The ganglia of the enteric nervous system are located in the submucosal and myenteric plexuses, and control the contractile, secretory, and endocrine functions of the gut.[15,16] Enteric ganglia receive inputs from the parasympathetic and sympathetic nervous systems, which serve to modulate their activity. Enteric neurons are cholinergic, adrenergic, and/or peptidergic, and may secrete one or more neurotransmitters (Fig. 1-5).

Gastrointestinal Smooth Muscle

Significant structural and functional differences exist between skeletal and smooth muscle, from innervation and gap junctions to sarcomeric organization, nuclear density, spread of depolarization, regulatory proteins, sources of calcium, contractile patterns, slow waves, and bioenergetics (Tables 1-1 and 1-2).[17]

Table 1-1 Structural Differences Between Striated and Smooth Muscles

Feature	Skeletal Muscle	Smooth Muscle
Innervation	Somatic	Autonomic
Nerve density	Each cell	Sparse (unitary)
Appearance	Striations	Nonstriated (smooth)
Nuclei	Multinucleated	Single nuclei
Depolarization	T tubules	Caveolae
Gap junctions	None	Many (unitary)
Thin filaments	Troponin	Calmodulin
Ca^{2+} source	Ca_i^{2+}	Ca_i^{2+}, Ca_o^{2+}

Table 1-2 Bioenergetic Differences Between Striated and Smooth Muscles

Parameter	Skeletal Muscle (Frog Sartorius)	Smooth Muscle (Hog Carotid Artery)
Stress	250 mN/mm^2	223 mN/mm^2
$T_{1/2}$ P_{max}	0.2 sec	70.0 sec
Velocity	1.9 L_o/sec	0.12 L_o/sec
J_{ATP}	50 µmol/g/min	1.2 µmol/g/min
Economy	930 µmol ATP/min/g/mN/mm^2	6.0 µmol ATP/min/g/mN/mm^2

ATP, adenosine triphosphate; JATP, joules of ATP consumed. L_o/sec, optimal muscle lengths per second; $T_{1/2}$ P_{max}, time to reach half-maximal contraction.

Innervation and Gap Junctions

Skeletal muscle contraction is voluntary and under the regulation of the somatic nervous system. Each skeletal muscle cell is innervated by a motoneuron, and each muscle fiber behaves as a single unit. Smooth muscle, on the other hand, is involuntary and under the regulation of the autonomic nervous system. GI smooth muscles are only sparsely innervated (referred to as unitary smooth muscle), and it is instead the gap junctions that permit the rapid spread of electrical activity from cell to cell followed by coordinated contraction. The multiunit smooth muscles of the iris and vas deferens have fewer gap junctions and little or no coupling between cells, and therefore are more dependent upon neural activation.

Sarcomeric Organization

Smooth muscle lacks striations because the thick and thin filaments are not organized into sarcomeres as they are in skeletal or cardiac muscle.

Nuclear Density

During embryonic development, skeletal muscle fibers develop through the fusion of myoblasts into multinucleated skeletal muscle cells. Nuclei are usually found at the periphery of the muscle fiber and the contractile proteins (e.g., myosin, active, troponin) are located more centrally in the fiber. Smooth muscle cells typically are uninucleate.

Spread of Depolarization

The rapid spread of depolarization of striated muscle is facilitated by an extensive transverse T-tubule system coupled to the sarcoplasmic reticulum. Smooth muscles are devoid of the T-tubule system and instead rely on a system of subplasmalemmal caveolae representing invaginations of the cell membrane. Caveolae link extracellular stimuli with intracellular effectors in smooth muscle cells. Caveolae, and their integral caveolin proteins, are believed to be the smooth muscle equivalent of the T-tubule system of striated muscle.

Regulatory Proteins

Contraction of striated muscle is a *thin*-filament regulated process. Ca^{2+} binds to troponin C, one of the thin filament proteins, producing a conformational change in the troponin–tropomyosin complex. The conformational change permits binding of actin to the myosin heads, activation of myosin adenosine triphosphatase (ATPase), and cross-bridge cycling. Contraction of smooth muscle is instead a *thick*-filament regulated process. Troponin C is not expressed in smooth muscle, and Ca^{2+} instead binds to the calcium-binding protein, calmodulin. In turn Ca^{2+}–calmodulin activates myosin light-chain kinase, permitting phosphorylation of the 20-kDa myosin light chains, activation of myosin ATPase, and cross-bridge cycling (Fig. 1-6).[18]

Sources of Calcium

Striated muscle cells derive calcium solely from internal stores, specifically the sarcoplasmic reticulum. Depolarization of the T-tubule system causes a conformational change in its voltage-sensitive dihydropyridine receptor, which, in turn, causes opening of the Ca^{2+}-release channel in the adjacent sarcoplasmic reticulum. Many GI smooth muscles have a similar dependence on sarcoplasmic reticulum Ca^{2+} release, but most smooth muscles also have a major (or minor) dependence on influx of extracellular Ca^{2+} through voltage-gated, ligand-gated, and inositol triphosphate (IP_3)-gated Ca^{2+} channels (Fig. 1-7).

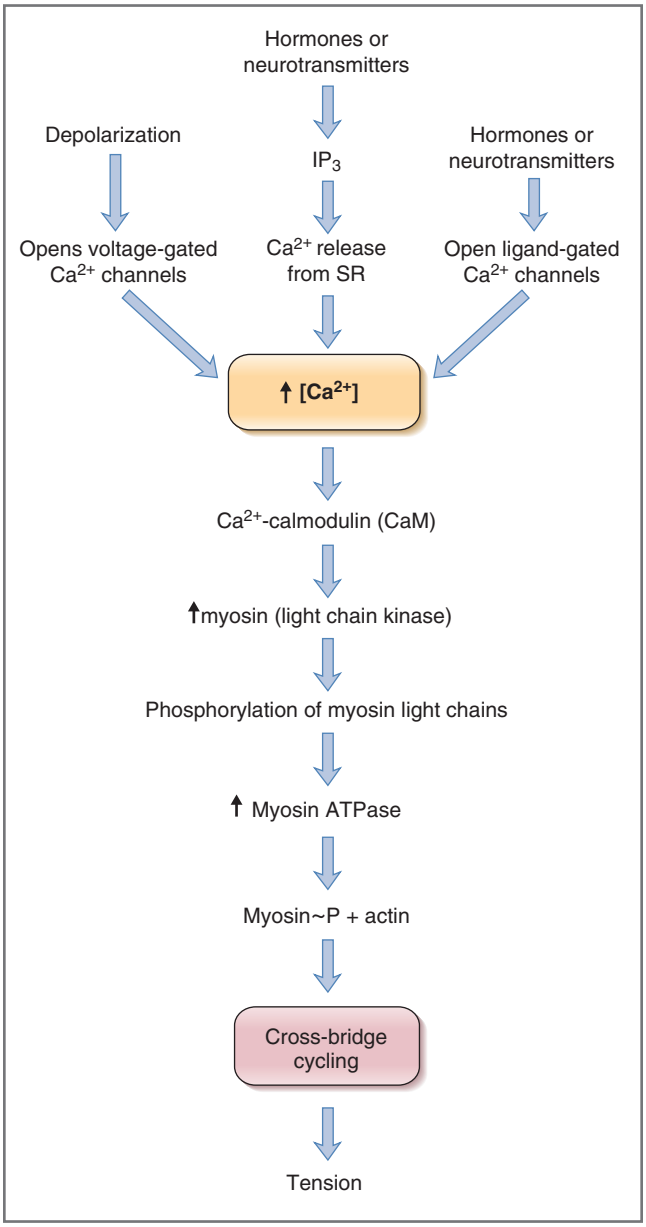


Figure 1-6 Biochemical activation of smooth muscle contraction. (From Costanzo L (ed): *Physiology*, 4th ed. Philadelphia: Saunders, 2010.)

Contractile Patterns

Length–tension and force–velocity relationships are apparent in both striated and smooth muscles, although some differences have been noted. Tetanic or tonic contractions are physiologically possible in striated muscle, but most striated muscle contractions are of the twitch or phasic type. Contractions of GI smooth muscle can be either phasic or tonic. Phasic contractions are periodic contractions followed by relaxation. Phasic contractions are often propagating and are found in the esophageal body, gastric antrum, small intestine, and colon. Tonic contractions maintain a constant level of contraction or tone with only intermittent periods of relaxation. They are found in the gastric fundus and in the gastroesophageal, pyloric, ileocolic, and internal anal sphincters.

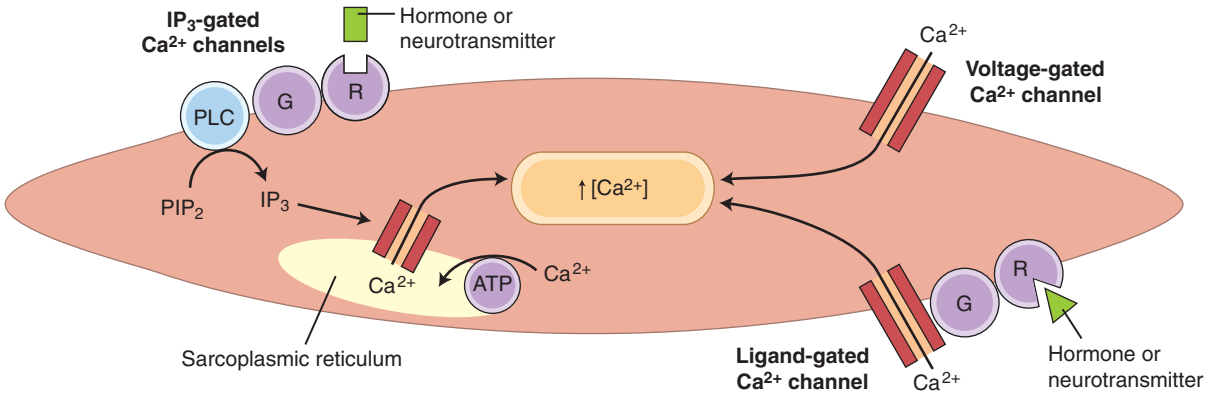


Figure 1-7 Dependence of gastrointestinal smooth muscle contraction upon extracellular and intracellular sources of Ca^{2+}. ATP, adenosine triphosphate; Ca, calcium; G, G protein; IP_3, inositol tris-phosphate; PIP_2, phosphatidyl inositol bisphosphate; PLC, phospholipase C; R, receptor. (From Costanzo L (ed): *Physiology*, 4th ed. Philadelphia: Saunders, 2010.)

Slow Waves

Action potentials in smooth muscle are triggered by oscillating depolarization and repolarization waves referred to as "slow waves."[19] Slow waves are a unique feature of the electrical activity of GI smooth muscle. The origin of the slow waves is still unsettled,[20] but it has been proposed that slow waves originate in the interstitial cells of Cajal (ICC) in the myenteric plexus.[19] Cyclic depolarizations and repolarizations of the ICC are postulated to rapidly spread to adjacent smooth muscle via low-resistance gap junctions. In this way the ICC could serve as "pacemakers" and set the slow wave frequency (from 3 to 12 slow waves per minute) along the GI tract. When slow waves depolarize the membrane potential to threshold, action potentials are superimposed on top of the slow waves giving rise to strong contractions.[19]

Bioenergetics

Smooth muscles contract much slower (P_{max} $t_{1/2}$ = 70 sec; shortening velocity = 0.12 Ls/sec) than striated muscle, but they nonetheless achieve the same overall force production (Ss = 223 mN/mm^2; see Table 1-2). Smooth muscles can develop and maintain this force at surprisingly low adenosine triphosphate (ATP) consumption (J_{ATP} = 1.2 μmol/g/min). Consequently smooth muscle contraction is more economical from a bioenergetics standpoint. It is this property (high-force output at low ATP consumption) that permits some smooth muscles, notably the GI tract sphincters, to maintain tone for prolonged periods of time.

Motility

Oropharynx and Esophagus

In the oropharyngeal phase of swallowing, the animal prehends food and water with teeth and tongue, masticates and mechanically reduces the size of the food particles, forms a bolus at the base of the tongue, and propels the bolus caudally to the cricoesophageal sphincter. The sphincter relaxes and the bolus passes into the cranial esophageal body. Oropharyngeal mechanoreceptors transmit mechanical forces through an afferent neural pathway to the brainstem and efferent neural pathway to induce cricopharyngeal relaxation, esophageal body contraction, and primary esophageal peristalsis. Following swallowing, the cricopharyngeus contracts, pharyngeal muscles relax, and the oropharyngeal phase is repeated until feeding is completed (Fig. 1-8).

Aside from fluid and electrolyte secretion, the major physiologic function of the esophagus is the transport of ingested liquids and solids from the oral cavity to the stomach. Anatomic structures that permit this function are the striated muscle of the cranial esophageal sphincter (cricopharyngeus), the striated and smooth muscle of the esophageal body, and the smooth muscle of the caudal esophageal (gastroesophageal) sphincter. An important species difference between the dog and cat is in the musculature of the esophageal body. The full length of the canine esophageal body is composed of striated muscle, whereas the distal one-third to one-half of the feline esophageal body is composed of smooth muscle. The striated muscle of the cranial esophageal sphincter and esophageal body are innervated by somatic branches (glossopharyngeal, pharyngeal, and recurrent laryngeal) of the vagus nerve arising from the brainstem nucleus ambiguus. The smooth muscle of the esophageal body and caudal esophageal sphincter are innervated by autonomic branches (esophageal) of the vagus nerve arising from the dorsal motor nucleus of the vagus.[21,22]

Primary peristaltic contractions associated with swallowing are reinforced by a secondary wave of contraction (secondary peristalsis) mediated physiologically by esophageal intraluminal distention. The gastroesophageal sphincter relaxes in advance of the propagated pressure wave to permit food to empty into the stomach. Once the bolus of food has passed into the stomach, the gastroesophageal sphincter resumes its high resting pressure.[23,24]

Stomach

Anatomically, the stomach is composed of five distinct components: cardia, fundus, corpus, antrum, and pylorus. Physiologically, the stomach behaves as a two-component structure: a proximal stomach (cardia, fundus, first one-third of the corpus) characterized by slow tonic contractions, and a distal stomach (distal two-thirds of the corpus and antrum) characterized by phasic propagating contractions (Fig. 1-9).[25] Slow waves without action potentials give rise to the sustained tonic contractions of the proximal stomach. During swallowing, gastroesophageal sphincter and intragastric pressure decrease to accommodate emptying of solids and liquids. This phenomenon, referred to as *receptive relaxation*, takes place with each swallow, and as a consequence, large volumes can be accommodated with minimal increases in intragastric pressure. The proximal stomach becomes much less compliant with fundic disease or fundectomy.

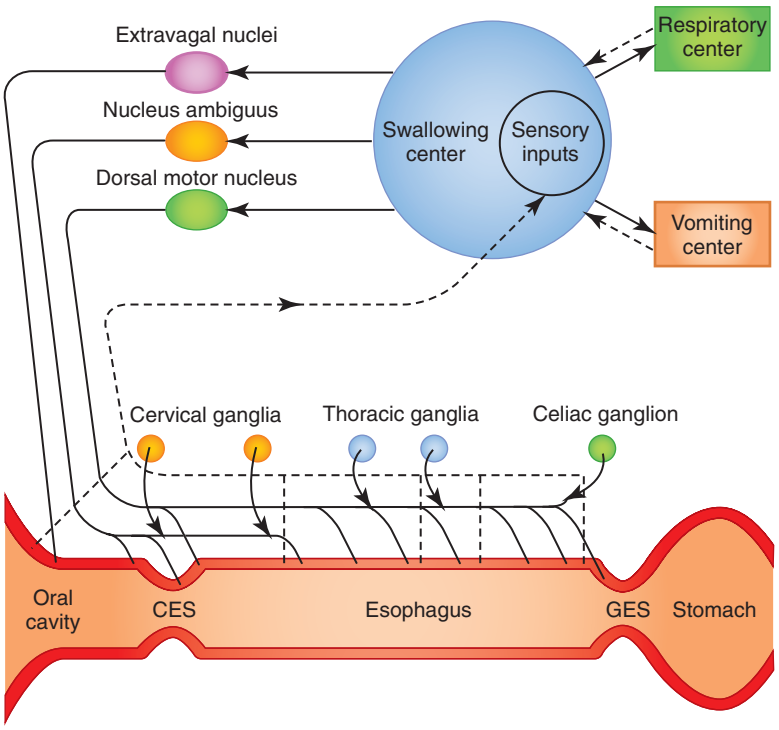


Figure 1-8 Regulation of oropharyngeal and esophageal motility. CES, Cricoesophageal sphincter; GES, gastroesophageal sphincter.

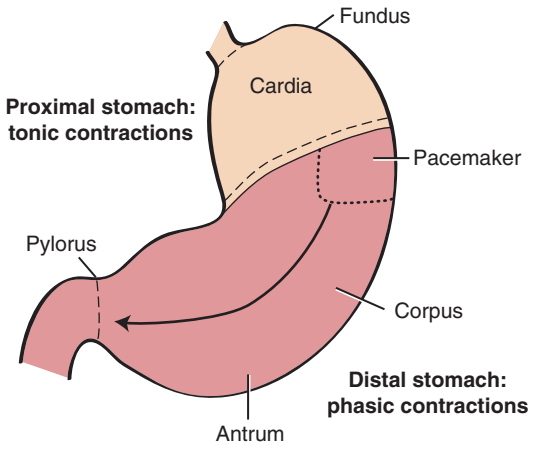


Figure 1-9 Tonic and phasic contractions in the regulation of gastric emptying.

A pacemaker site in the proximal fundus of the greater curvature generates action potentials and phasic contractions that propagate from the site of origin circumferentially and distally to the pylorus.[26] During feeding, phasic contractions of the distal stomach trigger a repetitive cycle of propulsion, trituration, and retropulsion that progressively reduces the size of the ingesta. Thus, the peristaltic qualities of the distal stomach regulate the emptying of solid particles into the duodenum. Antral disease or antrectomy abolishes this physiologic effect resulting in a "dumping syndrome" as a result of accelerated gastric emptying, nutrient overload in the small intestine, and osmotic diarrhea.

Gastric emptying is regulated by several physiologic parameters, including (a) pyloric resistance and pressure differential between the stomach and duodenum; (b) water content—liquids are emptied more rapidly than solids; (c) nutrient composition—carbohydrates are emptied more rapidly than proteins which, in turn, are emptied more rapidly than lipids; (d) nutrient acidity—delayed at acid or alkaline pH; (e) nutrient osmolality—delayed at high osmolality; and (f) hot or cold temperatures. Duodenal, jejunal, and ileal braking mechanisms also feedback inhibit gastric emptying through activation of mucosal sensory receptors for fatty acids, tryptophan, osmolality, and acid. Intestinal braking mechanisms serve to prolong transit time and nutrient contact time.[25]

During the fasting state the stomach is ordinarily empty, aside from swallowed saliva, a small amount of mucus, and cellular debris that collects in the gastric lumen. In addition, there may be particles of indigestible solids left from the previous meal. A mechanism exists to empty this fasting content: the migrating motility complex (MMC). The ability of the MMC to completely empty the stomach of residue is so striking that it is sometimes referred to as the "interdigestive housekeeper" of the GI tract.[25] The GI hormone, motilin, is involved in the regulation of the MMC. Cats and rabbits do not have an MMC, but instead have a less vigorous emptying pattern known as the migrating spike complex (MSC).[27,28]

Intestine

Contractions in the small intestine serve three general functions: mixing of the ingesta with digestive enzymes and other secretions; circulation of the intestinal contents to facilitate contact with the intestinal mucosa; and net caudal propulsion of the intestinal contents. Intestinal contractions are governed by four motility patterns: segmentation, peristalsis, intestinointestinal inhibition, and the MMC.[29]

Segmentation

If a contraction is not coordinated with activity above and below, intestinal contents are displaced both proximally and distally during the contraction and may, in fact, move cranially during the period of relaxation. Such contractions appear to divide the bowel into segments, which accounts for the term *segmentation* given to the

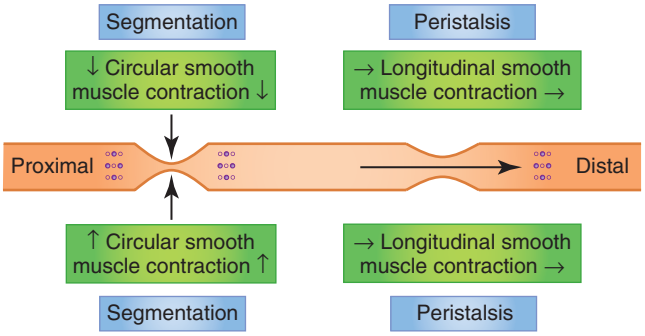


Figure 1-10 Segmentation and peristalsis patterns of the small intestine.

process. Segmentation serves to mix and locally circulate the intestinal contents. Segmentation primarily involves circular smooth muscle contraction (Fig. 1-10).

Peristalsis

The small intestine is also capable of eliciting a highly coordinated contractile response that is propulsive in nature. When the bowel is distended by a bolus of food there is contraction cranial to and relaxation caudal to the point of distention. The neurotransmitters involved in the cranial contraction are ACh and SP, and the neurotransmitters involved in the caudal relaxation are VIP and nitric oxide (NO). These events tend to move the material caudally. Short-segment peristalsis of the bowel is the norm in dogs and cats (Fig. 1-10). If short-segment peristalsis occurs sequentially, it can propel a bolus the entire length of the gut in a short period of time. This peristaltic response, first characterized by Bayliss and Starling, is referred to as the *law of the intestine*, and is less frequent than short-segment peristalsis.

Intestinointestinal Inhibition

If an area of the bowel is grossly distended, contractile activity in the rest of the bowel is inhibited. This reflex prevents the movement of ingesta into more distal segments of intestine that have been severely distended or obstructed. This reflex is mediated by the extrinsic (autonomic) nervous system.[30]

Migrating Motility Complex

The MMC moves indigestible materials, mucus, and secretions from the stomach to the colon during the fasting state. The enteric nervous system regulates the periodicity and migration of the MMC, and the gastrointestinal hormone motilin reinforces MMC activity.

Colon

The colon serves two important functions: (a) extraction of water and electrolytes from the luminal contents in the ascending and transverse colon and (b) storage of feces and control of defecation in the descending colon.[31] This specialization of function has been attributed to regional differences in colonic motility patterns. Electrical slow-wave frequency and rhythmic phasic contractions are slower in the proximal colon (cecum and ascending colon), thus facilitating extraction of water from the fecal mass by diffusion and active transport. Retrograde giant contractions and anti-peristalsis further facilitate mixing of contents in the proximal colon. In contrast, motility of the distal colon (transverse and descending colon) is characterized primarily by migrating spike bursts and powerful giant migrating contractions that propagate the fecal mass toward the rectum (Fig. 1-11).[31,32]

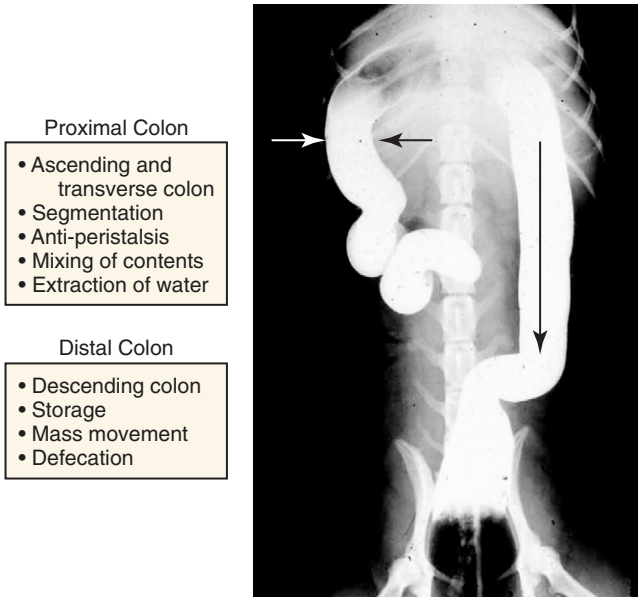


Figure 1-11 Motility patterns of the proximal and distal colon.

Segmentation

These types of contractions occur in both the proximal and distal colon. In the proximal colon, segmentation-type contractions serve to move the contents back and forth, mixing and exposing them to the mucosa for absorption of water and electrolytes. In the distal colon, segmentation activity serves to offer resistance and thus retard the flow of contents from more proximal regions into the rectum.

Mass Movement

Most colonic propulsion takes place during a characteristic sequence termed the *mass movement*. Segmental activity is inhibited and the colon undergoes a contraction that sweeps intraluminal contents caudally. Following mass movements, segmentations and phasic contractions return to the colon.

Defecation

Fecal accumulation in the anorectal canal stimulates smooth muscle contraction of the rectal wall and reflex inhibition of the internal anal sphincter (rectosphincteric reflex). Defecation does not occur immediately because the external anal sphincter, which is composed of striated muscle and therefore under voluntary control, is still tonically contracted. If environmental conditions are not appropriate for defecation, voluntary contractions of the external anal sphincter can overcome the reflex. Relaxation of the internal sphincter is transient because the receptors within the rectal wall accommodate the stimulus of distention. The internal anal sphincter regains its tone, and the sensation subsides until the passage of more contents into the rectum. If the rectosphincteric reflex is elicited at a time when evacuation is appropriate, defecation will occur.

Gastrocolic Reflex

Distention of the stomach by food increases the motility of the colon and increases the frequency of mass movements in the large intestine. This long arc reflex, called the gastrocolic reflex, has its afferent limb in the stomach. The efferent limb of the reflex, which produces increased motility of the colon, is mediated by the hormones cholecystokinin and gastrin.

Gallbladder

During fasting, the gallbladder is relaxed and stores bile. When feeding resumes, hormonal (cholecystokinin) and neural (acetylcholine) mechanisms stimulate simultaneous gallbladder contraction and sphincter of Oddi relaxation, thereby facilitating emptying of bile into the small intestine.[33]

Secretion

Salivary Gland

Dogs and cats both have four sets of salivary glands: parotid, mandibular, sublingual, and zygomatic, all under autonomic regulation. The structural unit of the salivary gland is the salivon, consisting of *acinar cells*, which secrete the initial fluid and mucin; *intercalated ducts*, which form a short connection to the striated ducts; *striated ducts*, which are composed of epithelial cells and which modify the final ionic composition; and *myoepithelial cells*, which contract and serve to expel salivary fluid into the oropharynx (Fig. 1-12).

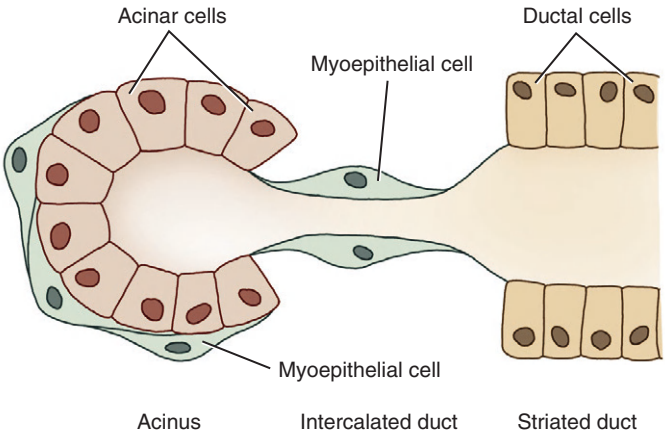


Figure 1-12 The salivon—the anatomic unit of the salivary gland.

Salivary secretions have five major functions: (a) hydration for mastication and deglutition; (b) evaporative cooling; (c) secretion of immunoglobulin (Ig) A; (d) HCO_3^- (bicarbonate) buffering prior to the initiation of digestion; and (e) release of R factor binding proteins for vitamin B_{12} transport.[34,35] Salivary amylase, which initiates starch digestion in man, is not found in dog or cat saliva.[34] Primary secretion from the acinus contains Na^+, Cl^-, and HCO_3^- actively transported from the blood to gland and duct. As saliva is transported down the collecting ducts, it is further modified by exchange of Na^+ for H^+ and K^+ and active reabsorption of Na^+ and Cl^-. At high flow rates, the salivary composition will resemble the primary secretion because there is less time for modification along the ducts (Fig. 1-13).[34]

Stomach

As a secretory organ, the stomach has several major functions, including initiation of protein digestion; inactivation of ingested bacteria, viruses, and parasites; secretion and binding of intrinsic factor to vitamin B_{12}; absorption of ferric iron; hormonal regulation of gastric and pancreatic secretions; mucous lubrication of the gastric contents; and protection of the gastric mucosa from the caustic effects of protons and pepsins.[36] The stomach accomplishes these diverse functions through the secretions of the gastric pit, the structural unit of the gastric mucosa. Gastric pits are branched tubular invaginations bearing multiple cell types and having multiple secretory functions: (a) parietal or oxyntic cells secrete protons and intrinsic factor; (b) chief cells secrete pepsinogens; (c) endocrine cells secrete the hormones gastrin and ghrelin; (d) surface epithelial cells secrete HCO_3^- and prostanoids; (e) neck and surface mucous cells secrete mucus containing sulfated glycoproteins; and (f) enterochromaffin cells secrete histamine (Table 1-3, Fig. 1-14).[36]

Cell Biology of Gastric Acid Secretion

Secretion of hydrochloric acid (HCl) is the major function of the parietal cells. H^+ ion secretion acidifies the gastric contents thereby permitting the conversion of inactive pepsinogens to active pepsins. Parietal cells generate protons through carbonic acid (H_2CO_3) synthesis and dissociation into H^+ and HCO_3^-.[37] Protons are actively

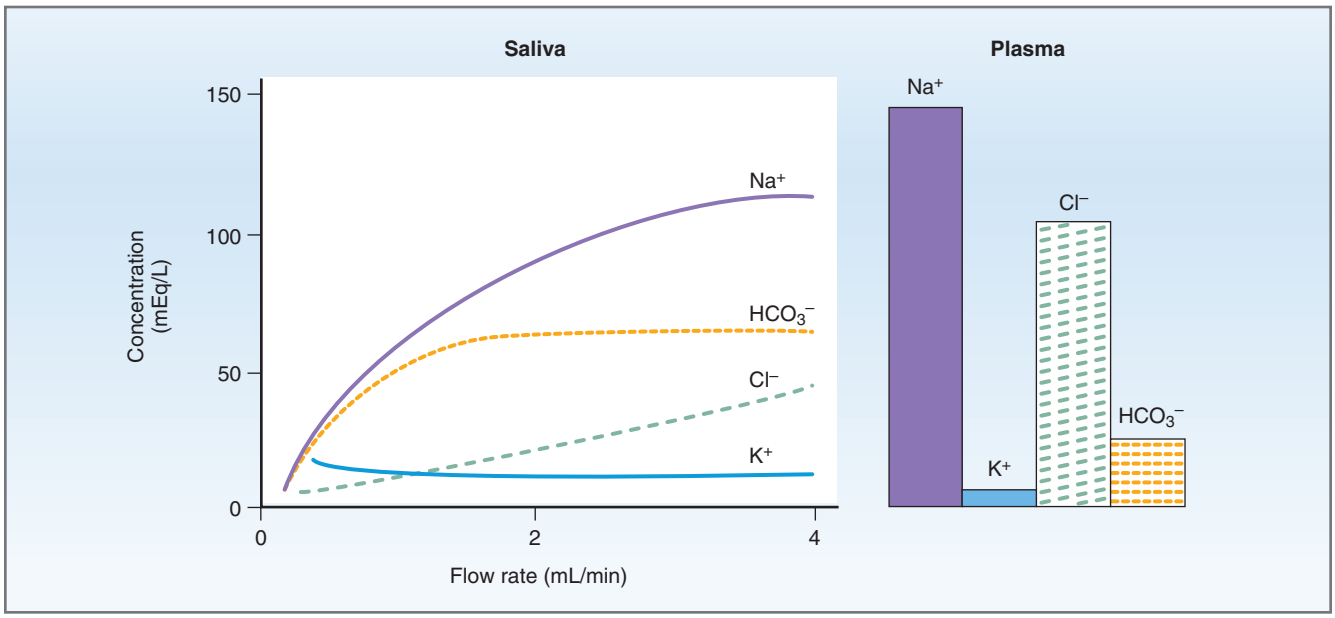


Figure 1-13 Composition of salivary secretion at low and high secretory rates. (From Costanzo L (ed): *Physiology*, 4th ed. Philadelphia: Saunders, 2010.)

Table 1-3 Cell Types, Secretions, and Functions in the Gastric Mucosa

Cell types	Secretion	Function
Parietal (oxyntic) cells	Protons	Activates pepsinogens
	Intrinsic factor	Binds vitamin B_{12}
Chief cells	Pepsinogen	Peptide bond hydrolysis
Mucous cells	Sulfated glycoproteins	Unstirred layer
	Pepsinogen	Peptide bond hydrolysis
Endocrine cells	Gastrin	Stimulates H^+ secretion
	Ghrelin	Stimulates feeding
Enterochromaffin cells	Histamine	Stimulates H^+ secretion
Epithelial cells	HCO_3^-	Neutralizes H^+
	Prostanoids	Gastric mucosal barrier

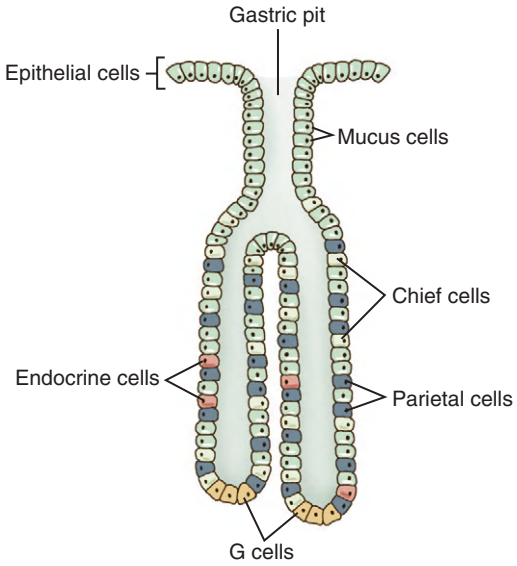


Figure 1-14 The gastric pit—the anatomic unit of gastric secretion.

secreted at the apical membrane along with Cl^- into the lumen of the stomach in exchange for K^+. An apical membrane H^+,K^+-ATPase actively transports H^+ and K^+ against their electrochemical gradients.[37] HCO_3^- is absorbed from the parietal cell into the blood via a Cl^-–HCO_3^- exchanger at the basolateral membrane. The absorbed HCO_3^- is responsible for the alkaline tide that is observed postfeeding. Eventually, this HCO_3^- will be resecreted into the GI tract in pancreatic and biliary secretions.

Physiology of Gastric Acid Secretion

The basal, cephalic, gastric, and intestinal phases of gastric acid secretion[36] were first characterized by Pavlov in his now-classic work on conditioned reflexes in the dog at the turn of the last century. *Basal* phase secretion is that small amount of gastric acid secretion that takes place in the absence of anticipation or physiologic stimulus. Along with the MMC, basal acid secretion serves to moderate bacterial flora and to degrade indigestible solids in the interdigestive state. The *cephalic* phase of gastric acid secretion results from olfactory, visual, and auditory cues, as well as from the mastication and swallowing of food. The cephalic phase accounts for 20% to 30% of the total acid secretory load and is mediated by vagal postganglionic neurons that stimulate parietal secretion directly or indirectly via gastrin release. The *gastric* phase accounts for 50% to 60% of the total acid secretory load and is mediated by the direct and indirect effects of gastric distention and amino acids on parietal and antral G cells (Fig. 1-15). The *intestinal* phase accounts for up to 10% of gastric acid secretion and is mediated by the effects of intraduodenal amino acids.

Pharmacology of Gastric Acid Secretion

Parietal cells are stimulated directly and indirectly by neural (acetylcholine), endocrine (gastrin), and paracrine (histamine) mechanisms.[36] In a neural mechanism, depolarization of vagal postganglionic nerve fibers releases ACh which then binds to the muscarinic M_3 receptor on parietal cells. Binding of ACh to the M_3 receptor activates the phospholipase C, IP_3, and diacylglycerol (DAG) signal transduction pathway whose final pathway is the apical H^+,K^+-ATPase (Fig. 1-16). In a concurrent paracrine mechanism, enterochromaffin cells release histamine into the extracellular space where it binds to a histamine H_2 receptor on parietal cells. Binding of histamine to the H_2 receptor activates the adenylate cyclase, cyclic adenosine monophosphate (cAMP), protein kinase A signal transduction pathway, leading to activation of the final common pathway—the apical H^+,K^+-ATPase. Coincident with the neural and paracrine effects, gastrin is released from antral G cells in response to ACh, gastrin-releasing peptide, and amino acids. Gastrin circulates as a GI hormone having a primary effect of binding gastrin (or CCK_B) receptors on gastric parietal cells. Like ACh, gastrin stimulates parietal cell H^+ secretion through the IP_3/DAG/Ca^{2+} second messenger system. Inhibition of parietal cell H^+ secretion is mediated primarily via the paracrine effects of somatostatin, prostaglandins, and adenosine. All three paracrines inhibit parietal cell adenylate cyclase and cAMP production. Somatostatin has the additional effect of both inhibiting histamine release from enterochromaffin cells and gastrin release from antral G cells.

Gastric Pepsinogen Secretion

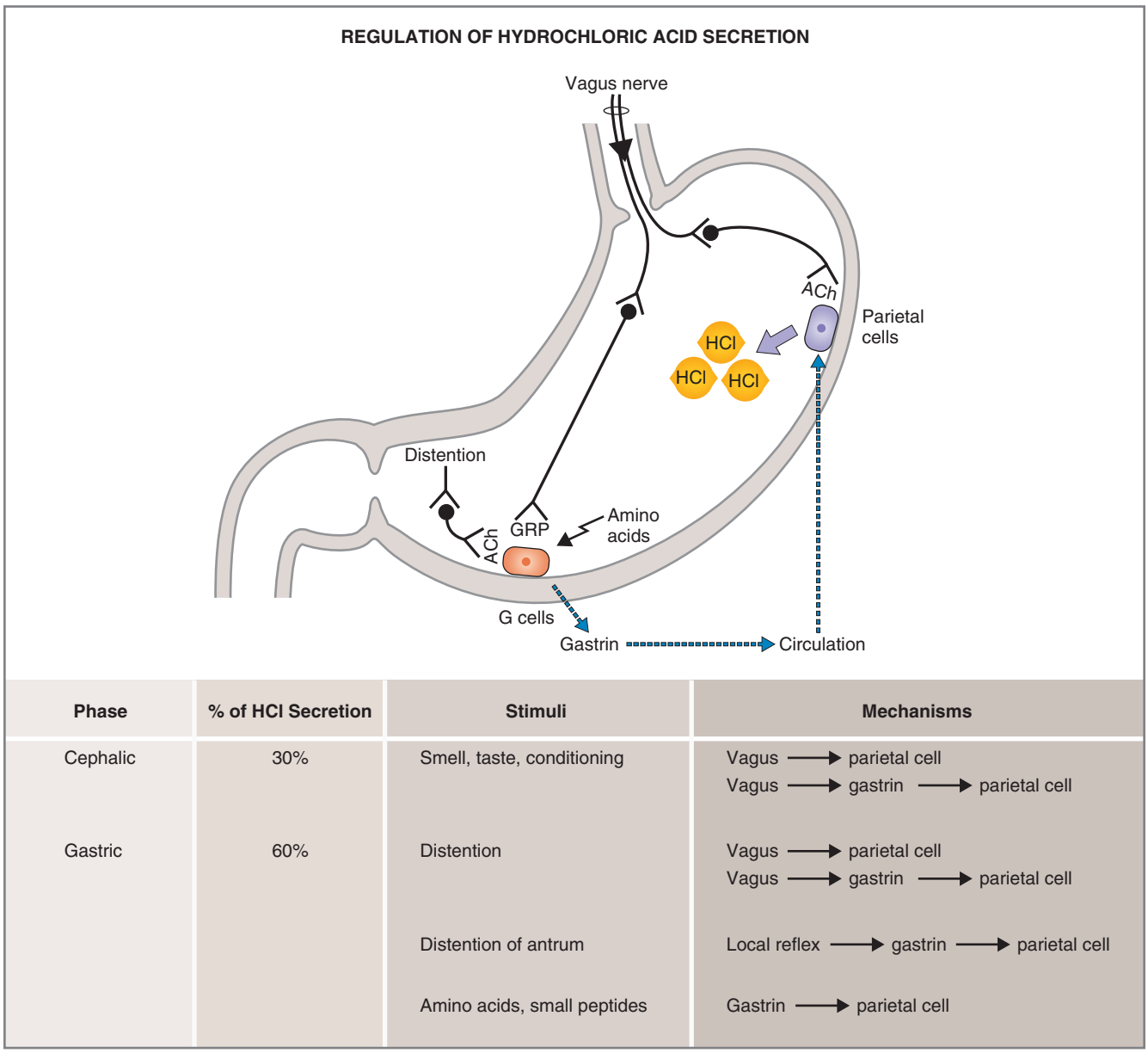
Chief cells and mucous cells secrete pepsinogen during the cephalic and gastric phases of gastric secretion.[38] H^+ ions secreted by the gastric parietal cells facilitate the conversion of inactive pepsinogen to active pepsin. Pepsin is optimally active at a pH of 1 to 2, and denatures at pH >5.0. Pepsin preferentially hydrolyzes peptide bonds containing aromatic amino acids such as phenylalanine, tryptophan, and tyrosine.

Gastric Intrinsic Factor Secretion

Intrinsic factor (IF) is a glycoprotein secreted by gastric parietal cells that serves to bind and transport vitamin B_{12} (cobalamin) to absorptive sites in the distal ileum. IF is produced by parietal cells in the dog, but not in the cat.[39,40] Pancreatic ductal cells are an alternate source of IF synthesis in both species, exclusively so in the cat.[40]

Gastric Mucus Secretion and the Gastric Mucosal Barrier

Sulfated glycoproteins produced by neck and surface epithelial cells are incorporated into the unstirred layer adherent to the gastric mucosa. Mucus serves to trap H^+ ion in this unstirred layer thereby preventing back-diffusion into the mucosa and submucosa. Other factors contributing to this gastric mucosal barrier include epithelial HCO_3^- secretion and acid neutralization, rapid epithelial migration to reconstitute the overlying epithelium, blood flow in the lamina propria to transport and buffer absorbed H^+, and the multiple cytoprotective effects of endogenous prostaglandins.[41]



Phase	% of HCl Secretion	Stimuli	Mechanisms
Cephalic	30%	Smell, taste, conditioning	Vagus → parietal cell Vagus → gastrin → parietal cell
Gastric	60%	Distention	Vagus → parietal cell Vagus → gastrin → parietal cell
		Distention of antrum	Local reflex → gastrin → parietal cell
		Amino acids, small peptides	Gastrin → parietal cell

Figure 1-15 Cephalic and gastric phase regulation of gastric acid secretion. ACh, acetylcholine; GRP, gastrin-releasing peptide; HCl, hydrochloric acid. (From Costanzo L (ed): *Physiology*, 4th ed. Philadelphia: Saunders, 2010.)

Endocrine Secretion

In addition to the role of gastrin in gastric acid and pancreatic enzyme secretion, the stomach secretes the hormone ghrelin, a growth hormone (GH)-releasing peptide that stimulates appetite, body growth, and fat deposition. The postprandial gastric expression of ghrelin suggests a GI–hypothalamic–pituitary axis that influences GH secretion, body growth, and appetite that is responsive to nutritional and caloric intakes. Ghrelin and leptin have been characterized as a "yin and yang" system that relays peripheral information to the brain and directs the body in the appropriate maintenance of energy reserves and nutritional intake.

Intestine

Epithelial cells are specialized for membrane brush-border digestion, fluid and electrolyte secretion, and absorption. Motility and blood flow support these processes. The crypt is the germinal center of the intestinal epithelium with stem cells differentiating into crypt and villus epithelia. Crypt epithelial cells are primarily secretory in function—water and electrolytes are secreted into the intestinal lumen to solubilize the chyme and neutralize gastric acid. Villus epithelial cells are primarily absorptive in function—water, solutes, glucose and other monosaccharides, amino acids and small peptides, free fatty acids and glycerol, minerals and vitamins, and other nutrients are absorbed from the lumen into villus epithelial cells. Under normal circumstances, water and electrolytes secreted by the crypt epithelial cells are absorbed by the villus epithelial cells and returned to the plasma volume. In disease states in which adenylate cyclase or calcium gating are maximally activated, fluid secretion by the crypt cells overwhelms the absorptive capacity of the villus epithelium resulting in severe diarrhea and dehydration.

In addition to fluid secretion from the mucosa, the duodenum has the additional function of mucus secretion from prominent

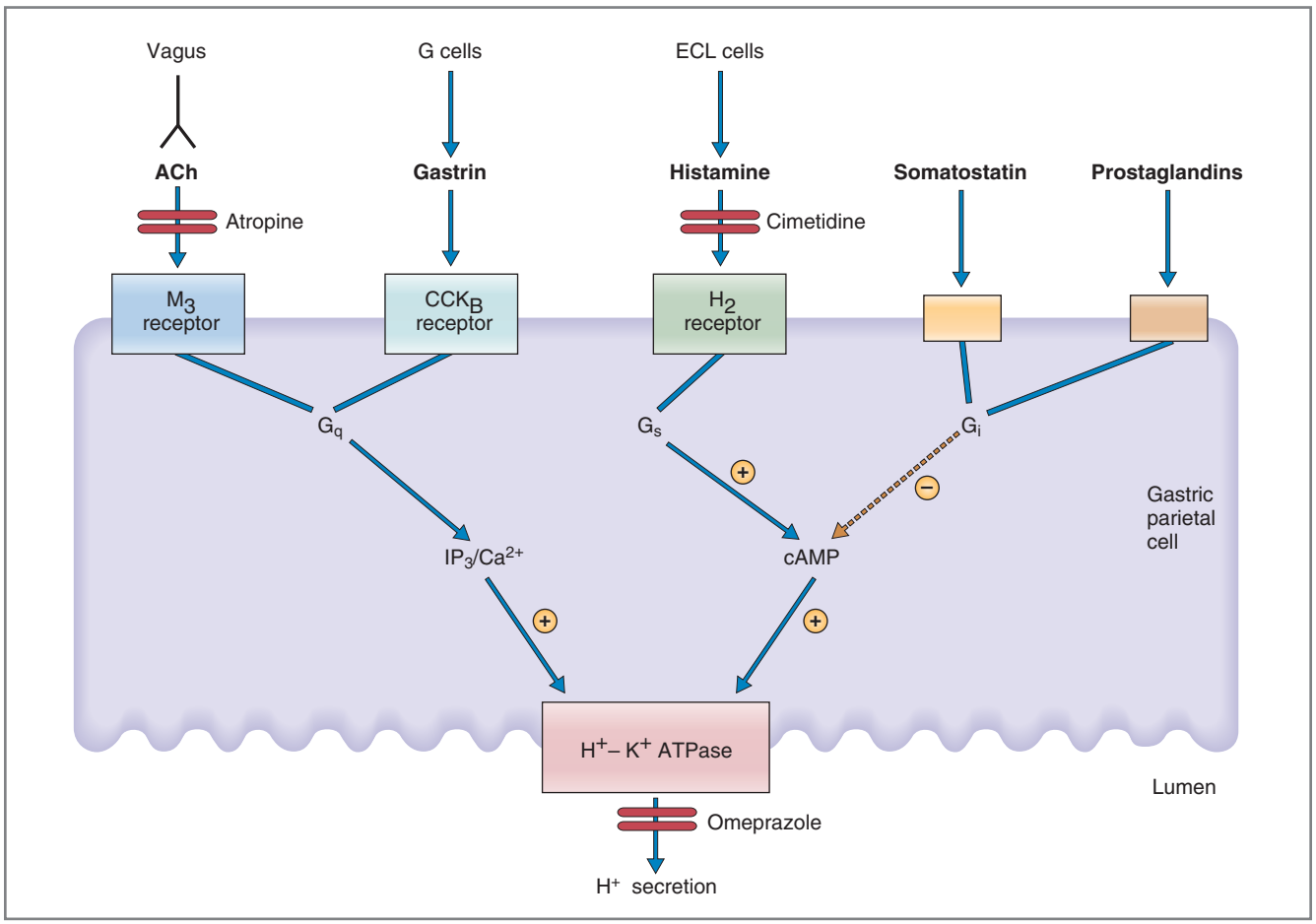


Figure 1-16 Acetylcholine (neurocrine), gastrin (endocrine), and histamine (paracrine) stimulate gastric acid secretion. Prostaglandins (paracrine) and somatostatin (multiple mechanisms) inhibit gastric acid secretion. ACh, acetylcholine; cAMP, cyclic AMP; CCK, cholecystokinin; ECL cells, Enterochromaffin-like cells; G cells, gastrin-producing cells; H, histamine; IP_3, inositol triphosphate; M, muscarinic. (From Costanzo L (ed): *Physiology*, 4th ed. Philadelphia: Saunders, 2010.)

submucosal Brunner's glands.[41] The main function of these glands is to produce a mucus-rich, alkaline secretion to (a) protect the duodenum from the acidic content of the chyme, (b) provide an alkaline environment for the optimal activation of lipase and colipase, (c) lubricate chyme transiting through the GI tract, and (d) trap, inactivate, and regulate intestinal bacteria. Brunner's glands are not found in the jejunal or ileal submucosa.

Chloride is actively secreted from the crypt epithelial cells, followed passively by H_2O, and this secretion is regulated by both branches of the autonomic nervous system (Fig. 1-17). VIP and ACh-containing parasympathetic neurons stimulate fluid secretion from crypt cells. Cholinergic regulation of chloride secretion is coupled to Ca^{2+} second-messenger signaling, whereas VIP regulation is coupled to stimulation of adenylate cyclase, cAMP production, and protein kinase A activation. Norepinephrine-containing sympathetic neurons inhibit fluid secretion from these same cells. Opioid neurons in the enteric nervous system provide an additional level of regulation by innervating crypt epithelial cells and, like sympathetic neurons, serve to inhibit fluid secretion from these cells.[42,43]

Intestinal inflammation is accompanied by crypt epithelial cell hypersecretion. Epithelial cells respond to bacterial infection, for example, by expressing the proinflammatory cytokines TNF-α and interleukin (IL)-1β, chemokines (IL-8), prostanoids, and leukotrienes, some of which activate crypt cells directly. Many enteric infections also involve the enteric nervous system. VIP and ACh secretomotor neurons, for example, are activated indirectly by SP-containing sensory neurons, 5-hydroxytryptamine (5-HT), histamine, and PGI_2 (prostacyclin), leading to excessive crypt fluid secretion and severe diarrhea (Fig. 1-17).[44]

Pancreas

The exocrine pancreas is a secretory organ with several physiologic functions. Exocrine pancreatic fluid contains digestive zymogens, which initiate protein, carbohydrate, and lipid digestion; HCO_3^- and water, which serve to neutralize the duodenum; intrinsic factor, which binds cobalamin (vitamin B_{12}) and facilitates its absorption in the distal ileum; and antibacterial proteins, which regulate the small intestinal bacterial flora.[3,5,39,45] Digestive zymogens and antibacterial proteins are secreted primarily by acinar cells, whereas HCO_3^-, water, and intrinsic factor are secreted primarily by ductal cells.

Pancreatic fluid is an isotonic solution containing Na^+, Cl^-, K^+, and HCO_3^-. The Na^+ and K^+ concentrations are the same as in plasma, but the Cl and HCO_3^- concentrations vary with pancreatic flow rate (Fig. 1-18). The net transport process is one of net HCO_3^- secretion into pancreatic ductal fluid, and net absorption of H^+ causing acidification of pancreatic venous blood. Pancreatic ductal cells secrete HCO_3^- in response to feeding, secretin release, and VIPergic neurotransmission.[46]

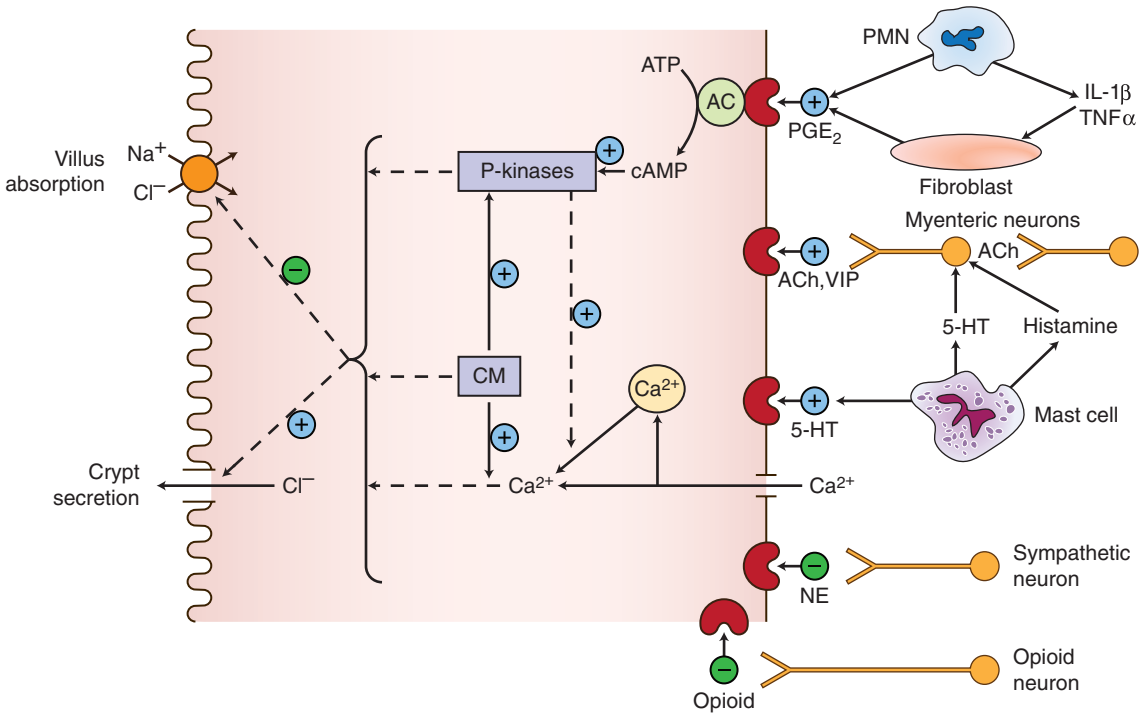


Figure 1-17 Regulation of fluid and electrolyte secretion by crypt epithelial cells, and fluid and electrolyte absorption by villus epithelial cells. 5-HT, 5-hydroxytryptamine; AC, adenylate cyclase; ACh, acetylcholine; ATP, adenosine triphosphate; Ca, calcium; cAMP, cyclic AMP; Cl, chloride; CM, calmodulin; Na, sodium; NE, norepinephrine; P kinases, protein kinases; PGE_2, prostaglandin E_2; PMN, polymorphonuclear leukocyte; VIP, vasoactive intestinal polypeptide.

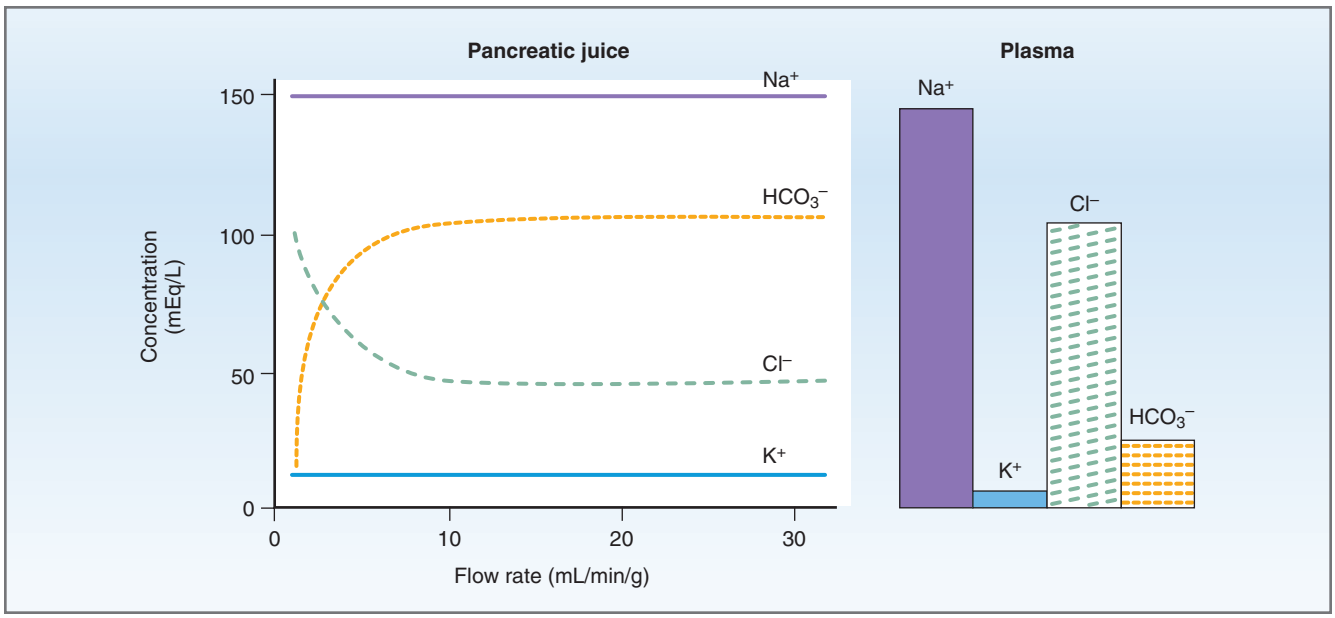


Figure 1-18 Relationship between composition of pancreatic fluid and pancreatic flow rate. (From Costanzo L (ed): *Physiology*, 4th ed. Philadelphia: Saunders, 2010.)

Pancreatic acinar cells secrete inactive zymogens into the pancreatic ductal system in response to feeding, cholecystokinin release, and cholinergic neurotransmission.[45] Pancreatic amylase and lipase are secreted in their active forms, but all other pancreatic enzymes are secreted in inactive zymogen form (e.g., trypsinogen, chymotrypsinogen, procarboxypeptidase, prophospholipase). Intestinal enteropeptidase removes the trypsinogen activation peptide to convert inactive trypsinogen to active trypsinogen, and trypsin acts catalytically to active other pancreatic proteases (Fig. 1-19).

Pancreatic acinar cells protect themselves from intraacinar activation of zymogen and acinar cell necrosis through several mechanisms.[47] (a) Digestive enzymes are synthesized in the form of inactive precursors or zymogens in the rough endoplasmic reticulum. (b) Zymogens are then transported to the Golgi complex where they

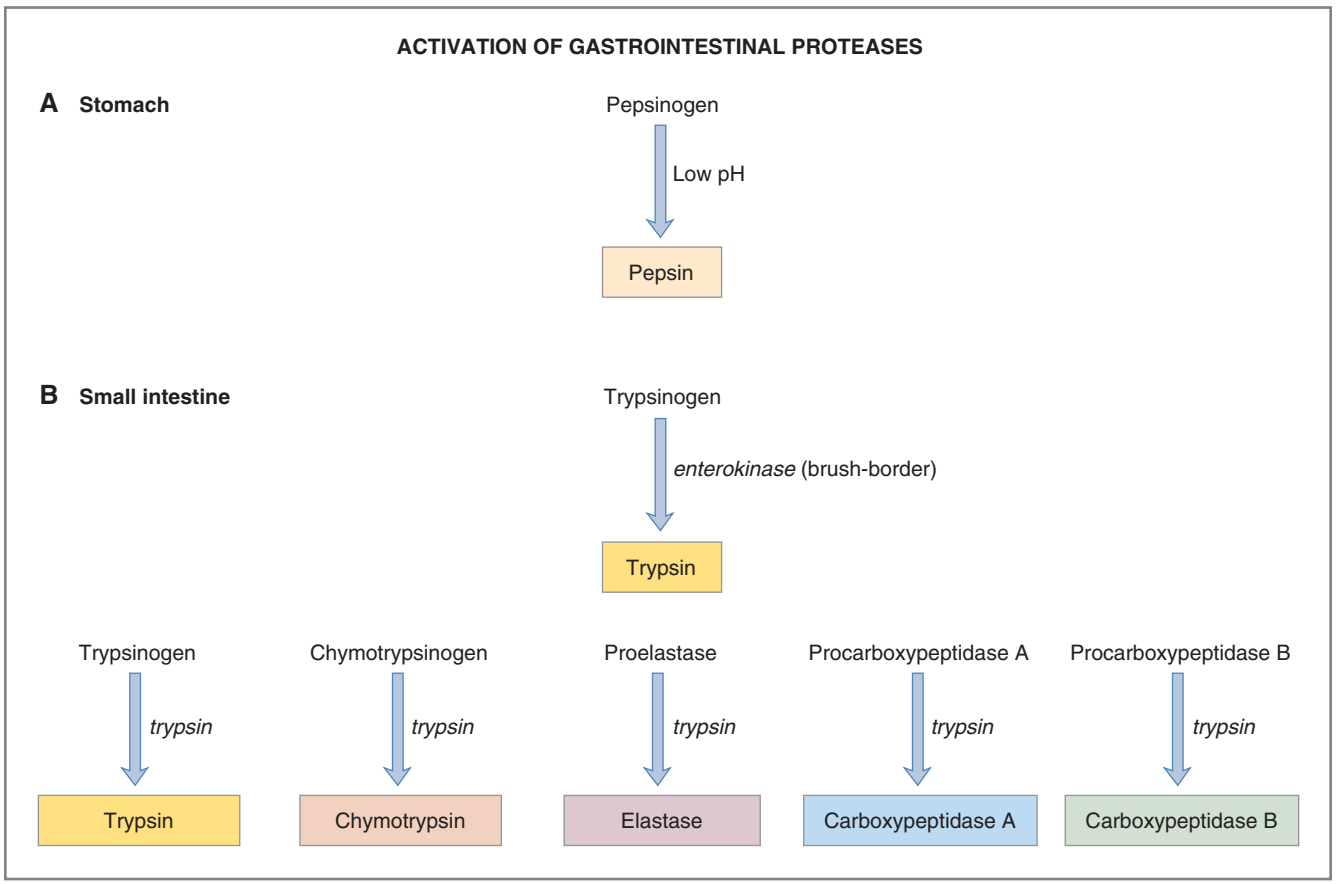


Figure 1-19 Activation of proteases in stomach and small intestine. (From Costanzo L (ed): *Physiology*, 4th ed. Philadelphia: Saunders, 2010.)

undergo selective glycosylation and phosphorylation. Lysosomal hydrolases that are eventually packaged in lysosomes are separated from zymogens bound for export as they pass through the Golgi complex. Lysosomal hydrolases are phosphorylated at the 6 position of mannose residues, bound to receptors specific for 6-phosphoryl mannose, and then transported to lysosomes where the acidic pH favors their dissociation from the receptors. Digestive enzymes lack the 6-phosphoryl mannose label, and are instead transported vectorially into a different secretory fraction. (c) Packaging of zymogens into maturing zymogen granules sequesters them from contact with other subcellular fractions. (d) Pancreatic secretory trypsin inhibitor (PSTI) is incorporated into the maturing zymogen granules. PSTI inactivates trypsin should there be any intra-acinar activation of trypsinogen. (e) Following stimulation (e.g., feeding and cholecystokinin secretion), mature zymogen granules and their contents are released from the cell into the ductal lumen in a process of membrane fusion and exocytosis. (f) Zymogens are activated physiologically only after they enter the duodenum, where the brush-border enzyme enteropeptidase activates trypsinogen, and trypsin then activates other pancreatic zymogens.[45,47]

As with gastric secretion, pancreatic secretion is stimulated during cephalic, gastric, and intestinal phases. During the *cephalic* phase, neural (ACh), endocrine (gastrin), and paracrine (histamine) inputs stimulate parietal cells to secrete H^+ ions, which in turn stimulate secretin release from duodenal endocrine (S) cells. Secretin circulates as a GI hormone, binds to secretin receptors on pancreatic ductal epithelium, and stimulates water and HCO_3^- secretion.[46] The *gastric* phase of pancreatic secretion is mediated by gastric peptides and gastric distention, both of which stimulate gastric H^+ secretion, intestinal secretin release, and secretin-induced pancreatic ductal HCO_3^- secretion. The *intestinal* phase of pancreatic secretion is the most important phase and has both endocrine and neural components. Gastric emptying of amino acids, peptides, and fatty acids stimulate duodenal (I) endocrine cells to release cholecystokinin (CCK). CCK circulates as a GI hormone, binds to CCK receptors on pancreatic acinar cells, and stimulates enzyme secretion.[45] Cholinergic neurotransmission stimulates pancreatic enzyme secretion parallel to the CCK endocrine effect.[45]

Biliary

Biliary secretions provide a source of bile acids for fat digestion and absorption, an excretory route for metabolites and xenobiotics, and additional HCO_3^- for buffering of H^+ ion in the duodenum. Bile acids are the major components of bile accounting for about one-half to two-thirds of the total solutes. Bile also contains water, electrolytes, cholesterol, phospholipids, hormones, protein, and bilirubin.

Bile components are synthesized, stored, and secreted from the hepatocytes into the biliary ductal system.[9] In the absence of neural or hormonal input (as in the fasting state), the gallbladder is relaxed, the terminal biliary ductal sphincter (sphincter of Oddi) is contracted, and bile is largely stored in the gallbladder. While stored in the gallbladder, water and large portions of the electrolytes are reabsorbed by the gallbladder mucosa, and the remaining constituents are thereby concentrated. During feeding, neural (ACh) and hormonal (CCK) mechanisms activate gallbladder contraction, biliary ductal sphincter relaxation, and emptying of bile into the

duodenum. Secretin and bile salts stimulate bile salt–independent and bile salt–dependent bile flow, respectively.[10]

Bile acids are synthesized from the cholesterol nucleus to which are attached a five- or eight-carbon side chain with a terminal carboxylic acid, and hydroxyl groups positioned at the C3, C7, or C12 carbon atom positions. The major primary bile salts are cholic acid and chenodeoxycholic acid in about equal molar quantities. When these primary bile acids are secreted into the lumen of intestine, a portion of each is dehydroxylated by intestinal bacteria to produce the secondary bile acids, deoxycholic acid and lithocholic acid.[8] Prior to secretion, bile acids are conjugated with taurine and/or glycine to form tauro- and glycoconjugated bile salts. Conjugation lowers the pK_a to well below the physiologic range of biliary and intestinal pH, and conjugated bile acids become ionized anions (referred to as bile salts) rather than undissociated bile acids. In the ionized form, they are less likely to be absorbed by the small intestine and so maintain a higher intraluminal concentration appropriate for emulsification, digestion, and absorption of lipids. Dogs and cats conjugate primarily with taurine. Dogs can convert to glycine conjugation if taurine is deficient, but cats cannot. Cats are obligate taurine conjugators, and have an essential dietary taurine requirement.[8]

Bile salts are amphipathic molecules with polar and nonpolar domains imparting two important functions. Bile salts have an initial detergent effect on fat particles in food permitting the breakup of fat globules into smaller sizes. This initial emulsification phase facilitates intraluminal hydrolytic digestion of lipids. Bile salts further assist in the absorption of fatty acids, monoglycerides, cholesterol, and other lipids through the formation of mixed micelles that serve to transfer digested lipids across the unstirred layer of the mucosa.

Following emulsification and micellarization of fat, most of the secreted bile salts are transported along the GI tract to the ileum where they are absorbed by ileal enterocytes and into the portal blood flow via Na^+–bile salt cotransporters.[8]

Colon

Electrolytes

The large intestine regulates the electrolyte and water composition of the feces. There are distinct differences in the mechanisms of electrolyte transport between the ascending and descending colon, but in general the canine and feline colon absorb water, sodium, and chloride while secreting potassium and HCO_3^-.[48] In the colon (but not in the small intestine), aldosterone stimulates synthesis of Na^+ channels, which leads to Na^+ retention and K^+ secretion. Bicarbonate secretion is another important feature of colonic electrolyte function that helps to neutralize acids produced by bacterial fermentation. Chloride–bicarbonate (Cl^-–HCO_3^-) exchange is the primary cellular mechanism responsible for bicarbonate secretion.

Mucus

A lubricant layer of mucus forms a crucial physiologic barrier between the colonic mucosa and the luminal environment. Mucus is a constantly changing mix of secretions and exfoliated epithelial cells, the chief determinants of which are high-molecular-weight glycoproteins or mucins. GI mucins are secreted from goblet cells as they ascend from their origin in the crypts to the colonic epithelium. Mucin secretion is dependent upon the close integration of the cystic fibrosis transmembrane regulator (CFTR), chloride secretion, and granule exocytosis. In addition to their physiologic role as a mucosal barrier, mucins may also have a pathologic role in the metastases of epithelial tumors and enhanced susceptibility to infection.[48]

Digestion

Hydrolysis

Hydrolytic digestion takes place both in the lumen and in the brush-border of the intestinal villus epithelium. Luminal digestion results largely from the effect of gastric (pepsin and lipase) and pancreatic (amylase, protease, and lipase) enzymes. Membrane digestion serves to further reduce the size of dextrins and disaccharides to monosaccharides, and small- and intermediate-size peptides to amino acids.

Carbohydrates

Starch and glycogen are the most important dietary carbohydrates. Luminal starch digestion begins in the stomach with some limited acid hydrolysis and ends in the small intestine with pancreatic amylase digestion. Amylase hydrolysis of starch yields α-limit dextrins, maltotriose, and maltose. Brush-border enzymes (maltase, isomaltase, lactase, sucrase) further hydrolyze these and other dietary sugars to yield monosaccharides. Glucose and galactose are actively absorbed by a Na^+-dependent carrier system, and fructose is transported by means of facilitated diffusion (Fig. 1-20).[49]

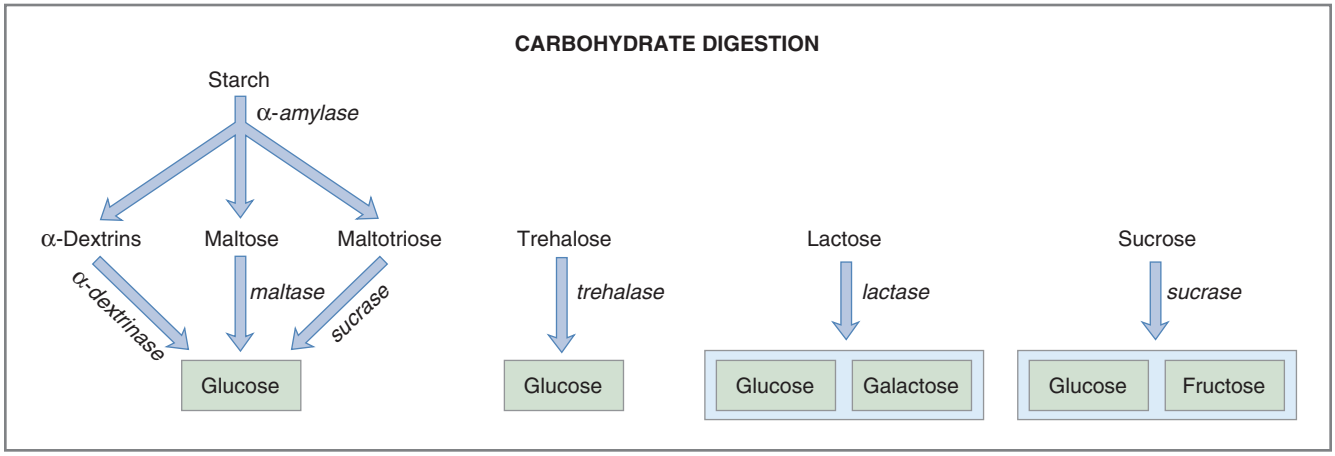


Figure 1-20 Carbohydrate digestion in the small intestine. (From Costanzo L (ed): *Physiology*, 4th ed. Philadelphia: Saunders, 2010.)

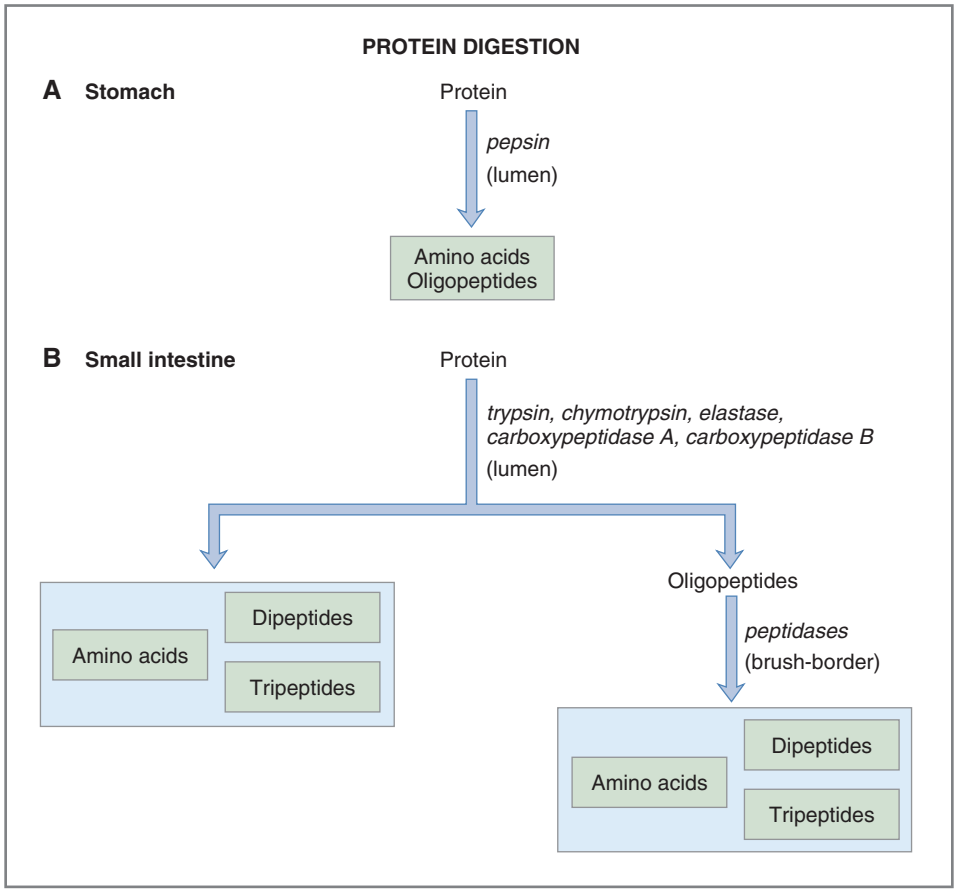


Figure 1-21 Protein digestion in the stomach and small intestine. (From Costanzo L (ed): *Physiology*, 4th ed. Philadelphia: Saunders, 2010.)

Protein

Intraluminal hydrolytic digestion of protein begins in the stomach with peptic digestion and ends in the small intestine with pancreatic protease digestion. Gastric pepsin is an endopeptidase that is secreted in response to a protein meal and low intragastric pH. Peptic activity terminates when gastric contents are mixed with bicarbonate in the small intestine. The presence of food in the small intestine provokes CCK release from the small intestine, which, in turn, stimulates the pancreas to secrete digestive enzymes. Trypsin, chymotrypsin, elastase, and carboxypeptidase are examples of pancreatic proteases, each having specific sites of proteolysis. Specific carrier systems exist for neutral, dibasic, and dicarboxylic amino acids, and some small- and intermediate-size peptides are readily absorbed intact across the enterocyte membrane (see also Figs. 1-19 and 1-21).[50]

Triglyceride

Triglyceride is the major dietary lipid, along with cholesterol, phospholipids, and fat-soluble vitamins. The digestion of dietary lipids begins in the stomach with the action of lingual and gastric lipases, and is completed in the small intestine with the actions of pancreatic lipase, cholesterol ester hydrolase, and phospholipase A_2. Lipid digestion and absorption is more complicated because of lipid solubility characteristics, and involves emulsification of fat by bile salts, hydrolysis of fat by pancreatic lipase and colipase, solubilization of fatty acids and monoglycerides into mixed micelles, absorption, reesterification, chylomicron formation, and transport into the intestinal lymphatics or portal circulation (Fig. 1-22).[51]

Fermentation

The colon contains the largest concentration of bacteria in the GI tract. The colonic microflora plays an important role in nutrition primarily via the production of short-chain fatty acids (SCFAs). Major fiber fermentation substrates include cellulose, hemicellulose, and pectin, substrates that typically are not digested by pancreatic or intestinal amylases. Acetate, propionate, and butyrate account for more than 85% of formed SCFAs, and they accumulate in concentrations up to 150 mmol/L in the canine and feline colon. SCFAs are rapidly absorbed by the colonic mucosa, are readily metabolized by colonic epithelial cells, and have various physiologic effects. Among their physiologic effects, SCFAs promote differentiation and proliferation of colonocytes, stimulate absorption of water and electrolytes, provide 10% to 14% of an animal's overall energy requirements, and influence or modify motility of the GI tract.[52]

Absorption

Intestine

The small intestine is primarily absorptive in function. Water, solutes, glucose and other monosaccharides, amino acids and small peptides, free fatty acids and glycerol, minerals and vitamins, bile salts, and other nutrients are absorbed from the lumen into villus epithelial cells (Table 1-4).[49-51]

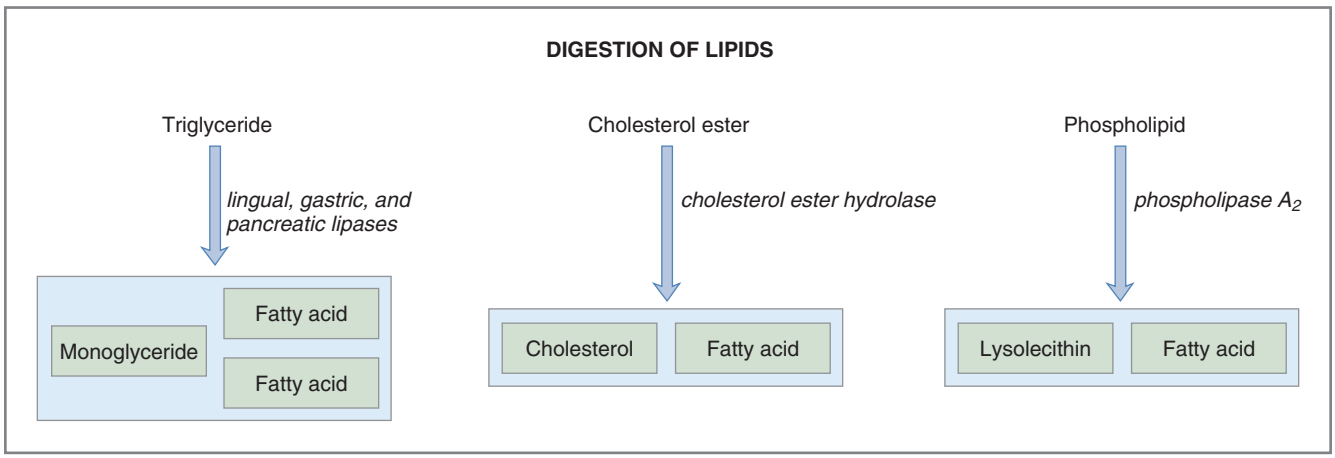


Figure 1-22 Lipid digestion in the small intestine. (From Costanzo L (ed): *Physiology*, 4th ed. Philadelphia: Saunders, 2010.)

Table 1-4 Summary of Small Intestinal Absorption

Nutrient	Digestion Product	Site of Absorption	Mechanism
Carbohydrates	Glucose	Small intestine	Na^+-glucose cotransport
	Galactose	Small intestine	Na^+-galactose cotransport
	Fructose	Small intestine	Facilitated diffusion
Proteins	Amino acids	Small intestine	Na^+-amino acid cotransport
	Dipeptides	Small intestine	H^+-dipeptide cotransport
	Tripeptides	Small intestine	H^+-tripeptide cotransport
Lipids	Fatty acids	Small intestine	Bile salts form mixed micelles
	Monoglycerides	Small intestine	Diffusion of monoglycerides, fatty acids, and glycerol
	Glycerol	Small intestine	Reesterification in the cell
Fat-soluble vitamins		Small intestine	Micelles form with bile salts
Water-soluble vitamins		Small intestine	Na^+-dependent cotransport
Cobalamin (B_{12})		Ileum	Intrinsic factor
Bile salts		Ileum	Na^+-bile salt cotransport
Ca^{2+}		Small intestine	Ca^{2+}-binding protein
Fe^{2+}	$Fe^{3+} \rightarrow Fe^{2+}$	Small intestine	Binds to apoferritin in the cell

Water and Solutes

Villus epithelial cells absorb Na^+, Cl^-, and H_2O, and this absorption is regulated by parasympathetic and sympathetic neurons (see Fig. 1-17). Vasoactive intestinal polypeptide and ACh-containing parasympathetic neurons inhibit fluid absorption from villus epithelial cells, while noradrenergic and opioid neurons stimulate fluid absorption from these same cells. The *jejunum* is the major site of Na^+ absorption in the small intestine. Na^+ is absorbed into jejunal enterocytes via several different Na^+-dependent cotransporters, including Na^+-monosaccharide cotransporters (Na^+-glucose and Na^+-galactose), Na^+–amino acid cotransporters, and Na^+–H^+ exchange. Cellular carbonic anhydrase is the source of protons for the Na^+–H^+ exchange. In the jejunum, there is a net absorption of $NaHCO_3$ (sodium bicarbonate), whereas in the ileum there is net absorption of NaCl. The *ileum* contains a unique Cl^-–HCO_3^- exchange mechanism, resulting in a net absorption of NaCl in the ileum.[53]

Cotransport

Sugars such as glucose and galactose are absorbed across the small intestinal brush-border membrane via carriers that couple their movements to that of sodium (Na^+). Coupling to Na^+ permits organic solutes to be transported against concentration gradients running opposite to that for Na^+. Organic solutes are ultimately transported from enterocyte to blood via basolateral membrane carriers. Some oligopeptides are absorbed intact along with single amino acids by a similar proton-coupled mechanism. This absorptive process is indirectly coupled to Na^+ transport, as protons are derived from Na^+–H^+ exchange, which acidifies the unstirred layer adjacent to the brush-border membrane. The Na^+ gradient, therefore, is the driving force for sugar, amino acid, oligopeptide, and vitamin absorption.[49,50]

Monosaccharides

Glucose and galactose are actively absorbed across the enterocyte epithelium via the sodium-glucose cotransporter protein, SGLT 1. Fructose absorption does not involve an energy-requiring step or a cotransporter in the apical membrane. All monosaccharides are subsequently transported from the enterocyte into the portal capillaries via facilitated diffusion (glucose transporter [GLUT] 2; Fig. 1-23).[49]

Amino Acids

Acidic, neutral, basic, and imino amino acids are actively transported into the enterocytes by specific carrier proteins coupled to Na^+ transport. Separate H^+-dependent cotransporters transport dipeptides and tripeptides from the intestinal lumen into the enterocyte, utilizing an H^+ ion gradient created by a Na^+–H^+ exchanger in

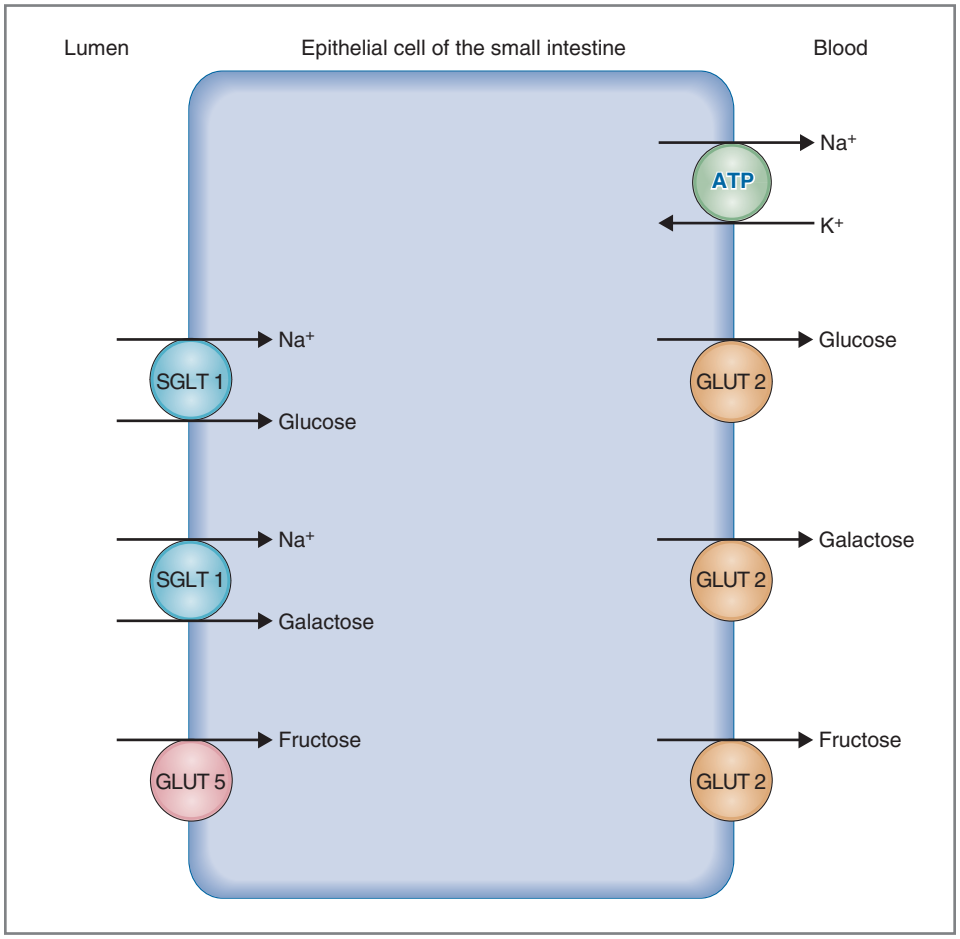


Figure 1-23 Carbohydrate absorption in the small intestine. GLUT 2, glucose transporter protein 2; GLUT 5, glucose transporter protein 5; SGLT 1, sodium/glucose cotransporter 1. (From Costanzo L (ed): *Physiology*, 4th ed. Philadelphia: Saunders, 2010.)

the apical membrane. Peptides are hydrolyzed within the cell, and all amino acids are subsequently transported from the cell to the portal circulation via facilitated diffusion (Fig. 1-24).[50]

Lipids

Mixed micelles of monoglycerides, lysolecithin, cholesterol, and free fatty acids are absorbed by mid-jejunal enterocytes. Bile salts are separated from the lipid fraction and reabsorbed further down the GI tract by ileal enterocytes. Within jejunal enterocytes, products of lipid digestion are reesterified with fatty acids to form triglycerides, phospholipids, and cholesterol ester. Reesterified lipids and apoproteins are subsequently incorporated into chylomicrons which are then transported primarily into intestinal lacteals, and secondarily into portal capillaries (Fig. 1-25).[51]

Water-Soluble Vitamins

The water-soluble vitamins (B_1, B_2, B_6, B_{12}, C, folic acid, nicotinic acid, and pantothenate) are absorbed by a Na^+-dependent cotransport mechanism. The exception is the absorption of vitamin B_{12} (cobalamin), which, instead, depends upon intraluminal binding to R proteins and intrinsic factor before presentation to, and absorption from, the ileal brush-border.

Fat-Soluble Vitamins

Fat-soluble vitamins (A, D, E, and K) are emulsified and micellarized by bile salts in the small intestine, separated from bile salts, absorbed into enterocytes, and incorporated into chylomicrons along with cholesterol, lipoproteins, and triglycerides, before being distributed into the lymphatic circulation.

Calcium

Vitamin D (1,25-dihydroxycholecalciferol) promotes Ca^{2+} absorption by inducing the synthesis of vitamin D–dependent Ca^{2+}-binding protein (calbindin D-28K) in intestinal epithelial cells.[54]

Iron

Iron is absorbed across the apical membrane of intestinal epithelial cells as free iron or as heme iron. Free iron and iron derived from heme are bound to apoferritin and transported across the basolateral membrane into the portal circulation. In the circulation, iron is bound to transferrin and stored in the liver and bone marrow.[54]

Colon

Solutes

The mechanisms of absorption in the large intestine are in many ways similar to those of the small intestine, but with several important differences (Table 1-5).[48] Active nutrient (glucose, amino acid, monoglyceride) absorption is prominent in the small intestine, but there is no evidence of active glucose or amino acid absorption in the colon except during the early neonatal period. Sodium absorption also differs in the colon. Glucose- and amino acid-stimulated sodium transport is a well-established property of the small intestine,

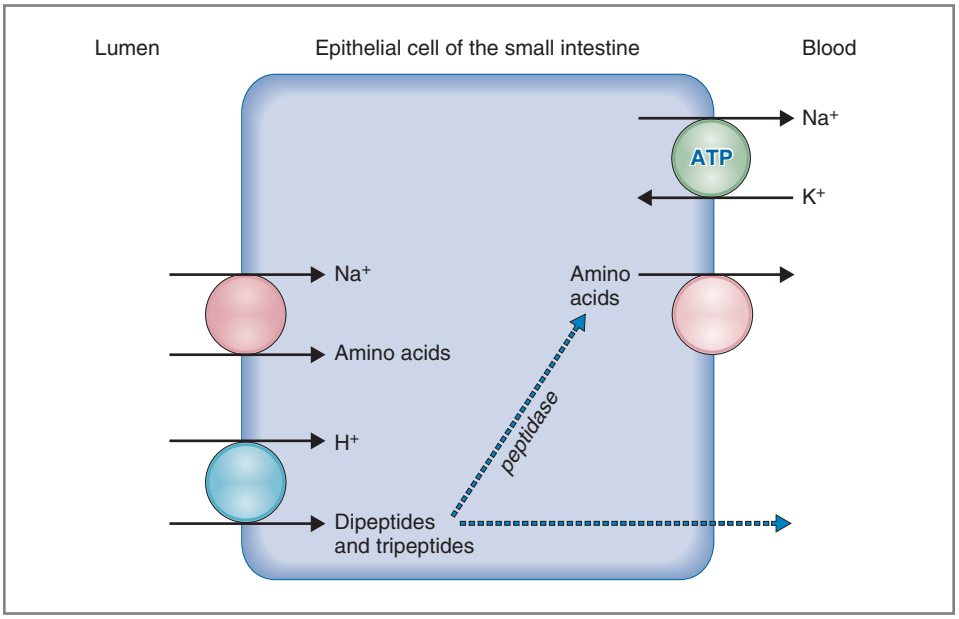


Figure 1-24 Protein absorption in the small intestine. (From Costanzo L (ed): *Physiology*, 4th ed. Philadelphia: Saunders, 2010.)

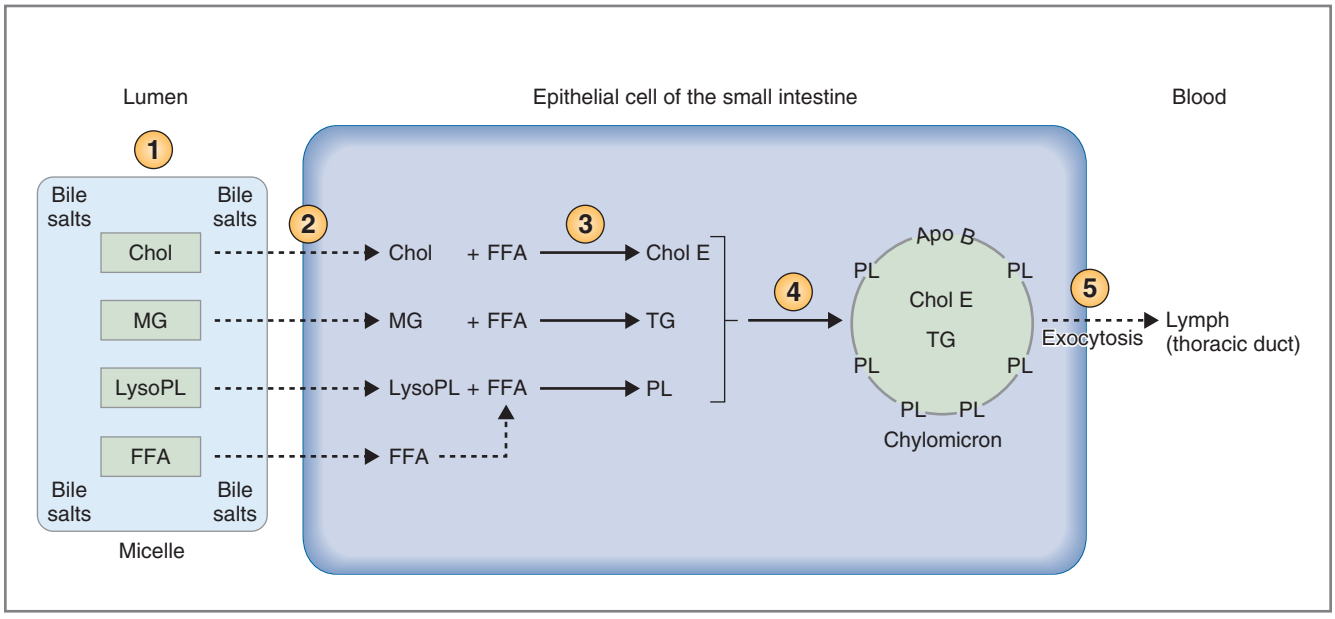


Figure 1-25 Lipid absorption in the small intestine. Apo B, apoprotein B; Chol, cholesterol; FFA, free fatty acids; LysoPL, lysophospholipids; MG, monoglyceride; PL, phospholipids. (From Costanzo L (ed): *Physiology*, 4th ed. Philadelphia: Saunders, 2010.)

so much so that oral glucose-electrolyte solutions have been used to reduce the morbidity of infectious diarrheal diseases of the small intestine. In contrast, glucose-coupled sodium transport does not take place in the colon; sodium transport in the colon instead relies upon electrogenic transport. The large intestine also differs in its response to mineralocorticoids. Aldosterone markedly increases sodium transport in the colon, but has only a modest effect in the small intestine.[48]

Ammonia

Ammonia is an important by-product of amino acid metabolism. The GI tract is the most important source of ammonia, which derives mostly from the colon through the action of bacterial urease on endogenous urea or dietary amines. Ammonia produced by colonic bacteria enters the portal circulation and is transported to the liver for urea cycle transformation.

Short-Chain Fatty Acids

SCFAs (acetate, propionate, butyrate) produced by microbial fermentation in the large intestine are absorbed by mechanisms governing weak electrolyte movement. In the un-ionized form, SCFAs are lipid soluble and can rapidly diffuse across the cell membrane (Fig. 1-26). In the ionized form, however, they are water soluble, and most are too large to traverse the pathways for small ions. SCFAs may account for up to 15% of the metabolic fuel of the canine and feline colon.[52]

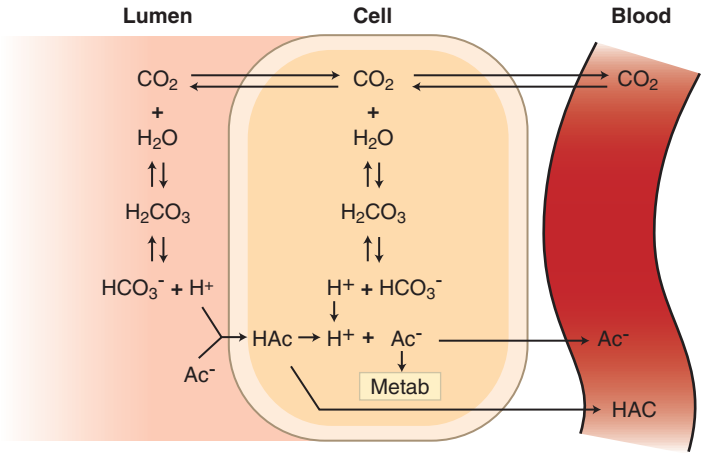


Figure 1-26 Short-chain fatty acid absorption in the colon.

Table 1-5 Differences in the Biologic Properties of the Small and Large Intestines

Biology	Small Intestine	Large Intestine
Villus projections (villi)	Present	Absent
Brush-border microvilli	Prominent	Sparse
Goblet cells	Sparse	Abundant
Endocrine cells	>20 cells	3 cell types
Crypt → epithelial migration	Rapid	Slow
Amino acid absorption	Present	Absent
Glucose absorption	Present	Absent
Lipid absorption	Present	Absent
Vitamin absorption	Present	Absent
Glucose/Na^+ absorption	Present	Absent
SCFA production/ absorption	Minimal	Prominent

SCFA, small-chain fatty acid.

Gallbladder

During fasting, water and electrolytes are reabsorbed from the lumen of the gallbladder. The organic components of bile (e.g., proteins, lipids, phospholipids, cholesterol, and mucus) are not absorbed and instead become concentrated during isotonic fluid removal. Dehydration of gallbladder bile during prolonged fasting may lead to gallbladder dysmotility, biliary stagnation, and supersaturation.

Blood Flow

The splanchnic vasculature constitutes the largest regional circulation derived from cardiac output. More than a quarter of the output from the left ventricle flows through the splanchnic vessels. The major function of the splanchnic circulation is to support the broad range of activities associated with the digestive system: motility, secretion, digestion, absorption, and metabolism. In addition, the splanchnic circulation serves as a storage site for a large volume of blood that can be mobilized during exercise.

The splanchnic circulation is more complicated, both anatomically and functionally, than most other regional circulations. The coronary circulation, for example, serves one major function—that is, support of myocardial contractility. In perfusing the digestive system, the splanchnic circulation subserves motility from the esophagus to the colon; fluid secretion from the GI tract, pancreas, and liver; hydrolytic digestion in the stomach and intestine; fermentative digestion in the colon; absorption in the intestine, colon, and gallbladder; and metabolic activity in the liver.

The splanchnic circulation is arranged both in parallel and in series. Its three major arteries—the celiac, superior mesenteric, and inferior mesenteric—form an extensive anastomosing network that is directed to the stomach, small and large bowel, spleen, pancreas, and liver. The hepatic branch of the celiac artery supplies the liver with 25% of its blood flow. From the other abdominal viscera, blood is taken up by the main portal vein and constitutes the remaining 75% of hepatic perfusion. Splanchnic circulation terminates with the hepatic veins, which return nearly all of the splanchnic blood flow to the caudal vena cava.

The highest tissue blood flows (2 to 4 mL of blood flow per gram of tissue) are found in the mucosa of hollow organs during secretion, digestion, and absorption. The next highest tissue blood flows are in solid organs, for example, the pancreas, at 0.5 mL of blood flow per gram of tissue. The lowest tissue blood flows are in the muscular outer coat of hollow organs at rest (0.1 mL of blood flow per gram of tissue).[16,55]

Branches of the splanchnic arteries give rise to smaller branches that penetrate the surface and muscular coat of the organ, and eventually enter an extensive submucosal network of small arteries. From this network the mucosal arterioles carry blood to the dense mucosal capillary beds. The submucosal vascular arrangement guarantees circulatory communication between segments of the gut and leads to great overlap in the distribution of blood by adjacent arterial branches. This anatomical organization helps to protect against a total loss of blood flow to a segment of gut if its major arterial branch is occluded by a thrombus or embolus.

Splanchnic blood flow is regulated by general hemodynamic principles (i.e., cardiac output, systemic arterial pressure, fluidity of the blood, and blood volume), the autonomic nervous system, neurohumoral substances, local metabolism, and local vascular properties.[16,55]

Bacteriology

The microflora of the GI tract constitutes a complex ecosystem of aerobic and anaerobic bacteria in dynamic equilibrium with viruses, protozoa, fungi, and GI epithelial cells. The diverse metabolic functions of the GI microflora include carbohydrate fermentation and

absorption, trophic effects, suppression of pathogenic bacteria, stimulation of the innate immune response, and prevention of carcinogenesis and allergenicity.[48] In general, there is a progressive colonization and successional ecology of the GI tract from the stomach to intestine and colon.[48] The flora is sparse in the stomach, relatively more populated in the upper small intestine, and of increasing complexity and volume in the ileum and colon. Bacteria are found in both the lumen and attached to the mucosa, but they do not normally penetrate the bowel wall. Bacteria make up most of the flora in the colon and up to 60% of the dry mass of feces. Somewhere between 300 and 1000 different species live in the gut, with most estimates at about 500 (see Chapter 2).

The colon contains the largest concentration of bacteria in the gastrointestinal tract, up to 10^{11} organisms per gram of feces.[48] The colonic microflora play an important role in the nutrition of the animal primarily via the production of SCFAs.[56] Major fiber fermentation substrates include cellulose, hemicellulose, and pectin, substrates that typically are not digested by pancreatic or intestinal amylases. Acetate, propionate, and butyrate account for more than 85% of formed SCFAs, and they accumulate in concentrations up to 150 mmol/L in the colon of dogs.[57] SCFAs are rapidly absorbed by the colonic mucosa, are readily metabolized by colonic epithelial cells, and have various physiologic effects. Among their physiologic effects, SCFAs promote differentiation and proliferation of colonocytes,[58] stimulate absorption of water and electrolytes,[59] provide 7% to 10% of an animal's overall energy requirements,[57] and influence or modify motility of the gastrointestinal tract.[60]

The GI flora is influenced by many factors, including host species, breed, developmental stage, dietary history, environmental conditions, geographic locale, colonic motility patterns, disease, and medication history.[48] A more detailed discussion of the GI microflora may be found in Chapter 2.

Immune Surveillance

The GI tract contains a diverse array of immune cells, including T and B lymphocytes, plasma cells, macrophages, dendritic cells, antigen-presenting cells, mast cells, eosinophils, and neutrophils.[61-68] The normal histology of the canine and feline GI tract is affected by many variables such as age of the animal,[69,70] dietary history, and medication history and has been the subject of considerable controversy. The World Small Animal Veterinary Association (WSAVA) GI Standardization Group used an evidence-based medicine approach[71] to establish a reference range for immunocytes in the GI tract of dogs and cats. Most of the studies employed microscopic evaluation of hematoxylin and eosin (H&E)-stained tissues,[72-79] whereas others used immunohistochemistry (IHC) to label and count leukocyte populations.[80-91] Details of these studies have been published in the GI Standardization Group's archives,[92] but summaries of studies in each anatomic area follow.

Gastric Body Mucosa

Two studies have characterized the leukocyte subpopulations within the superficial region of the normal canine gastric fundic mucosa.[85,91] In one of these studies,[91] a "mucosal unit" was defined as a 250-μm length of mucosa, in which $CD3^+$ intraepithelial lymphocytes (mean, 0.93; range, 0 to 2), $CD3^+$ lamina propria lymphocytes (mean, 4.2; range, 0.5 to 13), lamina propria eosinophils (mean, 0.45; range, 0 to 2), and lamina propria plasma cells (mean, 1.59; range, 0 to 5.83) were enumerated. Biopsy samples were derived from eight dogs, in which considerable interanimal variation in cell counts was noted.

Gastric Antral Mucosa

The leukocyte subpopulations within the superficial region of the normal canine antral mucosa have been characterized in two studies.[85,91] In one study,[90] a "mucosal unit" was defined as a 250-μm length of mucosa, in which $CD3^+$ intraepithelial lymphocytes (mean, 4.4; range, 1.5 to 8), $CD3^+$ lamina propria lymphocytes (mean, 10.7; range, 2.5 to 16.5), lamina propria eosinophils (mean, 2.7; range, 0 to 6), and lamina propria plasma cells (mean, 6.8; range, 0.5 to 15.5) were enumerated. Biopsy samples were derived from eight dogs in that study, in which considerable interanimal variation in cell counts was noted.

Duodenal Mucosa

Several studies have evaluated the normal canine and feline duodenal mucosa using H&E and immunohistochemical staining.[87,91-93] The normal villus length for an adult dog is 722 ± 170 μm, the normal crypt depth is 1279 ± 203 μm, and the normal villus to crypt ratio is 0.68 ± 0.30.[79,92,94] Normal dogs have a mean number of 3.6 ± 3.56 goblet cells per stretch of 100 villous enterocytes, and 9.3 ± 3.09 goblet cells per stretch of 100 cryptal enterocytes.[87] Villous intraepithelial lymphocytes are less numerous in the dog (20.6 ± 9.5 per 100 enterocytes) than in the cat (47.8 ± 11.7 per 100 enterocytes), but the number of cryptal intraepithelial lymphocytes in the dog (5.2 ± 2.33 per 100 enterocytes) is similar to that in the cat (4.6 ± 1.7 per 100 enterocytes).[87,91,92] In the dog, the total leukocyte count is greater in the cryptal lamina propria (156.3 ± 24.91 per 10,000 μm^2) than in the lamina propria of the base (128.3 ± 26.64 per 10,000 μm^2) or tip (100.7 ± 43.89 per 10,000 μm^2) of the villus.[87] Similarly, there are more eosinophils in the canine cryptal lamina propria (9.8 ± 7.51 per 10,000 μm^2) than in the lamina propria of the villus base (3.7 ± 3.52 per 10,000 μm^2) or tip (3.8 ± 6.06 per 10,000 μm^2).[87] In cats, a population of globular leukocytes sometimes is recognized within the intestinal epithelium. These cells have distinctive eosinophilic granules within the cytoplasm and express the molecule perforin as shown by IHC labeling with cross-reactive antisera.[95] This observation suggests that the cells are granular lymphocytes with cytotoxic function. In general, these cells do not appear to increase in number in feline inflammatory enteropathy, but neoplasia of this lineage is documented.[90]

Colonic Mucosa

In the colonic mucosa, there are, on average, 7.7 ± 3.7 intraepithelial lymphocytes per stretch of 100 colonocytes in the normal canine basal crypt epithelium.[87] In the lamina propria between the basal crypts of the canine colon there are approximately 5.5 ± 4.29 plasma cells and 3.8 ± 3.72 eosinophils per 10,000 μm.[87,88,96] Some studies have assessed the number of goblet cells in normal canine colonic cryptal epithelium (25.6 ± 7.32 per 100 colonocytes).[87,88,97] The GI Standardization Group recognized that measurement of goblet cells in colonic epithelium is not straightforward and that the number of such cells may be artifactually decreased by discharge of mucus during the biopsy process.

Along the length of the GI tract, immune cells are found in the epithelium, lamina propria, and submucosa. Appropriate interactions between these different cell types are essential in generating either immune responsiveness or tolerance to the large array of luminal antigens.[98,99] Differences abound along the GI tract, but some generalizations may be made. $CD8^+$ T cells are found primarily in the epithelium; fewer $CD8^+$ T cells are found in the lamina propria or submucosa. Most intraepithelial lymphocytes (IELs)

are $CD3^+/CD8^+$, a phenotype consistent with suppressor-cytotoxic functions. Lamina propria T cells on the other hand are predominantly of the $CD4^+$ helper phenotype. IgA-containing plasma cells are more prominent than IgG- or IgM-containing plasma cells in the lamina propria. In the healthy GI mucosa, a balance would appear to be maintained between helper and suppressor T-cell populations, which allows specific antigen responsiveness while avoiding hyperreactivity.[62,63,100] A more detailed discussion of gastrointestinal immunity may be found in Chapters 3 (Immunology) and 4 (Inflammation).

Liver Metabolism

The liver is involved in many aspects of intermediary metabolism.[7,8,10,13]

Carbohydrate Metabolism

The liver is at the center of carbohydrate metabolism through its role in maintaining normoglycemia. Carbohydrate stored in the liver as glycogen is hydrolyzed to glucose via glycogenolysis during periods of hypoglycemia. When the glycogen available is insufficient, glucose is produced from amino acids by gluconeogenesis. Glucose is also produced from glycerol and intermediates of glycolysis, such as lactic and pyruvic acids. With inadequate glucose in the diet, blood glucose is maintained at the expense of body proteins. Body lipid stores are also depleted during starvation, although lipids do not participate in the maintenance of blood glucose other than by serving as an alternate source of energy, as glucose cannot be synthesized from fatty acids.

Protein Metabolism

The liver is an important site of protein metabolism. Amino acids and proteins absorbed from the intestine or produced in the body are delivered to the liver. The liver deaminates amino acids and converts them to carbohydrates and lipids. Deamination produces α-keto acids, which can be metabolized for energy or used for synthesis of monosaccharides and fatty acids. The liver synthesizes amino acids from intermediates of carbohydrate and lipid metabolism by amination and transamination. Examples of amino acid transaminations include the following:

- Alanine + α-ketoglutarate ↔ pyruvate + glutamate
- Aspartate + α-ketoglutarate ↔ oxaloacetate + glutamate

The liver synthesizes many proteins, including albumin and fibrinogen, most α-globulins, and some of the β-globulins. Prothrombin and clotting factors V, VII, VIII, IX, and X are produced in the liver, as well as ceruloplasmin, ferritin, and many serum enzymes.

Lipid Metabolism

The liver is involved in the intermediary metabolism of lipids, most importantly triglyceride synthesis and fatty acid oxidation, as well as digestion and absorption from the GI tract, and cholesterol metabolism outlined below:

- Intestine → Cholesterol in Chylomicrons → Apoprotein B48 → Liver
- Muscle, Connective Tissue → Cholesterol in High-Density Lipoproteins (HDLs) → Liver
- Liver → Cholesterol in Very-Low-Density Lipoproteins (VLDLs) → Serum and Bile
- Blood → Cholesterol in Low-Density Lipoproteins (LDLs) → Apoprotein B100 → Liver

Nucleic Acid Metabolism

The urea cycle and the biosynthesis of pyrimidine nucleotides are the most important roles of the liver in nucleic acid metabolism. Ammonia is an important product of amino acid metabolism. The GI tract is the most important source, primarily the colon, through the action of bacterial urease on endogenous urea that diffuses to the intestine and on degraded dietary amines. Ammonia produced by the colonic bacteria enters the portal vein and is transported to the liver to be transformed by the urea cycle in the following stoichiometry:

- 2 NH_3 (ammonia) + CO_2 + 3 ATP + H_2O → urea + 2 ADP (adenosine diphosphate) + 4 P_i (phosphate inhibitor) + AMP (adenosine monophosphate) + 2 H

Coagulation Factors

The liver synthesizes plasma clotting factors I (fibrinogen), II (prothrombin), V, VII, VIII, IX, and X. Factors II, VII, IX, and X are vitamin K–dependent clotting factors.

Bile Secretion

The liver secretes a slightly alkaline isosmotic solution of bile containing bile salts, bilirubin, phospholipids, cholesterol, electrolytes, and water. Bile secretion serves many useful purposes, not the least of which is bile-salt generation and delivery for emulsification and micellarization of dietary fat. Bile salts are synthesized from cholesterol, conjugated to amino acids, secreted into the biliary tract, stored in the gallbladder, and subsequently delivered to the small intestine postfeeding. Intestinal bacteria may transform some of the primary bile acids into secondary bile acids. Ileal reabsorption of bile salts permits enterohepatic recirculation, liver reuptake, reconjugation, and resecretion.

Porphyrin Metabolism

Porphyrins are intermediates of the heme biosynthetic pathway. Porphyrins are found in hemoglobin, myoglobin, cytochromes, catalase, and peroxidase enzyme. The liver also serves as an excretory route for the porphyrins.

Metal Metabolism

The liver stores iron, which can be toxic in excessive amounts (hemochromatosis). The amount of iron in the body is largely determined by regulation of its absorption in the upper small intestine. Iron is stored intracellularly as ferritin in a number of tissues, with the liver having a large storage capacity. When the capacity of the liver is exceeded, iron accumulates as hemosiderin. The liver incorporates copper into specific copper proteins such as cytochrome c oxidase, mitochondrial monoamine oxidase, and ceruloplasmin. Mobilization of copper from hepatocytes takes place by at least two mechanisms: ceruloplasmin and bile secretion. Cholestatic liver disease is associated with secondary copper retention, which may then induce hepatocyte injury.

Vitamin Metabolism

The liver produces bile for absorption of fat-soluble vitamins (A, D, E, K), and the liver is an important site for vitamin storage. Vitamin A is stored in both Kupffer cells and hepatocytes. Approximately 95% of total body vitamin A is stored in the liver. Water-soluble vitamins, except for vitamin B_{12} (cobalamin), are readily absorbed from the small intestine. These vitamins are used primarily as coenzymes in various metabolic reactions. Large amounts of all water-soluble vitamins except vitamin C are stored in the liver.

Glutathione Metabolism

Glutathione (GSH) is synthesized in most if not all mammalian cells. The liver is particularly active and has relatively high levels of GSH. GSH performs a variety of physiologic and metabolic functions, including thiol transfer reactions which protect cell membranes and proteins; thiol-disulfide reactions involved in protein synthesis, protein degradation, and catalysis; reducing capacity; detoxification of hydrogen peroxide, organic peroxides, free radicals, and foreign compounds; and metabolism of various endogenous compounds.

Xenobiotic Metabolism

Numerous foreign compounds, including drugs, are so hydrophobic that they would remain in the body indefinitely were it not for hepatic biotransformation.

Hormone Metabolism

Natural and synthetic hormones are metabolized in the liver. The liver metabolizes mineralocorticoids (aldosterone), glucocorticoids (i.e., cortisol, corticosterone), and sex steroids (i.e., androgens, estrogens, progesterone).

Immune Surveillance

The "reticuloendothelial" system in the liver removes microbes, endotoxins, enterotoxins, and exotoxins from the portal circulation following their absorption from the intestine.

Neural, Endocrine, and Paracrine Activation

The many functions of the GI tract are integrated through the coordination of neural, endocrine, and paracrine mechanisms of activation (see Fig. 1-1; Fig. 1-27; Table 1-6). These functions include contraction and relaxation of smooth muscle; secretion of enzymes for digestion; secretion of fluids and electrolytes; nutrient absorption; and mucosal growth.

Endocrine Regulation

A GI hormone is classically defined as a substance that (a) is found in GI endocrine cells, (b) is released by physiologic stimuli, (e.g., feeding), (c) circulates in blood, (d) binds to a cell receptor at a distant site, and (e) evokes a biologic response.[101,102] However, the characterization of an event as the physiologic result of a hormonal action may be exceedingly difficult. It is now clear that many biologic substances previously classified as GI hormones are neither confined to the GI tract nor are solely blood-borne. For example, some of the peptides localized in gut endocrine cells (e.g., cholecystokinin, SP, neurotensin, and somatostatin) may be found in gut neurons and act as neurocrine substances.[103] As enteric neuropeptides, these substances may evoke similar or different biologic responses. Some of these same peptides are also located outside the enteric nervous system in vagal afferent fibers or CNS neurons. Thus, some GI hormones may also function as enteric or brain neuropeptides. A further complication is that some gut endocrine

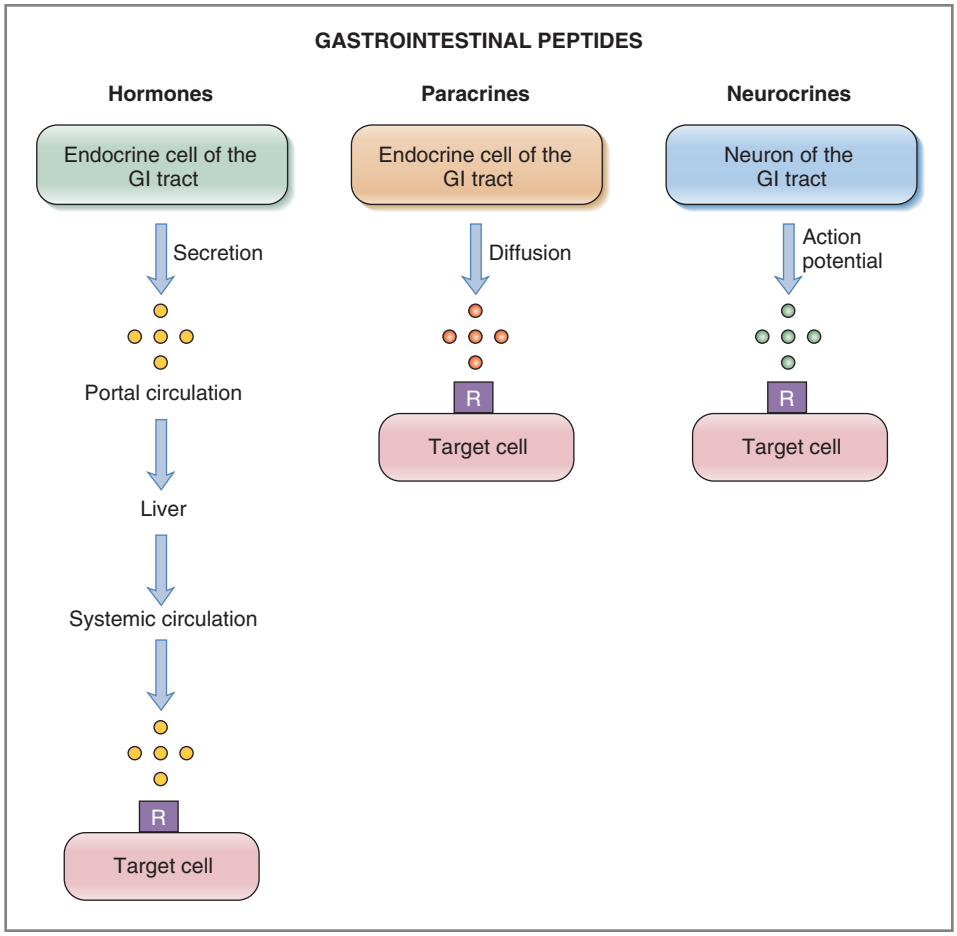


Figure 1-27 Classification of gastrointestinal peptides as hormones, paracrines, or neurocrines. (From Costanzo L (ed): *Physiology*, 4th ed. Philadelphia: Saunders, 2010.)

Table 1-6 Overview of Endocrine, Neural, and Paracrine Regulation in the Gastrointestinal Tract

Substance	Physiologic Release	Site of Action	Effect
GI Hormones			
Gastrin	Intragastric peptides, gastric distention	Gastric parietal and chief cells	H^+ and pepsinogen secretion
		Pancreatic acinar cells	Enzyme secretion
		Stomach, duodenum, pancreas	Growth
Cholecystokinin	Duodenal fatty acids, amino acids, H^+	Gallbladder	Contraction
		Sphincter of Oddi	Relaxation
		Pancreas	Enzyme secretion and growth
		Stomach	Inhibition of gastric emptying
Secretin	Duodenal H^+, fatty acids	Pancreatic duct cells	HCO_3^- and water secretion
		Biliary epithelium, duodenum	HCO_3^- and water secretion
Enteroglucagon			
Oxyntomodulin	Ileal/colonic glucose and lipid	Gastric parietal cells	Inhibits H^+ secretion
GLP-1		Pancreatic islet (β) cells	Stimulates insulin secretion (incretin during euglycemia)
GLP-2	Duodenal fatty acids	Stomach	Inhibits gastric emptying ("ileal brake")
	Ileal fatty acids	Small intestine, colon	Inhibits gastric emptying (ileal brake) and secretion
	Carbohydrates, lipids, SCFA		Crypt cell proliferation, suppression of apoptosis
			Reduces gut permeability and bacterial translocation
Gastric inhibitory polypeptide	Fatty acids, glucose, amino acids	Duodenum, jejunum, ileum	Inhibits gastric and intestinal motility; Stimulates insulin secretion (incretin during euglycemia)
Somatostatin	Lipids, protein, and bile	Stomach, intestine, pancreas	Inhibits gastric, intestinal, and pancreatic secretion
Motilin	H^+ and lipids	Stomach, duodenum, jejunum	Increases GES pressure, stimulates propulsive motility
			Stimulates gastric, pancreatic, and biliary secretion
Pancreatic polypeptide	Protein, cholinergic reflexes	Pancreas	Inhibits pancreatic enzyme and fluid secretion
Peptide YY	H^+ and lipids	Ileum and colon	Ileal brake, proliferation of gut mucosa
		Stomach and pancreas	Inhibits secretion (H^+, pancreatic enzyme)
5-Hydroxytryptamine	H^+	Intestine and colon	Stimulates motility and secretion
Ghrelin	Dietary protein	Pituitary	Stimulates growth hormone secretion
Enteric Neuropeptides			
Substance P	Luminal distention, H^+, hyperosmolarity	Stomach, intestine, colon	Sphincteric contractions, intestinal peristalsis
		Pancreas	Stimulates pancreatic enzyme secretion
Vasoactive intestinal polypeptide	Vagal stimulation	Stomach, intestine, colon	Increased blood flow, stimulation of fluid secretion
		Stomach, intestine, colon	Relaxation of smooth muscle
		Pancreas	Stimulates fluid and bicarbonate secretion
Opioids	Intestinal distention	Stomach, intestine, colon	Inhibits longitudinal smooth muscle contraction
			Stimulates circular smooth muscle contraction
			Inhibits water and electrolyte secretion
Bombesins (GRP and (neuromedin B)	Vagal stimulation	Stomach	Stimulates gastric acid secretion
		Pancreas	Stimulates pancreatic enzyme secretion
		Gallbladder	Stimulates gallbladder contraction
Somatostatin	Lipids and protein	Stomach, intestine, pancreas	Descending inhibitory reflex of peristalsis
Gastrin/CCK	Intestinal distention	Ileum and colon	Ileal and colonic contractions
Neuropeptide Y	Intestinal distention	Intestine and colon	Inhibits intestinal motility
5-Hydroxytryptamine	H^+ and hypertonic solutions	Stomach, intestine, colon	Regulates migrating myoelectric complex
Paracrine Mediators			
Histamine	Vagal stimulation	Stomach	Stimulates gastric acid secretion
Somatostatin	Lipids and proteins	Stomach	Inhibits gastrin secretion
		Pancreas	Regulates insulin and glucagon secretion
Prostaglandins	H^+, gastric distention	Stomach	Stimulates bicarbonate and glycoprotein secretion
			Stimulates epithelial cell renewal and blood flow
			Inhibits prostanoid receptors

CCK, cholecystokinin; GES, gastroesophageal sphincter; GLP-1, glucagon-like peptide-1; GLP-2, glucagons-like peptide-2; GRP, gastrin-releasing peptide; SCFA, small-chain fatty acid.

cells may release peptides into the extracellular fluid from which they diffuse to, and directly act on, neighboring cells. Consequently, a GI peptide may evoke a biologic response through a paracrine mechanism of activation that operates independently of, or in parallel to, an endocrine mechanism of activation. Somatostatin, for example, stimulates biologic responses through endocrine, paracrine, and neurocrine mechanisms—endocrine regulation of gastric acid secretion, paracrine regulation of antral gastrin secretion, and neurocrine regulation of smooth muscle contraction.

Gastrin-Cholecystokinin Family

The GI hormones[101,102,104] and related peptides have been divided into structurally homologous families. The first family consists of gastrin and CCK. Gastrin and CCK share five basic characteristics: (a) partial sequence homology; (b) similar biologic activities; (c) heterogeneity—each hormone exists in different molecular forms; (d) ubiquity—each hormone is synthesized in different cell types; and (e) differential principality—different molecular forms predominate in different tissues and cells.[101,104]

Gastrin exists in several molecular forms—G-34, G-17, and G-14—gastrin peptides that contain 34, 17, and 14 amino acids, respectively. G-34, also known as "big gastrin," is the most abundant form of gastrin in serum. G-17, known as "little gastrin," is less abundant than G-34 in serum but is more potent in stimulating gastric acid secretion. "Mini gastrin" (G-14) has little biologic effect. Endocrine cells (G cells) in the gastric antrum and duodenum secrete gastrin in response to protein meals and, to a lesser extent, gastric distention.[101,104] The most important biologic action of gastrin is the stimulation of gastric acid secretion by gastric oxyntic (parietal) cells. A substantial fraction of the gastric acid secretory response to protein meals is, in fact, mediated by gastrin. However, interactions between gastrin, ACh (neurocrine stimulant), and histamine (paracrine stimulant) determine the final gastric acid secretory output.[105] Most evidence suggests that the gastrin effect occurs through the binding of gastrin to CCK_B receptors on oxyntic cells. Other important biologic actions of gastrin include stimulation of gastric pepsinogen secretion, gastric mucosal blood flow, antral motility, and pancreatic enzyme secretion, and of pancreatic, gastric and duodenal growth.[101,104,106] Pancreatic islet cells (delta cells) are a site of gastrin synthesis and secretion in fetal and neonatal animals.[106] Malignant transformation of these islet cells in adult animals results in functional gastrinomas. All but one of the gastrinomas that have been reported to date in the dog or cat have been of pancreatic origin.

CCK also exists in several molecular forms: CCK-63, CCK-58, CCK-39, CCK-33, CCK-12, CCK-8, and CCK-5. The predominant forms in serum are CCK-33, CCK-39, and CCK-58 and probably account for most of the GI hormone responses.[101,102,104] CCK-8 is the predominant form found in neurons and probably accounts for most of the enteric and CNS neuropeptide responses. Endocrine cells (I cells) in the duodenum and jejunum secrete CCK in response to intraduodenal fatty acids, amino acids, and H^+ ion.[101,102,104] As a GI hormone, CCK evokes several important biologic responses, most importantly, contraction of the gallbladder and stimulation of pancreatic enzyme secretion. Although CCK receptors have been demonstrated on both gallbladder smooth muscle cells and pancreatic acinar cells, it is now clear that CCK evokes gallbladder contraction and pancreatic enzyme secretion through activation of pre-synaptic cholinergic neurons at both sites.[104,106]

Other important endocrine actions of CCK include augmentation of pancreatic fluid secretion in the presence of secretin, relaxation of the sphincter of Oddi, inhibition of the gastric emptying of liquids, and stimulation of pancreatic growth.[101,104] CCK has two important biologic actions as an enteric or brain neuropeptide (see "Enteric Neuropeptides" below).

Secretin-Enteroglucagon-Gastric Inhibitory Polypeptide Family

A second structurally homologous GI hormone family consists of secretin, enteroglucagon, gastric inhibitory polypeptide (GIP), as well as the enteric neuropeptides VIP and peptide histidine-isoleucine (PHI). All of these substances share considerable sequence homology.

Like gastrin and CCK, secretin exists in several molecular forms: 27–, 28–, 30–, and 71–amino-acid polypeptides.[107] Acidification of the duodenum and jejunum by gastric H^+ is the most important stimulus for secretin secretion by endocrine cells (S cells) in the small intestine.[101,104] Intraduodenal lipid may also stimulate secretin release in some species. The most important biologic action of secretin is secretion of a bicarbonate-rich pancreatic fluid from pancreatic ductal cells.[106,107] Pancreatic bicarbonate is important in neutralizing gastric acid delivered to the small intestine and in creating an alkaline environment that is close to the pH optimum of pancreatic lipase and co-lipase. Less important biologic actions of secretin are stimulation of secretion of bile bicarbonate and pancreatic enzymes.[101,106] The latter effect is observed only in the presence of CCK. Secretin has also been identified in brain neurons, but a functional role for secretin in these neurons has not yet been elucidated.

Enteroglucagon and pancreatic glucagon arise from the same gene precursor through posttranslational processing. Several molecular forms of enteroglucagon have been characterized, including enteroglucagon or oxyntomodulin, a 37–amino-acid peptide; glicentin, a 69–amino acid, C-terminal extended form of oxyntomodulin; glucagon-like peptide (GLP)-1; intervening peptide-2; and GLP-2. Endocrine cells (L cells) in the terminal ileum and colon secrete enteroglucagon(s) in response to intraluminal glucose and lipid. The most important GI action of the enteroglucagons is the inhibition of gastric acid secretion.[101,104] GLP peptides are also involved in the regulation of insulin secretion and glycemic control. GLP-1 is reported to stimulate proinsulin expression, and to delay intestinal glucose absorption through inhibition of gastric emptying,[108] thus acting as an incretin hormone during euglycemia to lower blood glucose. GLP-2 is a 33–amino-acid peptide hormone released from intestinal endocrine cells following nutrient ingestion.[109] It exerts trophic effects on the small- and large-bowel epithelium via stimulation of cell proliferation and inhibition of apoptosis. GLP-2 also upregulates intestinal glucose transporter activity, and reduces gastric motility and gastric secretion.[110]

GIP is a 54–amino-acid peptide that exists in a single molecular form.[111] It is secreted by endocrine cells of the proximal small intestine in response to intraduodenal glucose, fatty acids and amino acids. Two important biologic actions of GIP are inhibition of gastric acid secretion and stimulation of intestinal fluid secretion. The third, and likely most important, biologic action of GIP is the stimulation of pancreatic insulin release during hyperglycemia. It has been suggested that GIP and GLP-1 function as incretins and are the substances responsible for increased glucose disposal and enhanced insulin responses during intestinal absorption of glucose.[101,104,111]

Somatostatin

Somatostatin, or somatotropin release-inhibiting factor, was originally isolated from the hypothalamus and found to inhibit GH and thyrotropin release from the pituitary. Somatostatin was

subsequently found in gut endocrine cells and gut neurons and shown to have endocrine, neurocrine, and paracrine biologic effects. Two molecular forms of somatostatin have been identified in gut endocrine cells: somatostatin-14 (SS-14) and somatostatin-28 (SS-28). Endocrine cells (D cells) throughout the GI tract secrete somatostatin in response to protein, lipid and bile. As a GI hormone, somatostatin inhibits gastric acid and pepsin secretion, pancreatic enzyme and fluid secretion, gallbladder contraction, and intestinal amino acid and glucose absorption.[101,104] In addition to its role as a GI hormone, somatostatin also functions as an enteric neuropeptide (e.g., inhibition of intestinal motility) and as a paracrine substance (e.g., inhibition of gastrin secretion).

Motilin

Motilin is a 22–amino acid peptide found in endocrine cells of the proximal small intestine. Motilin secretion is stimulated by H^+ and lipid during the fed state, but motilin secretion appears to be most important in the interdigestive (fasting) state. During fasting, motilin is released episodically into the serum and initiates phase III of the MMC.[112] The MMC is a motility pattern that empties the stomach and small intestine of indigestible solids that accumulate during feeding. The cyclic release of motilin from the small intestinal mucosa during fasting is also thought to coordinate gastric, pancreatic, and biliary secretions with phase III of the MMC.[113]

Neurotensin

Neurotensin is a 13–amino-acid peptide, isolated from dog ileal and jejunal mucosal endocrine cells (N cells), for which no definitive endocrine function has been established. Intraluminal lipid stimulates neurotensin release from these endocrine cells. Neurotensin has been shown to inhibit gastric emptying and to stimulate pancreatic and biliary secretion. One of the most likely potential roles of neurotensin is that of a physiologic enterogastrone that mediates inhibition of acid secretion after fat ingestion.[101,104]

Pancreatic Polypeptide

Pancreatic polypeptide (PP) is a 36–amino-acid peptide that shares sequence homology with the enteric neuropeptide known as neuropeptide Y (NPY). PP is found exclusively in pancreatic islet cells (F cells). PP release is stimulated by protein meals and by cholinergic reflexes. The most important biologic action of PP is the inhibition of pancreatic enzyme and fluid secretion.[101,104] Islet cell PP secretion likely autoregulates acinar and ductal cell secretions because of the islet–acinar portal venous system. Other possible endocrine functions of PP include relaxation of gallbladder smooth muscle, mild stimulation of gastric acid secretion, and initiation of the MMC along with motilin.[113]

Peptide YY

Peptide YY is a 36–amino-acid peptide with structural similarities to PP and to NPY. Peptide YY may function as a physiologic enterogastrone similar to neurotensin in inhibiting pancreatic and gastric secretions.[101,104]

5-Hydroxytryptamine

5-Hydroxytryptamine (5-HT or serotonin) is found in endocrine cells (e.g., enterochromaffin cells) and enteric neurons throughout the GI tract of most animal species.[1,2,4] In some species, 5-HT is also found in intestinal mucosal mast cells, pancreatic islet cells, and bronchial endocrine cells. 5-HT secreted by enterochromaffin cells may act through an endocrine or paracrine mechanism to stimulate GI smooth muscle contraction and intestinal electrolyte secretion.[102]

Ghrelin

Ghrelin is a 28–amino-acid octanoylated peptide found most abundantly in endocrine cells of the stomach.[114,115] It stimulates pituitary GH secretion. Ghrelin administration also has been shown to stimulate appetite, body growth, and fat deposition. The postprandial gastric expression of ghrelin suggests a GI–hypothalamic–pituitary axis that influences GH secretion, body growth, and appetite that is responsive to nutritional and caloric intakes. Ghrelin and leptin may be the "yin and yang" of a system that relays peripheral information to the brain and directs the body in the appropriate maintenance of energy reserves and nutritional intake.

Enteric Neuropeptides

A substance may be defined as an enteric neuropeptide if (a) it can be demonstrated histochemically in enteric neurons, (b) mechanisms for its biosynthesis exist in enteric neurons, (c) it is concentrated in nerve terminals, (d) it is released from nerve terminals by depolarizing stimuli through a calcium-dependent mechanism, and (e) mechanisms for the breakdown, reuptake, or removal of the substance exist.[103]

Tachykinins

The tachykinin family is represented by SP, substance K, neuromedin K, physalaemin, kassinin, and eledoisin. SP is probably the most important enteric neuropeptide of this group. SP is distributed in enteric neurons throughout the GI tract and pancreas, and it is released from these neurons in response to luminal distention or depolarization. SP has three important biologic actions as an enteric neuropeptide.[103] First, it causes contraction of GI smooth muscle through an indirect effect of mediating cholinergic transmission and a direct effect on smooth muscle during the peristaltic reflex. Second, SP is located in primary sensory afferent fibers and may be important, along with calcitonin gene-related peptide, in pain input to the CNS. Finally, SP neurons stimulate pancreatic enzyme secretion.

Vasoactive Intestinal Polypeptide/Peptide Histidine-Isoleucine

The classic enteric neuropeptides VIP and PHI share sequence homology with one another and with the GI hormones secretin, enteroglucagon, and GIP. VIP and PHI have many similar biologic activities and are derived from the same biosynthetic precursor. VIP and PHI are released by vagal stimulation and have four important biologic actions[103]: (a) stimulation of pancreatic fluid and bicarbonate secretion, (b) stimulation of salivary and intestinal fluid secretion, (c) increasing intestinal blood flow, and (d) relaxation of GI smooth muscle. This last property of VIP/PHI is felt to be important in descending intestinal inhibition (along with somatostatin) and in sphincter relaxation.

Opioids

Opioid neurons are distributed throughout the GI tract. Methionine-enkephalin, leucine-enkephalin, and dynorphin are the most representative members of the opioid enteric neuropeptide family.[103] At least three different types of binding sites for these opioid peptides can be distinguished in the gut (μ, δ, and κ) but there may be others (ε and σ). The binding sites for these opioids are located on other neurons, smooth muscle cells, and epithelial cells. Opioid binding results in (a) inhibition of contraction of longitudinal smooth

muscle through inhibition of ACh release from myenteric plexus neurons, (b) direct stimulation of circular smooth muscle contraction, and (c) inhibition of intestinal water and electrolyte secretion through inhibition of submucosal plexus neurons. These effects account for the potent antidiarrheal properties of morphine and other opiate alkaloids.[103]

Bombesins

The bombesins are so-named because of their original isolation from the skin of the frog genus *Bombina*. The mammalian bombesins that have been identified as enteric neuropeptides are GRP and neuromedin B. GRP is released by vagal stimulation, and it stimulates gastrin release from antral G cells. Thus, GRP acts a cotransmitter (along with ACh) to stimulate gastrin release.[103] GRP also stimulates pancreatic acinar cell enzyme secretion.[103,106]

Somatostatin

In addition to its role as a GI hormone, somatostatin (SS-14) has been identified as an enteric neuropeptide in neurons throughout the GI tract. Somatostatin inhibits ACh release from myenteric plexus neurons and may be involved in the descending inhibitory reflex of peristalsis.[103] Somatostatin neurons in the submucous plexus have a mucosal projection suggesting a further role for neuronal somatostatin in the control of mucosal function.

Gastrin-Cholecystokinin

CCK-8 is an important enteric neuropeptide in the ileum and colon, particularly in the cat. Intraluminal distention activates CCK-8–containing neurons, which then stimulate the release of ACh from myenteric plexus neurons. CCK-8 thus acts as an excitatory transmitter in stimulating the peristaltic reflex in ileum and colon.[101,103] Brain CCK-8 neurons are involved in mediating the satiety response following feeding.

Pancreatic Polypeptides

A 36-amino-acid peptide, NPY shares structural similarities with the GI hormones PP and peptide YY. Neurons containing NPY decrease ACh release from myenteric plexus neurons and hence inhibit small intestinal smooth muscle contraction.[103]

5-Hydroxytryptamine

In addition to its role as an endocrine/paracrine substance of the GI tract, 5-HT is also found in enteric neurons where it is believed to regulate the migrating myoelectrical complex and the intestinal peristaltic reflex.[58]

Paracrine Substances

A substance may be defined as having a paracrine mechanism of activation if (a) the substance is found within an effector cell, (b) receptors for the substance exist on an adjacent paracrine target cell, (c) the effector cell and paracrine target cell are in close proximity, and (d) the substance when applied to the paracrine target cell evokes a biologic response.[101,102] Histamine, somatostatin, adenosine, and prostaglandins have been shown to satisfy these criteria.

Histamine

Histamine is formed from the decarboxylation of histidine in enterochromaffin-like cells found throughout the GI tract of the dog. In the dog, gastric mucosal histamine stores appear fully accounted for by mast cells, there being no evidence to indicate histamine is stored in endocrine cells.[105] Histamine released from mast cells diffuses into the interstitial milieu and is believed to bind parietal cell H_2 receptors to stimulate H^+ secretion.[105]

Somatostatin

As a paracrine substance, somatostatin has an important role in the inhibition of gastrin release. Somatostatin cells in the gastric antrum have long cytoplasmic processes that terminate adjacent to antral G cells. Paracrine release of somatostatin by these somatostatin cells is postulated to mediate the negative feedback inhibition of H^+ on gastrin release.[116] Somatostatin released from pancreatic islet cells (D cells) may also autoregulate pancreatic insulin and glucagon secretion through a local paracrine mechanism.[117]

Prostaglandins

Prostaglandins are long-chain fatty acids that are distributed throughout the GI tract. The role of prostaglandins as paracrine substances is perhaps best understood in the gastric mucosa, where they bind to inhibitory prostanoid receptors on gastric oxyntic cells. These receptors are coupled to inhibitory G proteins and subsequent inhibition of adenylate cyclase and H^+ secretion.[118] A "cytoprotective effect" of prostaglandins, separate from the direct inhibition of acid inhibition, has also been implied. Gastric prostaglandins, for example, stimulate mucosal bicarbonate and glycoprotein secretion, epithelial cell renewal, and mucosal blood flow. These effects are all central to the barrier properties of the gastric mucosa.[119]

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CHAPTER 2

Gastrointestinal Microbiota

Jan S. Suchodolski

The intestinal microbiota is the collection of all live microorganisms that inhabit the gastrointestinal (GI) tract. The word *microflora* is often used synonymously, but *microbiota* (from *bios*, Greek: life) is the technically correct term. The intestinal microbiota plays an important role in GI health and disease, yet our understanding of the composition, dynamics, and functionality of the intestinal ecosystem remains rudimentary. The total microbial load in the intestine is estimated to be 10^{12} to 10^{14} organisms, approximately 10 times the number of body cells. It is estimated that the intestine harbors several thousand bacterial strains.[1,2] This mutually interacting system comprising the host cells and the resident microbes is termed the *intestinal microbiome*. The microbiota can be influenced by exogenous factors such as diet and antibiotic administration, but it is usually resilient to these changes and returns rapidly to its pretreatment state. Therefore long-term treatment strategies for modulating the microbiota are necessary. New molecular tools have improved our understanding of microbial diversity in the intestine. Although the major phylogenetic lineages are similar, the microbiota differs substantially at the level of species and strain in each individual animal of the same species. Yet despite these differences, the metabolic end products in the intestine are very similar between individuals. New metagenomic approaches suggest the presence of a "core microbiome," where the function of the intestinal ecosystem is independent of the presence of specific bacterial species or strains. For better understanding of microbial–host interactions in health and disease, future work must focus on the intestinal microbiome as one entity, evaluating its phylogenetic composition as well as metabolic functions.

Methods for Characterization of the Intestinal Microbiota

Practical Considerations

Methods for characterization of the intestinal microbiota are based on cultivation techniques or molecular tools (Fig. 2-1). The selection of the best approach depends on the study problem (e.g., detection of specific pathogens in clinical specimens, or general characterization of the intestinal ecosystem), the cost, and the availability of technologies. Each method has strengths but also limitations (outlined below). For general ecologic surveys of microbial communities, molecular high-throughput sequencing techniques yield the most information as they allow in-depth identification of microorganisms. For screening of specific pathogens, culture techniques and species specific polymerase chain reaction (PCR) assays may be most useful. Both of these methods are sensitive to sample handling and processing. Detailed instructions for sample collection and shipping for each particular assay should be acquired before sample submission as many laboratories use their own in-house culture or PCR assays. In the case of molecular methods, there is usually no standardization of DNA extraction or PCR protocols among laboratories, and such factors impact on the sensitivity and specificity of the assays. Improper DNA extraction, especially from fecal samples, may result in the presence of residual PCR inhibitors that cause false negative results. Because of the high sensitivity of PCR assays (theoretically a single target copy can be amplified), any DNA contamination can lead to false-positive results. A laboratory should be chosen that has expertise in molecular analysis, and that has validated each assay in the target specimen.

Bacterial Culture

Traditional evaluation of the composition of the canine and feline intestinal microbiota has been obtained using culture techniques. Bacterial culture is useful for assessing the viability of organisms, determination of an active infection, and antibiotic susceptibility testing in clinical specimens. Individual isolates can be typed for epidemiologic surveys of specific strains and their virulence factors. Culture is also valuable for understanding the metabolic properties of individual microbes. The value of bacterial culture is greatest when a clinical sample is evaluated for the presence of specific pathogens (e.g., *Salmonella*, *Campylobacter jejuni*).

Several limitations are associated with culture methods, especially if they are used to survey for the presence of unknown microorganisms in intestinal samples. Bacterial culture underestimates total bacterial numbers in the intestine, as microscopic counts (especially when using fluorescent dyes) are typically higher than the total viable counts obtained from culture. Although the majority of intestinal bacteria cannot be cultured, this does not necessarily mean that they are uncultivable, but rather, that insufficient information is currently available about their optimal growth requirements. Furthermore, many microbes depend on mutualistic interactions with other bacteria and the host, hindering their successful isolation in vitro. While recent advances have increased the cultivable fraction,[3] it is estimated that less than 10% of intestinal bacteria can be cultured, and an even smaller fraction can be correctly classified. Therefore studies of the intestinal ecosystem may

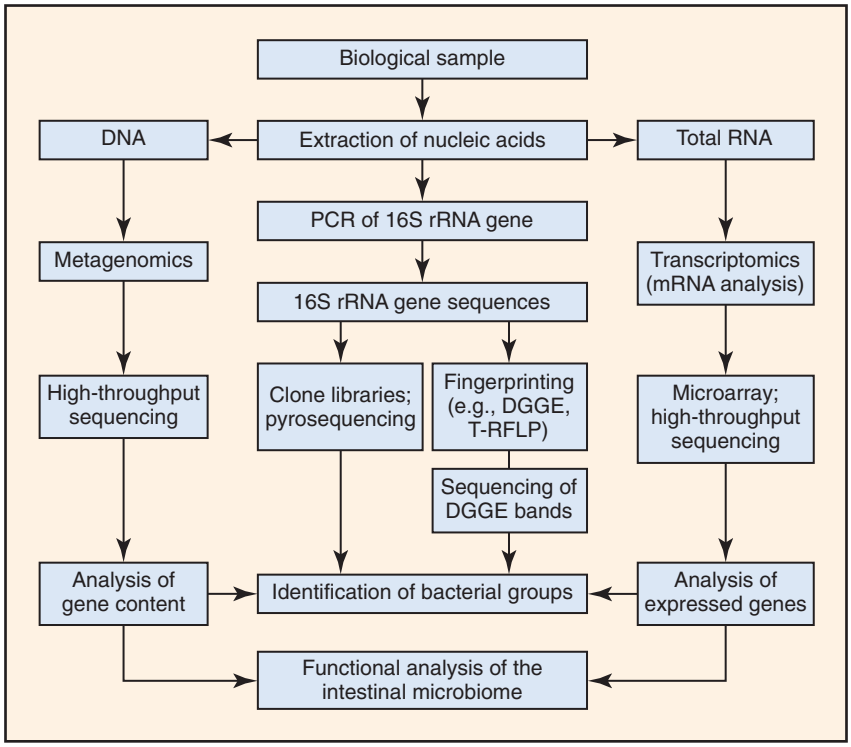

Figure 2-1 Molecular methods for characterization of the intestinal microbiome. PCR amplification of the 16S rRNA (ribosomal RNA) gene allows either direct identification of bacterial phylotypes or the creation of a molecular fingerprint representing the bacterial diversity in a sample. New metagenomic and transcriptomic approaches, based on high-throughput sequencing of DNA or messenger RNA (mRNA) without prior amplification of a specific gene, yield an overview over the gene content of the sample and therefore the functional properties of the intestinal microbiome.

exhibit bias toward the minor cultivable portion of the gut microbiota. The analytical sensitivity of bacterial culture depends on the organism and its growth requirements. Bacterial culture is associated with difficulties in handling, storing, and shipping of clinical specimens. Ideally, samples should be processed immediately to preserve anaerobic species. Many selective culture media lack sufficient specificity, and often organisms other than the target are enumerated.[4] Phenotypic and biochemical identification systems often fail to accurately classify many microorganisms, requiring DNA sequencing of isolates.

Molecular Techniques

Because bacterial culture underestimates microbial diversity, the use of molecular tools has now become the standard approach in microbial ecology.[5-7] The principle of these methods is that DNA or RNA is extracted from intestinal samples, and a specific gene is amplified with universal primers that target conserved regions (located up- and downstream of variable regions within the gene).[8] This approach allows in theory the amplification of DNA from all known and unknown bacterial species in a sample (see Fig. 2-1). The mixture of sequences can then be separated by subcloning and identified by sequencing, or they can be separated by methods that yield a "fingerprint" of the bacterial community.[8,9] The 16S ribosomal RNA (rRNA) gene is most commonly targeted as more than 1.6 million unique sequences are available in public databases (Ribosomal Database Project; http://rdp.cme.msu.edu/). Other more rarely used genomic targets include the 16S to 23S internal transcribed spacer (ITS) region or the chaperonin (cpn60) sequences.[10] If the sequence for a particular phylotype is known, specific PCR assays can be designed for its detection. Real-time PCR assays (with universal-, group-, or species-specific primers) can be used for quantitative analysis. Novel techniques analyze total genomic DNA or messenger RNA (mRNA) without prior amplification of specific genes and yield information about the gene content (metagenomics) or the expressed genes (transcriptomics) of the intestinal microbiome.

Molecular Fingerprinting

Molecular fingerprinting techniques are used for simultaneous analysis and comparison of microbial communities in multiple samples. These techniques provide information on microbial changes over time and in response to treatment. Available techniques include denaturing gradient gel electrophoresis (DGGE), temperature gradient gel electrophoresis (TGGE), and terminal restriction fragment length polymorphism (T-RFLP). The goal is to separate the mixture of PCR amplicons that were generated with broad range primers (universal or group specific) to yield a "fingerprint" of the bacterial community. This is achieved as each bacterial phylotype has a unique nucleotide composition (i.e., guanine+cytosine content). These differences in nucleotide composition result in unique melting behaviors of PCR amplicons. Each PCR amplicon reaches a specific melting point in a different position in a polyacrylamide gel, where it will denature and slow its migration. This banding pattern illustrates the bacterial diversity in the sample (Fig. 2-2). In DGGE, a gel containing a linear gradient of DNA denaturants is used, whereas in TGGE a temperature gradient is used for separation. Bands of interest can be excised and sequenced. DGGE and TGGE are inexpensive and rapidly performed. However, because DGGE/TGGE bands are usually short, only limited resolution of PCR amplicons can be achieved, and many bacterial phylotypes will have similar or

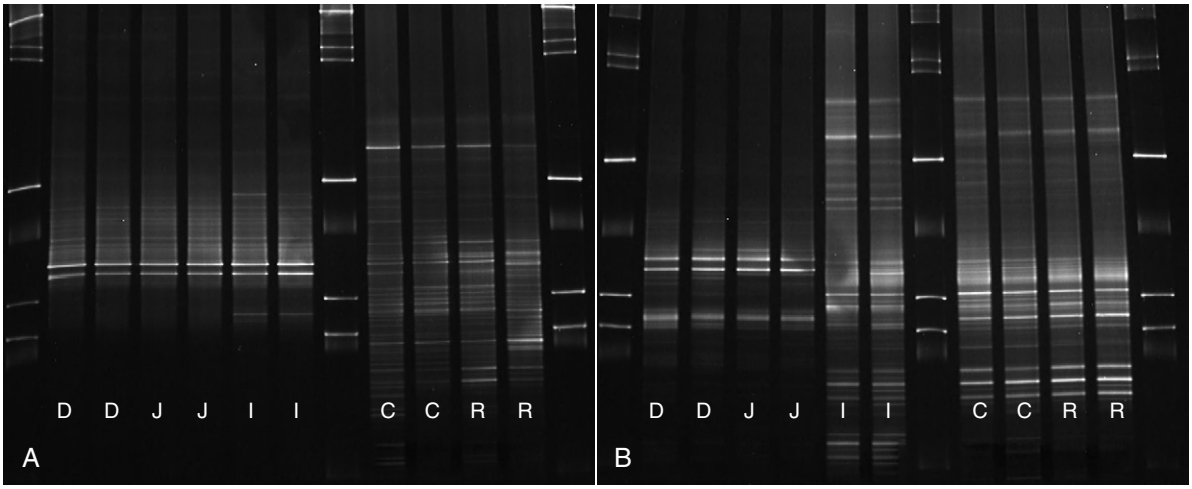

Figure 2-2 Denaturing gradient gel electrophoresis (DGGE) as an example for the use of molecular fingerprinting for profiling and comparison of microbial diversity between intestinal samples. This figure illustrates the differences in bacterial diversity in the various segments of the canine GI tract and the differences in bacterial communities between individual dogs (samples analyzed in duplicate). (C, colon; D, duodenum; I, ileum; J, jejunum; unlabeled lanes represent gel markers).

the same melting behaviors. Therefore, these techniques yield typically only 20 to 40 bands, capturing only changes in the predominant bacterial groups. The use of T-RFLP allows profiling, but also quantification of microbial communities. Bacteria are amplified in PCR assays containing a fluorescent labeled primer. The PCR products are then fragmented by size with sequence specific restriction enzymes. The fragments are separated by capillary electrophoresis with subsequent quantitative measurement of the fluorescence.

Identification of Bacterial Groups

The amplification of the 16S rRNA gene with universal primers that target conserved regions allows amplification of theoretically all bacteria present in the sample. For identification of individual bacterial phylotypes, PCR amplicons must be separated and sequenced. A commonly used method is the construction of 16S rRNA gene clone libraries.[6,7,10] The PCR amplicons are separated by ligation into plasmid vectors with subsequent transformation into *Escherichia coli* cells. These cells are plated on culture medium and grown overnight. Each cell forms a colony containing one plasmid with the original amplified 16S rRNA gene sequence. This plasmid can then be purified and sequenced. Although this approach is informative, it is laborious and not well suited for analysis of large sample numbers. Recently, new high-throughput sequencing platforms have been introduced that allow automated separation of PCR amplicons without the need for subcloning. These platforms (e.g., 454-pyrosequencing, Illumina) allow several thousand sequences to be analyzed within a few hours, yielding a deep coverage of the microbiota.[2,11] However, because of the high bacterial diversity in the intestine, groups of low abundance (especially pathogens of interest) may constitute such a low proportion of the total bacteria, that they still escape identification. Therefore, for the detection of particular groups of interest (i.e., *Bifidobacterium* spp.), the use of group specific PCR primers is recommended.

Techniques based on the 16S rRNA gene also have limitations. Bias is inherent during DNA extraction, primer selection, PCR amplification, and sequence analysis. Some commonly used primers and PCR protocols underestimate the presence of specific bacterial groups, especially those with a high guanine+cytosine content (e.g., *Bifidobacterium* spp.),[7] and some researchers use either a primer mix or group-specific primers for more accurate amplification.[11]

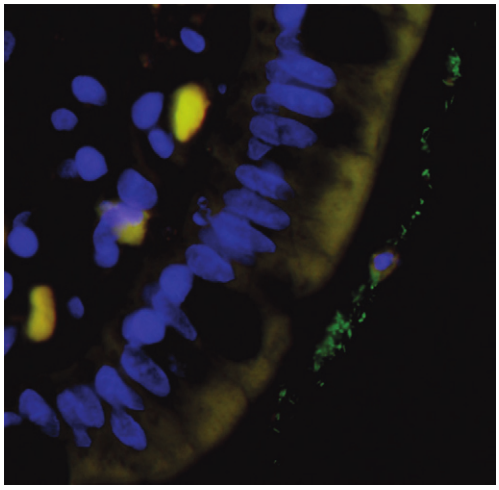

Figure 2-3 Fluorescent in-situ hybridization (FISH). The use of fluorescence-labeled FISH probes allows quantification and visualization of bacteria in relation to the epithelial mucosa (i.e., mucosa-adherent or invasive). This figure shows normal intestinal epithelium. Bacteria (*green*) are located in the mucus adherent to the epithelial cells. (Green, eubacterial probe labeled with 6-FAM; blue, nuclei of epithelial cells labeled with DAPI.) (Courtesy of Kenneth W. Simpson, Cornell University.)

Quantification of Bacterial Groups

Commonly used methods include quantitative real-time PCR assays,[10,12] fluorescent in-situ hybridization (FISH),[13] RNA dot blot hybridization,[14,15] and flow cytometry of fluorescent-labeled probes. Universal-, group-, or species-specific primers can be utilized. FISH allows for quantification of bacterial groups (Fig. 2-3), and this method also permits visualization of the location of bacteria in relation to the epithelium (i.e., intracellular, adherent, or invasive).

There is an inherent bias in use of the 16S rRNA gene for the purpose of absolute quantification. The 16S rRNA genes of bacteria

are organized into "operons" that vary in number from 1 to 15 among individual phylotypes. The operon number may also change during the growth phase and altered activity of cells.[16,17] Consequently, molecular results should be related to absolute cell counts with caution. It is more appropriate to express quantitative results as relative proportions to either total bacteria or to other bacterial groups.

Metagenomics and Transcriptomics

Analysis of 16S rRNA genes has provided new information about the phylogenetic diversity of the intestinal microbiota. However, to understand the impact of the microbiota on GI health it is necessary to (a) identify members of the intestinal ecosystem, and (b) explore the functionality of the microbial community. Metagenomics and transcriptomics are emerging fields in microbiology that are based on high-throughput sequencing techniques or the use of microarrays (see Fig. 2-1). In metagenomics, DNA extracted from a sample is sequenced without prior amplification of specific genes. This results in a snapshot of the gene pool and functional potential of the microbiome. For example, metagenomic approaches have revealed the existence of a "core microbiome" in the intestine, because despite obvious differences in bacterial composition between individuals, these individuals share common microbial genes and metabolic pathways.[18] In transcriptomics, mRNA is analyzed to provide a measure of gene expression within the intestinal microbiome. These techniques are expected to yield more in-depth understanding of microbial-host interactions in health and disease.

The Intestinal Ecosystem in Dogs and Cats

As a result of anatomical and physical differences, each intestinal compartment constitutes a unique ecosystem where microorganisms have their own niche and provide specialized functions by utilizing host nutrients and in return providing metabolites for host uptake (Table 2-1). Molecular studies reveal that each dog and cat has a unique microbial profile.[6,19] The microbiota is similar at higher phylogenetic level between individual animals of the same species, but it differs substantially at the level of species and strain, with typically only 5% to 20% overlap in bacterial species between individual animals. Bacterial counts and diversity increase along the GI tract and may vary between the intestinal lumen and the mucosa.[19,20] Bacterial counts vary between the fed and fasting state. The oral cavity is an important part of the intestinal ecosystem, because bacteria are constantly swallowed and they may be able to colonize parts of the intestine. The composition of the oral microbiota is complex. In one study, 84 different cultivable phylotypes were identified in the oral cavity of dogs, with the major groups being *Actinomyces*, *Porphyromonas*, *Fusobacterium*, *Neisseria*, and *Streptococcus* spp.[21] Oral bacterial counts can reach up to 10^7 colony-forming units per gram (CFU/g). The stomach harbors 10^1 to 10^6 CFU/g, while bacterial counts in the duodenum and jejunum of dogs and cats range from 10^2 to 10^9 CFU/g. This is considerably higher than found in the human duodenum ($<10^5$ CFU/g). Cats appear to have higher counts of anaerobic bacteria in the small intestine compared with dogs.[22] The ileum is a zone of transition between the small and large bowel and contains a more diverse microbiota and higher bacterial numbers (10^7 CFU/mL of contents) than the proximal small intestine. Colonic bacterial counts range between 10^9 and 10^{11} CFU/g of intestinal content. The predominant bacterial groups cultured from the canine and feline intestine include *Bacteroides*, *Clostridium*, *Lactobacillus*, *Bifidobacterium* spp., and Enterobacteriaceae (Table 2-2).

Because the vast majority of intestinal bacteria are not cultivable, molecular analysis (typically based on characterization of 16S rRNA) has expanded knowledge of diversity within the mammalian gut.[2,7] Several thousand individual phylotypes are estimated to inhabit the human colon.[1] There are approximately up to 900 bacterial phylotypes in the canine jejunum.[2] Despite this vast diversity, only 12 of the 55 known major phylogenetic lineages have been observed in the mammalian GI tract (see Table 2-2). The phyla *Firmicutes*, *Bacteroidetes*, *Proteobacteria*, *Actinobacteria*, *Spirochaetes*, and *Fusobacteria* constitute almost 99% of all gut microbiota in dogs and cats. The remaining 1% is represented by the phyla *Tenericutes*, *Verrucomicrobia*, *TM7*, *Cyanobacteria*, *Chloroflexi*, and a few unclassified bacterial lineages. The relative proportions of these groups vary along the GI tract (see Table 2-2). Generally, proportions of aerobic bacteria or facultative anaerobic bacteria are higher in the proximal intestine, while anaerobes predominate in the colon. In the stomach, mucosa-adherent *Helicobacter* spp. predominate, followed by various lactic acid bacteria (e.g., *Lactobacillus* and *Streptococcus* spp.) and *Clostridium* spp. The proximal small intestine is more diverse than the stomach and harbors approximately 10 different bacterial phyla, with Clostridia, *Lactobacillales*, and *Proteobacteria* dominating.[2] *Proteobacteria* and *Spirochaetes* are present in higher proportion in the proximal GI tract and typically represent <1% of sequences in the large intestine of healthy animals. *Firmicutes* is the major group represented in fecal samples (ranging

Table 2-1 Examples of Biochemical Reactions Performed by the Intestinal Microbiota

Microbial Activity	Products	Representatives
Decarboxylation, deamination of amino acids	Ammonia	*Clostridium* spp., *Peptostreptococcus* spp., *Peptococcus* spp.
Deconjugation/dehydroxylation of bile acids	Secondary bile acids (cholate/deoxycholate)	*Clostridium hiranonis*, *Lactobacillus* spp.
Vitamin synthesis	Vitamins K_2, B_{12}, biotin, folate	*Enterococcus* spp., *Pseudomonas* spp., *Sphingomonas* spp., *Lactobacillus* spp.
Carbohydrate fermentation	Lactate, propionate, acetate, butyrate	*Clostridium* cluster XIVa, *Prevotella* spp., *Faecalibacterium* spp., *Bifidobacterium* spp.
Amino acid fermentation	Hydrogen, methane, amines, phenols, ammonia (NH_3), organic acids, hydrogen sulfite	Sulfate-reducing bacteria (SRB), *Desulfovibrio* spp., *Clostridium* spp., *Peptostreptococcus* spp.
Degradation of oxalate	Formate and CO_2	*Oxalobacter formigenes*
Inulin and starch degradation	Lactate	*Bifidobacterium* spp.
Metabolism of alcohols and acetic acid	Methane and CO_2	Methanobacteria

Table 2-2 Predominant Bacterial Groups in the Canine and Feline Gastrointestinal Tract

CULTURE RESULTS		16S rRNA GENE RESULTS	
Bacterial Group	**Counts (Log CFU/g)**	**Bacterial Group**	**(% of Total Sequences)**
Stomach			
Streptococcus spp.	3.0-5.9	*Helicobacter* spp.	>90
Lactobacillus spp.	1.0-5.4	*Burkholderiales*	<1
Bacteroides	0-4.2	*Clostridiales*	<1
Clostridium perfringens	0-3.2	*Lactobacillales*	<1
Enterobacteriaceae	1.0-3.3	Other	<1
Small Intestine			
Spiral-shaped rods	3.0-6.8	*Clostridiales*	30-50
Bacteroides	0-5.5	*Enterobacteriales*	20-60
Lactobacillus spp.	1.0-5.4	*Lactobacillales*	5-30
Streptococcus spp.	3.0-5.2	*Bacteroidales*	0-5
Escherichia coli	2.3-5.0	*Campylobacterales*	0-2
C. perfringens	1.0-2.5	*Actinomycetales*	0-3
		Fusobacteriales	0-10
		Pasteurellales	2-5
		Spirochaetes	0-12
Large Intestine			
Bacteroides	7.3-10.2	*Clostridiales*	60-78
Bifidobacterium spp.	8.0-10.0	*Lactobacillales*	1-5
Clostridium spp.	7.3-9.5	Erysipelotrichales	0-8
Streptococcus spp.	8.8-9.1	*Bacteroidales*	0.5-5
Lactobacillus spp.	5.5-9.0	*Coriobacteriales*	1-2.5
E. coli	6.4-8.6	*Enterobacteriales*	0.1-2
Prevotella	7.0-8.5	*Fusobacteriales*	0.3-10
Ruminococcus	7.0-8.0	*Aeromonadales*	0.2-0.5
C. perfringens	5.5-8.0	*Bifidobacterium* spp.	N/A
Staphylococcus spp.	5.2-5.3	*Desulfovibrio* spp.	N/A

Results were obtained either by bacterial culture,[1,7] 16S rRNA gene sequencing,[36,48] sequencing of the cpn60 gene,[8] or FISH.[23]

between 30% to 95% of 16S rRNA gene sequences in various studies), followed by *Bacteroides*, *Actinobacteria*, and *Fusobacteria*. *Firmicutes* are a heterogenous bacterial phylum. They are represented mainly by the *Clostridiales* and Erysipelotrichaceae. Within those orders, *Clostridium* spp., *Ruminococcus* spp., *Faecalibacterium* spp., *Dorea* spp., and *Turicibacter* spp. are the major groups. Based on phylogenetic analysis, the *Clostridiales* are comprised of at least 70 different species (Table 2-3), which are organized into phylogenetically distinct *Clostridium* clusters. These clusters differ in abundance in different parts of the intestine. Clusters XIVa and IV encompass many important short-chain fatty acid-producing bacteria (see Table 2-3) and predominate in the ileum and colon of both cats and dogs. Cluster XI and I (*Clostridium perfringens* group) are the second most abundant groups in the small and large intestine of dogs and cats.[6,7]

Presence of a Core Microbiome and Functional Redundancy

There are marked differences in the composition of the microbiota between individuals, and even between monozygotic twins. However, the metabolic end products are similar between individuals. Additionally, although some environmental influences lead to significant changes in bacterial groups, these changes are not immediately associated with any obvious changes in gut function in healthy animals. New metagenomic studies have evaluated the gene content of the intestinal microbiota and suggest that the intestine harbors a "core microbiome," because despite observed differences

Table 2-3 Most Abundant Representative of the Various *Clostridium* Clusters in Canine and Feline Fecal Samples

Cluster I
Clostridium perfringens
Clostridium colicanis
Clostridium disporicum

Cluster IV
Faecalibacterium spp.
Clostridium methylpentosum
Ruminococcus spp.

Cluster XI
Clostridium hiranonis
Clostridium bartlettii
Clostridium lituseburense
Clostridium sordellii
Clostridium glycolicum
Peptostreptococcus spp.

Cluster XIVa
Dorea spp.
Roseburia/Ruminococcus group
Clostridium saccharolyticum
Clostridium celerecrescens
Clostridium symbiosum
Clostridium bolteae
Clostridium oroticum
Clostridium methoxybenzovorans
Clostridium algidixylanolyticum
Clostridium hathewayi
Clostridium amygdalinum
Lachnospiraceae

Cluster XVIII
Clostridium cocleatum
Clostridium ramosum

The order *Clostridiales* is the most abundant and most diverse group in the large intestine of dogs and cats, is comprised of at least 70 known species, and constitutes approximately one-third of total colonic bacteria.

in bacterial phylotypes among individuals, the microbiome of each individual appears to have similar gene content and therefore similar functions.[18] Furthermore, a functional redundancy exists in the GI tract. Several members of the community can perform similar functions, and if one group is displaced because of perturbations (e.g., antibiotic therapy), other members of the community are able to maintain a stable ecosystem. These findings highlight the need to evaluate the intestinal microbiome as an entity, including phylogenetic relationships and metabolic functions (i.e., metagenome, transcriptome, and metabolome).

Other Members of the Intestinal Ecosystem

Besides bacteria, the GI tract harbors fungi, archaea, protozoa, and viruses (including bacteriophages). Recent molecular studies have provided information about the diversity of these microorganisms, but their interactions, their influences on the host, and their role in health and disease remain unclear.

Fungi

Specific fungal organisms (e.g., *Histoplasma capsulatum*) are associated with GI disease, but the role of fungal organisms in the intestinal ecosystem has not been studied extensively. Identification and characterization of fungi is technically challenging. Special staining techniques (e.g., Gomori methenamine silver, Gridley fungus, and periodic acid-Schiff stains) improve the detection sensitivity on histologic sections or fecal smears, but do not allow identification of the organisms.[23] Fungal culture is technically challenging, and serologic tests and immunoassays for the detection of fungal antibodies and antigens are only available for specific pathogens.

The significance of fungi for the GI health of dogs and cats remains unclear. Yeasts and molds have been cultured from the intestine of 25% of healthy Beagles, with mean counts of 10^1 CFU/g jejunal content and 10^5 CFU/g of feces.[20,24,25] A higher prevalence of fungal DNA (76% of dogs) was reported in the proximal small intestine in healthy dogs and dogs with chronic enteropathies using a panfungal PCR assay.[26] A total of 51 different phylotypes were identified in the duodenum of 135 healthy and diseased dogs, with the majority of dogs harboring only one phylotype.[26] Fungi were more frequently adherent to the intestinal mucosa than in the luminal content.[26,27] Recent unpublished data from the author's laboratory obtained using panfungal PCR primers followed by 454-pyrosequencing revealed four fungal phyla in canine and feline fecal samples, with the majority of sequences belonging to Ascomycota (>90%) and *Neocallimastigomycota* (>5%). Saccharomycetaceae were the predominating fungal group in fecal samples of dogs and cats (Table 2-4). All 19 animals evaluated harbored fungal organisms, and multiple species (median, 40; range, 10 to 98) were observed in each sample. Each animal had a unique fungal profile.

Table 2-4 Most Prevalent Fungal Genera Identified in Canine Fecal Samples

Fungal Genus	Mean % of Fungal Population	% of Dogs (n = 19)
Catenulostroma	11.4	94.7
Candida	11.6	94.7
Penicillium	2.8	89.5
Aureobasidium	2.9	84.2
Myrothecium	5.6	78.9
Bipolaris	4.2	78.9
Keissleriella	1.0	73.7
Teratosphaeria	1.1	73.7
Phoma	2.7	73.7
Phomatospora	6.0	73.7
Cochliobolus	7.1	68.4
Cladosporium	5.5	57.9
Pyrenophora	1.6	57.9
Aspergillus	1.3	57.9
Hypocrea	1.2	47.4
Phaeosphaeria	2.4	47.4
Shiraia	1.1	47.4
Saccharomyces	0.8	47.4
Pleiochaeta	0.1	42.1
Engyodontium	0.5	42.1
Nomuraea	0.2	31.6
Alternaria	0.7	31.6
Trematosphaeria	0.3	31.6
Dendryphion	0.3	31.6
Helicoön	0.1	31.6
Sporisorium	0.2	31.6
Fusarium	0.1	31.6
other	27	N/A

Fecal samples from 19 dogs living in various environments were analyzed by fungal tag-encoded FLX amplicon pyrosequencing (fTEFAP). Fungi were present in all 19 samples. Multiple species (median, 40; range, 10 to 98) were observed in each sample, but each dog harbored a unique fungal profile.

Archaea

Archaea are single-celled microorganisms with structure similar to bacteria. They are evolutionarily distinct from bacteria and eukaryotes and form the third domain of life. Archaea are obligate anaerobes living in environments low in oxygen (e.g., water, soil). Archaea are commensal in the intestine of ruminants and have recently been described in the human intestine, with *Methanobacteriales* most commonly reported.[28,29] Recent 16S rRNA gene-based studies in the author's laboratory revealed two distinct archaeal phyla in the intestine of dogs and cats: *Crenarchaeota* and *Euryarchaeota*. Similar to man, Methanobacteria were the most abundant class of archaea.

The role of archaea in GI health and disease remains unclear. Methanogens are associated with periodontal disease in man.[30] They are considered commensal in the GI tract, but they may contribute to pathogenicity through mutualistic interactions with other microbes.[31] One major function of methanogens is the scavenging of various fermentation products produced by other microbes (e.g., CO_2, H_2, alcohols, and acetic acid), resulting in the production of methane and CO_2. The reduction of hydrogen promotes an environment that favors the growth of polysaccharide fermenting bacteria, leading to a higher energy utilization of the diet. For example, higher numbers of methanogenic archaea have been observed in obese people.[29] It has also been hypothesized that reduction in hydrogen concentrations results in lower production of hydrogen sulfite by sulfate reducing bacteria, thus reducing damage to epithelial cells.

Viruses

Knowledge of viral communities in the GI tract of dogs and cats is limited to a few families (including rotavirus, coronavirus, and parvovirus). Recent human studies revealed that the viral community in the GI tract is as diverse as the bacterial, with several hundred different phylotypes.[32] The vast majority of these are bacteriophages. It is likely that a similar viral community is present in the intestine of dogs and cats. It remains technically challenging to characterize the viral community because of their heterogeneity (i.e., DNA

viruses, RNA viruses, single-stranded DNA [ssDNA] viruses). Consequently, a universal approach as used for bacteria and fungi is not feasible. New metagenomic approaches show the most promise for the characterization of intestinal viruses.

Dynamics of the Intestinal Microbiota

Host genetics substantially influence the overall composition of the intestinal microbiota. Environmental factors such as antibiotic administration and dietary changes cause shifts in microbial groups, but these changes are individualized for each animal.[2,33] The qualitative microbial composition is stable over long periods of time, but the proportions of individual bacterial groups may have substantial day-to-day variation. The small intestinal microbiota has greater temporal variation compared with the more diverse large intestine.[25]

Changes in Intestinal Microbiota During Life Stages

The intestine harbors permanently colonizing microorganisms that are acquired at birth and remain largely stable over life. Passing microbes (i.e., swallowed) are present only transiently in the GI tract. Within hours after birth, the sterile intestine becomes colonized by bacteria present in the birth canal, milk, and surrounding environment.[34] Shifts in relative proportions of bacteria occur during postnatal development. In one study, bacterial counts in the small intestine were highest in one-day-old puppies and decreased significantly thereafter. They remained stable at approximately 10^7 CFU/g over the observation period of 42 days.[34] Aerobes predominate in the first weeks of life, but the proportion of anaerobes gradually increases with age, mostly because of an increase in *Bacteroidetes*. The major shifts in microbial populations correlate with dietary changes (i.e., suckling and transition to solid food) and the physiologic development of the host's ability to metabolize dietary substrates (e.g., development of intestinal brush-border enzymes) in the first weeks after birth.[34,35] The microbiota increases in diversity in the first few months of life and remains remarkably stable during adulthood. More pronounced changes are observed in older animals (i.e., dogs older than 11 years), especially in the large intestine.[20] These changes are most likely caused by the changing structure and function of the GI tract with increasing age. Older dogs have more *Clostridium perfringens* and *Streptococcus* spp., and fewer *Bacteroides*, *Bifidobacterium*, and *Lactobacillus* spp.[20] DGGE fingerprinting profiles also cluster according to age, and levels of *Bacteroides* are significantly lower in older dogs.[33]

Mechanisms Regulating the Intestinal Microbiota

Several physiologic mechanisms regulate bacterial colonization in the intestine. Gastric acid, bile, and pancreatic enzymes inactivate most ingested microorganisms. Intestinal motility is an important regulator of bacterial counts in the intestine, as microbes that are not able to adhere to the epithelium will be quickly eliminated. In contrast, higher numbers of bacteria are present in the large intestine as a consequence of stagnant flow of luminal content and the abundance of nutrients. The ileocolic valve together with normal intestinal motility prevents retrograde migration of bacteria from the large into the small intestine.[36] Any changes in these control mechanisms may lead to alterations to community composition or total bacterial count. For example, atrophic gastritis or acid suppressant therapy leads to an increase in duodenal bacterial counts in man.[37] Similarly, dogs with experimentally induced exocrine pancreatic insufficiency (EPI) have increased bacterial number in the proximal small intestine.[38] Anatomical malformations (e.g., strictures, surgically created blind loops) associated with altered motility are a common site of bacterial overgrowth in man.

Role of Microbiota in Immunity, Host Defense, and Energy Regulation

A balanced intestinal ecosystem primes and stimulates the immune system, aids in defense against intestinal pathogens, and provides nutritional benefits to the host. Animals can live well when raised under germ-free conditions. However, morphologic and immunologic differences between germ-free and conventionally raised animals suggest that that the commensal microbiota is a significant contributor to the development and maintenance of gut physiology and immune function.[39] Germ-free animals have an altered mucosal architecture (i.e., thinner lamina propria) and reduced turnover of epithelial cells compared with conventionally raised animals.[39] The underdeveloped immune system is rapidly restored upon introducing bacteria into germ-free mice.[40] Bacteria communicate with the host via Toll-like receptors (TLRs) and dendritic cells. The resident intestinal microbiota is a crucial part of the intestinal barrier that protects the host from invading pathogens. This mechanism is called *colonization resistance*. Proposed defenses include the competition for oxygen, nutrients, and mucosal adhesion sites, and the creation of a physiologically restrictive environment for nonresident bacterial species (e.g., secretion of antimicrobials, alterations in pH, and hydrogen sulfide production).[41] Other crucial parts of the intestinal barrier are the intestinal epithelial cells, protective mucus, and the gut-associated lymphoid tissue (GALT). The increase in diversity of the colonizing microbiota at weaning strengthens the colonization resistance against pathogens. Furthermore, the resident microbiota drives maturation of the intestinal immune system. Younger animals with underdeveloped microbial diversity and immature GALT are dependent on protective colostral antibodies and milk components. Younger animals are typically more susceptible to invading pathogens (e.g., *Campylobacter* spp.). Studies of murine models have suggested that the pattern of microbial colonization in early life may impact on host physiology and colonizing resistance far into adulthood.[42]

Bacteria in the large and small intestine can differ in their contribution to GI health. The large intestinal microbiota is mainly beneficial to the host. Clostridiaceae, *Dorea* spp., Lachnospiraceae, *Ruminococcus* spp., *Faecalibacterium* spp., and *Roseburia* spp. are the predominant bacteria in the colon. The majority of colonic bacteria are anaerobic and their main functions are to produce energy from undigested food and to help in the competitive exclusion of potential pathogens. The slower flow of ingesta and the increased time and availability of nutrients favors microbial diversity in the colon. Bacteria within this ecosystem have developed cooperative strategies to transform the complexity of nutrients to their own and the host's benefit. Colonic bacteria provide digestive enzymes that allow utilization of complex carbohydrates. For example, 8% of the genome of *Bifidobacterium longum* is comprised of genes needed for carbohydrate metabolism.[43] Microbes metabolize sloughed epithelial cells, endogenous mucus, and nondigested substrates that have passed through the small intestine. The latter are predominantly complex carbohydrates, including starch and dietary fiber such as cellulose, pectin, and inulin. The fermentation of these substrates results mainly in the production of short-chain fatty acids (e.g., acetate, propionate, and butyrate) that provide energy for bacterial metabolism and for epithelial cell growth. Up to 7% of the metabolic energy of dogs, and to a lesser extent in cats, is produced by

microbial fermentation.[44] Peptides, amino acids, and intermediate products of microbial metabolism such as ethanol, lactic acid, and succinic acid are further metabolized into short-chain fatty acids. Some members of the *Clostridium* cluster XIVa also utilize lactate for butyrate production, thus preventing lactate accumulation in the human colon. However, colonic microbial metabolism of some substrates, mainly proteins, may also yield toxic intermediates with negative effects on epithelial cells.

Small intestinal bacteria have a more delicate relationship with the host. As a result of increased intestinal motility, they are predominantly adherent to the mucosa. These organisms are an important stimulator of mucosal immunity. Subtle changes in this balance may impact on the health of the host. The predominantly facultative anaerobic bacteria may compete with the host for nutrients and may produce deleterious metabolites. In pigs, up to 6% of dietary energy may be lost to the host as a result of bacterial uptake in the small intestine.[45] Small intestinal microbiota, especially *Lactobacillus* spp. and *Clostridium* spp. (*C. hiranonis* and *C. scindens*) deconjugate bile acids, impairing fat absorption and producing secondary bile acids that may damage the epithelium.[46] Other abnormal functions may be dehydroxylation of fatty acids, destruction of brush-border enzymes, damage of carrier proteins, and competition for nutrients (e.g., cobalamin).

Gastrointestinal Microbiota in Disease

The close contact between microbiota and host has significant impact on GI health. Colonization with transient pathogens, overgrowth of resident opportunistic commensals, or altered communication between the intestinal innate immune system and the commensal microbiota may result in GI disease. Invasion of specific pathogens (i.e., *Salmonella*, enterotoxigenic *C. perfringens*, *Campylobacter jejuni*, and others) may profoundly disturb the structure of the GI mucosa. Enteric pathogens can penetrate into the submucosa and Peyer's patches, or produce exo- or enterotoxins that alter enterocyte function. Enterotoxins often stimulate mucosal fluid secretion, while villus effacement and loss of surface area diminishes mucosal absorptive capacity, resulting in diarrhea. Dysfunction of the mucosal barrier can lead to increased intestinal permeability and clinically significant bacterial translocation.[47]

Several GI diseases are associated with nonspecific alterations in the microbiota. Small intestinal bacterial overgrowth or antibiotic-responsive diarrhea (also known as tylosin-responsive diarrhea) is suspected to be caused by an intestinal dysbiosis.[48] Rapid diet changes or dietary indiscretion, changes in the architecture of the intestine, or changes in intestinal motility (e.g., surgical creation of intestinal loops, short bowel syndrome, and resection of the ileocolic valve) are also associated with alterations in the intestinal ecosystem. EPI is associated with an increase in bacterial counts in the canine small intestine, which often is reversible upon pancreatic enzyme supplementation.[38] Such alterations may lead to various mechanisms that will negatively impact the function of the GI tract. Examples are an altered intestinal barrier with increased intestinal permeability, and direct damage to the intestinal brush-border and enterocytes leading to nutrient and vitamin malabsorption. Overgrowth of specific bacterial groups may lead to increased competition for nutrients and vitamins and increased deconjugation of bile acids and creation of potentially deleterious metabolites.

The commensal intestinal microbiota is also thought to play an integral part in the pathogenesis of inflammatory bowel disease (IBD) in man, dogs, and cats.[1,13,49] In man, the microbiota is implicated because inflammation is present in gut compartments with the highest bacterial counts and the diversion of the fecal stream or antibiotic therapy improves clinical signs. In murine models of IBD, inflammation develops only in the presence of bacteria. The cause–effect relationship between microbial alterations and inflammation is not well determined. It is suspected that intestinal inflammation causes a shift toward Gram-negative bacteria (e.g., *Proteobacteria*) that may perpetuate the disease in genetically susceptible individuals. New hypotheses also suggest that intestinal inflammation may trigger alterations in the immune system, which, in turn, diminish the colonization resistance of the resident microbiota, resulting in an overgrowth of pathogens.[50] One current hypothesis implicates an abnormal interaction between commensal bacteria and the intestinal immune system in genetically predisposed individuals.[51] For example, a subset of people with Crohn's disease may not be able to effectively clear commensal or pathogenic bacteria, resulting in overcompensating antibacterial effector T cells that may, in turn, cause tissue damage.[51] People with Crohn's disease have a decrease in the bacterial phyla *Firmicutes* and *Bacteroidetes*, and an increase in *Proteobacteria* and *Actinobacteria*.[1] In most studies of human IBD, a reduction in the diversity of *Clostridium* clusters XIVa and IV (e.g., *Lachnospiraceae*, *Ruminococcaceae*, *Faecalibacterium prausnitzii* and *Clostridium coccoides* subgroups) was identified, suggesting that these bacterial groups, which are mainly producers of short-chain fatty acids, may play an important role in maintenance of GI health. Alterations in microbial composition have also been recently reported in dogs and cats with IBD.[13,49] Similar to people, dogs and cats with idiopathic IBD had significantly more Proteobacteria and reductions in *Clostridium* clusters XIVa and IV in their duodenum compared with healthy animals.[13,49,52] Boxer dogs with histiocytic ulcerative colitis respond to therapy with fluoroquinolones, and in this disease there is an association between the presence of adherent and invasive *Escherichia coli* (AIEC) and inflammation.[53] These AIEC isolates share similarities to those obtained from ileal tissues of people with Crohn's disease.[53]

Modulating the Intestinal Microbiota

Members of *Clostridium* clusters XIVa and IV (e.g., *Dorea* spp., *Lachnospiraceae*, *Ruminococcus* spp., *Faecalibacterium* spp., and *Roseburia* spp.) are consistently depleted in people with IBD and acute colitis,[51] suggesting that these organisms are important in maintaining intestinal homeostasis. This observation emphasizes the need to distinguish the presence of beneficial clostridial groups from opportunistic commensals such as *C. perfringens* and *Clostridium difficile*. Changes in proposed beneficial bacterial groups such as *Bifidobacterium* spp. have also been observed in GI disease, although to a lesser extent. Modulating the intestinal microbial ecosystem is therefore a rational therapeutic approach in animals with GI disease. Clinical experience shows that dietary changes or antibiotic administration often leads to an improvement in GI signs. However, the exact mechanism remains elusive. Antibiotics can eliminate specific pathogens or can, as is also proposed for diets, lead to more general modulations of the intestinal microbiota. This potentially results in a reduced burden of stimulating antigens or the creation of an environment within the GI tract (e.g., changes in osmolarity and pH) that allows for more effective utilization of ingesta.

Because of vast interindividual differences in the intestinal microbiota, it is difficult to define what constitutes a normal and balanced intestinal ecosystem. Dietary manipulation, the administration of antibiotics or pre- and/or probiotics are commonly used modulating strategies. It is important to note that although such interventions may cause shifts in the composition of the intestinal microbiota, these

changes are largely individualized for each animal. Bacterial groups of a higher phylogenetic level (i.e., order or family) may show a synchronized response to the environmental influence, but these changes are rarely associated with one specific bacterial species or bacterial strain that is consistently altered in every individual. As a consequence of the complexity of the microbiota, the vast majority of bacterial groups within the ecosystem remain typically unaffected by diet or nutraceuticals.[33,54] This complicates the prediction as to which animal may benefit most from a selected strategy. Probiotics can lead to a transient increase in the administered target species, but this has an insignificant impact on the composition of the total microbial ecosystem. Furthermore, probiotics are typically eliminated from the intestine within a few days after ending administration. Therefore administration of high doses over prolonged periods of time is usually required. Prebiotics are typically complex carbohydrates that are added to diets to enhance the growth of endogenous microorganisms; including *Bifidobacterium* spp. Increases in bacterial groups that utilize these nutrients have been demonstrated.[55] Such changes are again typically very minor within the entire ecosystem, as the administered prebiotics fulfill only some of the nutrient requirements for their target bacteria, but other essential nutrients remain at growth-limiting amounts. At this point, the significance of altering a rather minor proportion of the ecosystem remains unclear. It is also now well recognized that the microbiota is generally resilient to change and returns rapidly to its pretreatment state within a few days. Consequently, long-term modulation is needed to maintain a desired ecosystem. Antibiotic usage has a more pronounced effect and may disrupt the microbial ecosystem for prolonged periods of time (weeks to months). In one study evaluating the fecal microbiota of healthy people, approximately 30% of all bacterial taxa were affected, some of them for up to six months.[11] Similarly, administration of tylosin for 14 days led to significant modifications in the jejunal microbiota of dogs, with some bacterial groups depressed for more than 14 days.[2] However, highly individualized responses for some bacterial groups were observed in each animal.

Based on these findings, it remains challenging to provide a universal algorithm for modulation of the microbiota. Every animal may require individualized management consisting of combinations of dietary modification, antibiotics, and pro- or prebiotics. Therefore, therapeutic modulation is currently based on empirical approaches with improvement of clinical signs as the most useful outcome measure. New molecular tools such as metagenomics and transcriptomics will be useful for elucidating how such modulatory strategies affect the gene content within the intestinal microbiome. This may help to customize treatment strategies for individual animals and conditions.

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CHAPTER 3

Gastrointestinal Immunology

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Introduction

Gastrointestinal (GI) or gut-associated lymphoid tissue (GALT) is part of the mucosal immune system and comprises up to 70% of total body lymphoid tissue. Despite exposure to a vast array of exogenous antigens, the GI immune system is able to discriminate innocuous antigens from pathogens, deploying an array of protective mechanisms to prevent damaging immune responses.

Gastrointestinal Immunoanatomy: Inductive and Effector Sites

The GI immune system is compartmentalized into (a) afferent or inductive sites, where antigen-presenting cells (APCs) prime naive T and B cells to initiate the immune response, either by processing and presenting local antigens or by migration from the lamina propria (LP), an important site of antigen sampling, and (b) efferent or effector sites, where antibody and T-cell–mediated responses are mounted after extravasation, retention, and further differentiation of the lymphocytes. The afferent arm of the GI immune system comprises Peyer patches (PPs), isolated lymphoid follicles (ILFs), and mesenteric lymph nodes (MLNs), while the efferent arm comprises lymphocytes located in the LP and epithelium; cryptopatches, loosely organized clusters of approximately 1000 cells located at the base of the intestinal crypts, have also been described in the mouse. Cryptopatches were originally thought to be sites of extrathymic intraepithelial lymphocyte (IEL) development, but more recent studies suggest that they are precursors of ILFs. Additional species-specific accumulations of lymphocytes include the rare T-cell–dominated "lymphocyte-filled villi" of rats and man, colonic "lymphoglandular complexes" of pigs, and the "continuous ileal PP" of ruminants, pigs, and dogs, which appears to be a primary lymphoid organ responsible for B-cell development.[1-3] Located throughout the small intestine, PPs comprise at least three aggregated lymphoid follicles with an overlying follicle-associated epithelium (FAE) containing microfold (M) cells, specialized epithelial cells that transport antigens from the lumen to the underlying lymphoid tissue. This process, called *transcytosis*, is mediated by mechanisms that include endocytosis of clathrin-coated vesicles, actin-dependent phagocytosis, and fluid-phase pinocytosis or macropinocytosis. M cells express a receptor for secretory (s) immunoglobulin (Ig) A on their apical surface, which facilitates the transcytosis of IgA-coated bacteria to the underlying APC-rich dome region of the PP. M cells lack a rigid internal cytoskeleton and are easily deformed by lymphoid cells migrating into the epithelium; this flexibility allows the creation of a pocket beneath the M cells, from which lymphoid cells can enter and leave without breaching the M-cell membrane. These pockets are thought to represent specialized extensions of the germinal centers of the underlying follicles, and contain equal proportions of memory T and B cells. The subepithelial dome region is rich in $CD11b^-$ and $CD11b^+$ $CD8\alpha^-$ dendritic cells (DCs), potent APCs that capture antigens transported across the M cells. The FAE expresses the chemokines CCL20, CXCL16, and CCL9, creating a micromilieu that attracts the underlying DCs. Following antigen uptake, the DCs either migrate directly to the adjacent interfollicular T-cell zones of the PPs, or pass to the MLNs where they may interact with naive T cells (Fig. 3-1).

The latest literature describes the GALT as including PPs, ILFs, and the appendix, while MLNs are now considered to lie outside the GALT as they do not directly sample luminal antigens. Similarly, the effector sites are not considered *bona fide* lymphoid tissue on the basis of established terminology.

What Is Known in Dogs and Cats?

PPs are recognized in both the dog and cat. There are approximately 20 PPs in the dog, spanning the whole of the small intestine and ranging in size from a few millimeters to 4 cm.[4] The single ileal PP in the dog differs from those of the duodenum and jejunum, with large follicles, a small dome and very little interfollicular tissue.[2,3] The ileal PP has fewer T cells than the proximal PPs, consistent with its putative role in B-cell ontogeny.[2,3] Pinpoint-sized collections of lymphoid follicles resembling PPs are occasionally present in the stomach, colon, and rectum of the dog.[4] Lymphocytes in the paracortical and interfollicular areas of PPs are predominantly $CD4^+$, while B cells in the dome region of canine PPs express IgA or IgG.[2,3] Lymphoid follicles are present throughout the intestine and are the predominant type of aggregated lymphoid tissue in the canine colon and rectum. They comprise isolated follicles of 0.5 to 3 mm that occupy the LP and submucosa, and serve a similar function to the follicles within PPs.[4]

The intestinal LP of the dog contains plasma cells, T cells, and putative DCs.[4-6] Plasma cells are predominantly IgA^+ and are concentrated within the crypt regions in the small intestine and deep LP in the colon; fewer of them are found within the villi and superficial LP of the colon and there is a progressive decline in the density of IgA^+ plasma cells from the duodenum to the ileum.[6-9] In contrast, $CD4^+$ and $CD8^+$ T cells present within the canine LP are concentrated toward the tips of the villi, with no apparent differences in proximal to distal small intestinal distribution.[6,10] The ratio of

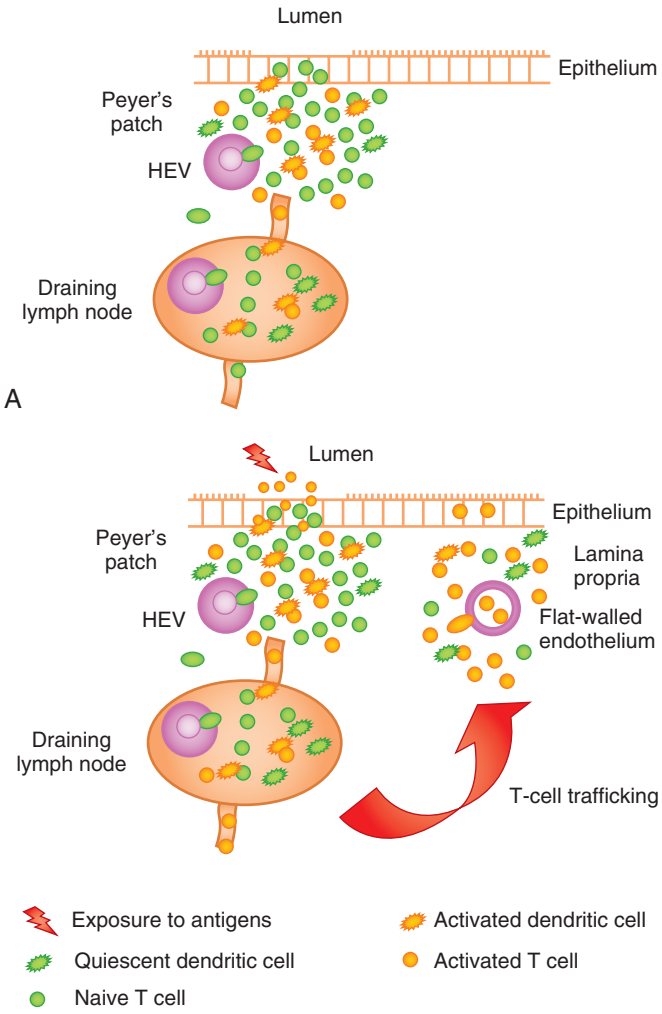

Figure 3-1 Gastrointestinal immunoanatomy: inductive and effector sites. **(A)** Naive T cells continuously migrate from the bloodstream into the inductive sites of the GI immune system, traversing the high-endothelial venules (HEVs) in a multistep extravasation cascade. The lymphocytes then migrate through the tissue in search of their cognate antigens. If these antigens are not found, the T cells leave the lymphoid tissue by means of the efferent lymphatics, to be carried back to the bloodstream via the thoracic duct. From there the cells can continue their journey to other secondary lymphoid organs. **(B)** However, if cognate antigens are encountered, the naive lymphocytes are activated and are imprinted with a preference to home back to the tissues in which they were primed by the resident dendritic cells (DCs), mediated in the case of the GI immune system by upregulation of $\alpha_4\beta_7$ and CCR9 expression by the T cells. Thus, on returning to the systemic circulation via the efferent lymphatics, they preferentially home back to the intestinal lamina propria (LP) to execute their effector functions, this time gaining access to the tissue via the normal flat-walled endothelium of postcapillary venules. Naive B cells also undergo recirculation in a similar manner. The GI immune system is constantly exposed to a plethora of luminal antigens, sampled by M cells and DCs that extend dendrites between the enterocytes; a certain low-level paracellular leak of antigens into the GI mucosa is also thought to occur. Given this constant antigenic exposure, it is not surprising that the majority of LP T cells have an activated or memory phenotype, though recent studies have suggested that constitutive migration of naive $CD4^+$ and $CD8^+$ T cells into the small intestinal LP may also occur. An overly aggressive immune response to luminal antigens, particularly the microbial flora, is thought to underlie inflammatory bowel disease. (Images reproduced with permission from the contributing author.)

$CD4^+$:$CD8^+$ T cells is approximately 60:40 in the LP and 15:85 in the epithelium.[10] Subtractive analysis suggests that a population of $CD3^+CD4^-CD8^-$ cells exists in the canine villus epithelium, thought to represent γδ T cells.[10] Immunohistochemical studies have suggested that αβ and γδ IELs are present in approximately equal numbers in the canine duodenum, jejunum, and ileum.[11] Up to 20 IELs per 100 enterocytes have been counted in each region of the small intestine.[6,11] A more recent flow cytometric study has suggested that αβ IELs outnumber γδ by up to 2:1 in the proximal small intestine and by up to 5:1 in the colon, perhaps reflecting the greater sensitivity of this technique.[12] The distribution of T cells is similar in the feline LP[13,14]; however, IELs in cats are more numerous, with more in the villus than crypt epithelium and a rising count from the duodenum (50 IELs/100 enterocytes) to ileum (80 IELs/100 enterocytes).[14] The majority of feline IELs are $CD8^+$ (up to 50%), with fewer $CD4^+$ cells (up to 10% to 15%) and a sizable population of $CD3^+CD4^-CD8^-$ cells (thought to be $\gamma\delta^+$).[13,14] IgA^+ plasma cells predominate in the small intestine, with increasing numbers around the crypts; however, in contrast to the dog, there is a trend for the number of IgA^+ cells to increase from the duodenum to ileum.[14] IgG^+ plasma cells are more numerous in the feline colon, with fewer IgA^+ and IgM^+ cells.[15] A small number of IgM^+ IELs may be observed in cats,[14] but these are not documented in other species and their significance remains unclear.

A significant number of lymphoid cells within the canine LP are $CD45R^+$, raising speculation that a proportion of the T cells found within this compartment are naive, in contrast with the predominantly effector/memory T-cell phenotype observed in the murine and human LP.[6] A recent study demonstrated that the LP of random source cats has more $CD4^+$ T cells expressing the activation marker CD25 (the interleukin [IL]-2 receptor α chain) than that of specific pathogen-free cats, suggesting that exposure to luminal antigens increases the number of activated/memory T cells within this compartment, in common with other species.[16] Examination of expression of class II molecules of the major histocompatibility complex (MHC) in the canine small intestine reveals a web of subepithelial dendritic-like cells in the villus LP.[10,17] However, the strongest MHC class II expression occurs within the PPs and some expression of this antigen is also apparent within the epithelium, particularly within the ileum.[10,17] A similar pattern of LP MHC class II expression has been documented in the cat, although epithelial labeling was negative in one study[13] and weak and restricted to PPs in another.[14]

Innate and Adaptive Arms of the Gastrointestinal Immune System

Overview

Box 3-1 summarizes the defense mechanisms of the GI tract, including both nonimmune and immune-mediated components.

Pattern Recognition Receptors and the Epithelium

There is increasing recognition of the importance of the innate immune system to GI homeostasis and the pathogenesis of inflammatory bowel disease (IBD). Macrophages, neutrophils, dendritic cells, and intestinal epithelial cells are all able to recognize pathogen-associated molecular patterns (PAMPs) on the surface of a wide variety of microbes by means of pattern recognition receptors (PRRs). Characterized by extracellular leucine-rich repeat domains and the activation of signaling pathways that converge on nuclear factor-kappa B (NF-κB), the Toll-like receptors (TLRs) have emerged as preeminent PRRs of the innate immune system and play

Box 3-1 Defense Mechanisms of the Gastrointestinal Tract

Physical/Biochemical/Microbial
- Normal motility, gastric and pancreatic juices; proteolysis (e.g., lysozyme)
- Cellular proliferation, epithelial barrier (e.g., dynamic tight junctions, mucus[1], trefoil peptides[2], glycocalyx)
- Natural microbial flora (i.e., biofilm)

Innate Immunity
- Complement, defensins,[3] Toll-like receptors (TLRs)[4]
- Intracellular pattern recognition receptors (e.g., nucleotide-binding, oligomerization domain 2 [NOD2])[5]
- Autophagy[6]
- Mast cells, macrophages, neutrophils

Adaptive Immunity
- IgA, IgG, IgM, IgE; dendritic cells, T cells, B cells, plasma cells

Notes:
1. See reference 18 for further information.
2. Members of the trefoil family are characterized by the possession of at least one copy of the trefoil motif, a 40-amino-acid domain that contains three conserved disulfides.[19] Trefoil peptides are synthesized by mucin-secreting GI epithelial cells, including goblet cells, and function to stabilize the mucus barrier. Upregulated at sites of mucosal injury, they also promote angiogenesis and stimulate epithelial cells to migrate into the denuded area of mucosa. Deficient expression of trefoil peptides is thought to predispose to intestinal inflammation and malignancy.
3. Defensins are antimicrobial peptides of two structurally different families (α and β) expressed by Paneth cells in the small intestine (α-defensins) and epithelial and plasma cells in the colon (β-defensins; Paneth cells are rare in the colon). They form micropores in the phospholipid bilayer of bacterial membranes, thus causing loss of structural integrity. Defective synthesis of defensins is thought to contribute to the pathogenesis of Crohn's disease.
4. See next section for information on this important family of pattern recognition receptors.
5. NOD2 is a prototypical NOD-like receptor (NLR) expressed by monocytes, macrophages, dendritic cells, and Paneth cells; it acts as an intracellular microbial sensor whose ligand is muramyl dipeptide, a peptidoglycan motif common to both Gram-positive and Gram-negative bacteria. NOD2 polymorphisms are associated with Crohn's disease, thought to be caused by a decrease in the negative regulation of TLR responses occurring in the normal GI tract, and thus a pathologic increase in responses to the normal flora.
6. "Autophagy" (more specifically: macroautophagy) is a process characterized by the formation of double-membrane cytosolic vesicles (autophagosomes) that deliver their cargo to the lysosome for degradation. The autophagosome is formed by a dynamic process of membrane expansion, rather than budding off from preexisting organelles. Autophagy is important in the maintenance of cellular homeostasis, complementing the ubiquitin-proteasome system in the clearance of proteins; it may also eliminate damaged or surplus organelles. By sequestering invasive microbes, autophagy is thought to play a role in intestinal defense, and abnormalities in autophagy have been associated with Crohn's disease.

an important role in the GI tract. Thus, TLR signaling triggered by commensal bacteria contributes to the maintenance of intestinal epithelial barrier function. Moreover, TLR-9 signaling via exposure to unmethylated CpG motifs (common in bacterial DNA), plays a role in the inhibition of colonic inflammation in a murine model of IBD and is thought to mediate the antiinflammatory effects of probiotics in this system. Several protective strategies have evolved to ensure that inappropriate TLR signaling does not occur in health; for example, expression of TLRs 2 and 4 is confined to crypt enterocytes and the LP in man, niches that would not normally be colonized by commensal flora. Similarly, TLR-5 expression is confined to the basolateral membranes of murine intestinal epithelial cells, ensuring that activation only occurs upon breach of the epithelial barrier by bacteria bearing the TLR-5 ligand, flagellin. In contrast, TLR-3 is mostly expressed by mature epithelial cells facing the lumen, since its ligand (viral double-stranded RNA [dsRNA]) is not normally a component of the GI microflora and would therefore warrant an inflammatory response if detected. The intestinal epithelium is thus increasingly recognized as a sentinel for the GALT, interrogating the composition of the microbial flora and helping to orchestrate appropriate immune responses in health. It is a source of a wide range of cytokines that can promote the recruitment and activation of immune cells, including tumor necrosis factor (TNF)-α; transforming growth factor (TGF)-β; IL-1, IL-6, IL-7, IL-8, and IL-10; monokine induced by interferon (IFN)-γ (MIG); IFN-inducible T-cell-α chemoattractant (ITAC); macrophage inflammatory protein (MIP)-3α; CXCL-9, -10, and -11; and fractalkine. A triad of cytokines produced by the intestinal epithelium (thymic stromal lymphopoietin [TSLP], IL-25 [IL-17E], and IL-33) promotes the development of T-helper type 2 (Th2) responses and serve immunoregulatory properties. These latter may be direct, for example, TSLP-mediated inhibition of IL-12/23p40 expression by GALT DCs and facilitation of the peripheral induction of regulatory T cells (Tregs), or indirect, for example, IL-25- and IL-33-mediated downregulation of IFN-γ and IL-17A by the reciprocal induction of Th2 cytokines.

To date, TLRs 2 to 5, 7, and 9 have been cloned in the dog, and peripheral blood mononuclear cells are known to express TLRs 2 and 4.[20-22] The complete sequences of TLRs 4 and 9 have been cloned in the cat,[20] but only partial sequences have been cloned for TLRs 1 to 3 and 5 to 8.[23] Real-time polymerase chain reaction (PCR) assays have been developed for detection of messenger RNA (mRNA) encoding TLRs 1 to 9, and these have shown mRNA encoding TLRs 2 to 5 and 7 to 9 within feline T and B cells.[23] Immunohistochemistry and immunogold electron microscopy have provided evidence for the expression of TLR-4 (the receptor for lipopolysaccharide [LPS]) by macrophages in the canine lung, small intestine, liver, and spleen; epithelial cells within the lung, small intestine, cornea, and renal tubules were also labeled by this cross-reactive antibody.[24] Primary colonic epithelial cells in the dog express mRNA encoding the nucleotide-binding oligomerization domain 2 (NOD2) and TLRs 2 and 4, and IL-7 and IL-8 responses can be elicited by exposure of these cells to the respective ligands, peptidoglycan (TLR-2) and LPS.[25] A recent study has also suggested that TLRs 2, 4, and 9 (all responsive to bacterial products) are upregulated in canine IBD; furthermore, respective mRNA transcript abundance showed no change with therapy despite clinical improvement, raising the intriguing possibility of a primary defect representing a genetic predisposition, as described in human IBD.[26] This important group of PRRs is likely to remain the focus of continuing research.

Lymphocyte Trafficking, Activation, and Gastrointestinal Imprinting

Naive T cells continuously migrate from the bloodstream into the inductive sites of the GALT, traversing the high-endothelial venules (HEVs) in a multistep extravasation cascade involving (a) tethering and rolling mediated by sialomucins and selectins (e.g., peripheral lymph node addressin [PNAd] expressed by HEVs interacting with L-selectin [CD62L] expressed by naive T cells); (b) activation, firm adhesion, and transmigration, mediated by chemokines, integrins, and Ig superfamily members (e.g., intercellular cell adhesion molecule-1 [ICAM-1] and mucosal addressin cell adhesion

molecule-1 [MAdCAM-1] expressed by HEVs respectively interacting with leukocyte function antigen-1 [LFA-1] and the integrin $\alpha_4\beta_7$ expressed by naive T cells); and (c) chemotaxis mediated by chemokines (e.g., CCL19 and CCL21 produced by stromal cells and presented on the luminal face of HEVs, interacting with CCR7 expressed by naive T cells). The lymphocytes then migrate through the tissue parenchyma in search of cognate antigen. If these antigens are not found, the T cells leave the lymphoid tissue via the efferent lymphatics, to be carried back to the bloodstream via the thoracic duct; from there, the cells can continue their journey to other secondary lymphoid organs. However, if cognate antigens are encountered, the naive lymphocytes are activated and are imprinted with a preference to home back to the tissues in which they were primed by the resident DCs, mediated in the case of the GI immune system by upregulation of $\alpha_4\beta_7$ and CCR9 expression by the T cells. Thus, on returning to the systemic circulation via the efferent lymphatics, these T cells preferentially home back to the intestinal LP to execute their effector functions, this time gaining access to the tissue via the normal endothelium of postcapillary venules (see Fig. 3-1). To an extent, they may also re-enter the PPs and MLNs by means of $\alpha_4\beta_7$–MAdCAM-1 interactions. The vitamin A metabolite, retinoic acid (RA), appears to be implicated in imprinting intestinal tropism (high-level $\alpha_4\beta_7$ and CCR9 expression) onto activated $CD4^+$ and $CD8^+$ T cells. DCs from MLNs and PPs express the enzymes catalyzing the production of RA from retinol, thus equipping them with the molecular machinery required for imprinting. CCL25 expressed by the small intestinal epithelium and presented on the surface of HEVs is also important in mediating the chemotaxis of $CCR9^+$ T cells into the LP and towards the epithelium. Naive B cells undergo recirculation in a similar manner; however, CXCL13 presented by HEVs adjacent to or within the lymphoid follicles interacts with CXCR5 expressed by naive B cells, which are, in turn, attracted to the mantle zone by CXCL13 deposited on the dendrites of follicular DCs. B cells undergo priming just outside the lymphoid follicles by interactions with cognate T cells and APCs, before reentering the follicles and migrating to the germinal centers. The B cells may then leave the follicles as memory/effector cells. During inflammation, the recirculation routes of lymphocytes may be broadened, thus helping to explain the extraintestinal manifestations of certain GI infections and IBD. In contrast to the conventional view that naive T cells migrate only to lymphoid tissues, failing to gain access to extralymphoid sites, recent studies show constitutive migration of naive $CD4^+$ and $CD8^+$ T cells into the small intestinal LP. However, the majority of cells in this compartment show an activated or memory phenotype.

The polymeric Ig receptor (pIgR) is expressed on the basolateral surface of intestinal epithelial cells and mediates endocytosis and transcytosis of J chain–linked dimeric IgA or pentameric IgM (Fig. 3-2). The ectodomain of the pIgR, termed the *secretory component* (SC), is cleaved at the junction with the membrane-spanning region and binds covalently to one of the sIgA molecules in each dimer, affording protection against proteolysis; it associates with the IgM molecules in a noncovalent manner, remaining in dynamic equilibrium with free SC in the local microenvironment. There are two potential routes of transmission of locally produced and serum-derived IgG into the intestinal lumen. The first is passive, involving the paracellular diffusion of IgG, whereas the second involves the neonatal Fc receptor (FcRn), which is an MHC class I–related molecule that binds to the Fc domain of IgG. The FcRn is important in neonatal life as it mediates transfer of colostral IgG across the intestinal epithelium. Expression of FcRn is downregulated at the time of weaning in rodents, but continues into adulthood in man. Little is known about the FcRn expression in other species, although FcRn was recently characterized in piglets.

FcRn is expressed by placental syncytiotrophoblasts, endothelial cells, pulmonary and mammary epithelial cells, renal podocytes, hepatocytes, monocytes, macrophages, dendritic cells, and neutrophils. The receptor is thought to have an important role in GI immune surveillance as it shuttles IgG from the basolateral to apical membrane of enterocytes, where IgG binds bacterial antigens. The IgG-antigen then undergoes transcytosis back to the basolateral membrane where there is stimulation of local and systemic immune responses. FcRn can thus act as an immunologic sensor for activity within the lumen of the human GI tract, but it is not known whether there is a similar role for FcRn in dogs and cats. Similar antibody shuttling from the basolateral to the apical membrane of enterocytes and back has been described for IgE in the context of food allergy or the presence of parasites, but this involves the CD23 molecule.

Mucosal Ig in the dog and cat is thought to derive from serum transudation (IgG) and local production by resident plasma cells (IgA and IgM; and IgG in the colon).[5,27,28] A canine small intestinal explant culture system has confirmed that IgA is synthesized by local plasma cells.[29] Canine serum IgA is dimeric and largely synthesized by GI lymphoid tissues,[30] but there is a lack of correlation with duodenal secretory IgA, suggesting that measurement of serum IgA concentration is a poor correlate of GI mucosal immunity.[31] Similarly, salivary IgA concentration also correlates poorly with duodenal IgA concentration.[31] The value of measuring fecal IgA is controversial, one study suggesting that it may reflect mucosal secretory IgA concentration[32] and another concluding that it is of limited value.[33] This discrepancy may in part relate to the reagents used in the IgA detection system employed in some investigations.[33] Quantitative reverse transcriptase (RT) PCR has revealed the presence of mRNA encoding the α chain, pIgR, and J chain in the canine duodenal mucosa, suggesting that dogs employ a similar mechanism of IgA transcytosis to that of other species, but differences in expression were not found when tissues from animals with and without chronic diarrhea were compared.[34] Four different allelic variants of the canine *IGHA* gene are reported,[35,36] but the functional significance of this finding is unclear. Feline IgA has been studied as a human allergen,[37,38] but little is known about epithelial transcytosis of this molecule.

Immune Privilege and Oral Tolerance

Overview of Mechanisms

The conventional paradigm of immune privilege as a form of protection from immune responses that is conferred by anatomical sequestration has been revised in recent years. There is now increasing recognition of the part played by active immunologic mechanisms at these sites (e.g., apoptosis of autoreactive T cells mediated by Fas-FasL interactions) and modern immunology has adopted a broader, more inclusive concept of this phenomenon, which now embraces all sites harnessing regulatory mechanisms to suppress pathologic immune responses against local antigens. Thus, the GI tract may be considered as a site of immune privilege resulting from the complex interactions between the microflora, dietary antigens, and GI immune system. Tolerance of dietary and GI microbial antigens (oral tolerance), defined experimentally by the inability to elicit systemic immune responses to antigens sampled by the oral route, is achieved following interactions between the intestinal barrier and epithelial tight junctions, phagocytes, tolerogenic DCs, and Tregs. Breakdown in these mechanisms is thought to underlie

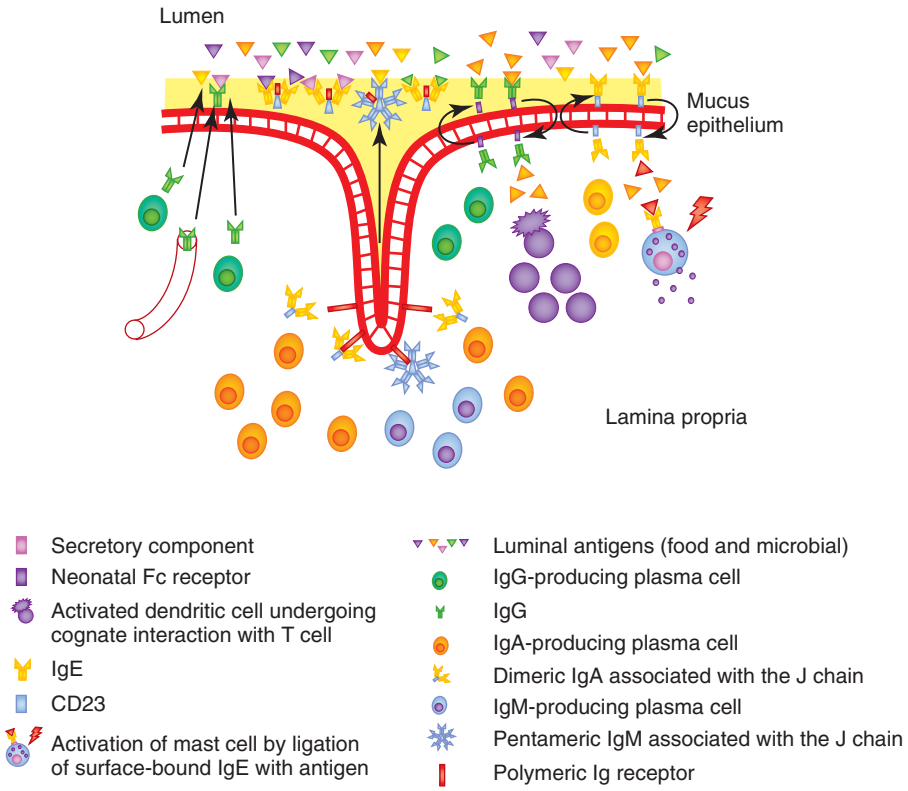

Figure 3-2 An overview of gastrointestinal immunoglobulins. The predominant gastrointestinal immunoglobulin (Ig) is IgA, produced as a dimer associated with the J chain; IgM is also produced by mucosal plasma cells in association with the J chain, in the form of a pentamer. In addition, the J chain is synthesized by a proportion (70% to 90%) of IgG-producing plasma cells, but does not combine with this isotype and thus undergoes intracellular degradation. IgA and IgM molecules are transported across the epithelium by means of the polymeric Ig receptor (pIgR), expressed on the basolateral surface of secretory epithelial cells. At the apical surface, the extracellular ligand-binding region of pIgR, known as the secretory component (SC), is cleaved and released in the free form or as a component of secretory IgA or IgM. SC has intrinsic antimicrobial properties and protects secretory IgA (sIgA) and sIgM from proteolytic degradation. Expression of the pIgR is regulated by microbial products via Toll-like receptor signaling and host factors, such as proinflammatory cytokines. Locally produced and plasma-derived IgG makes its way into the lumen via paracellular pathways and by active shuttling mediated by the neonatal Fc receptor; antigen molecules captured at the luminal surface may then be transported into the mucosa, where they may be sampled by local dendritic cells (DCs), leading to their activation and interaction with cognate T cells either in situ or following DC migration to the mesenteric lymph nodes. A similar cycling of IgE mediated by CD23 also occurs in allergic states, leading to the degranulation of mast cells and a local type I hypersensitivity response. Ig molecules act as a first line of defense, mediating immune exclusion of antigens in the mucus layer. IgA is also thought to bind antigens in the lamina propria, "excreting" them into the lumen, and has an antimicrobial action within the epithelium. (Image reproduced with permission from the contributing author.)

IBD. Tregs playing a role in the immunologic homeostasis of the GI tract include those characterized by constitutive expression of the CD25 and the transcription factor FoxP3 ($CD4^+CD25^+FoxP3^+$), and others characterized by the synthesis of immunomodulatory cytokines, such as IL-10 (Tr1) and TGF-β (Th3). These distinctions are not absolute and cells with overlapping characteristics are described in murine models. The mechanisms responsible for the induction of oral tolerance are believed to be dependent on the feeding protocol used. High doses of oral antigen favor clonal deletion or functional quiescence (anergy) of T cells and low doses favor the induction of Tregs. However, Tregs have been elicited by both low- and high-dose protocols, and the different mechanisms are not mutually exclusive. Oral tolerance suppresses experimental autoimmune diseases following feeding of incriminated antigens. Experimental autoimmune encephalomyelitis, arthritis, and type 1 diabetes mellitus have been prevented or ameliorated in this way. These observations have underpinned clinical trials that have assessed the efficacy of this approach in human patients with type 1 diabetes mellitus, multiple sclerosis, rheumatoid arthritis, and uveitis, but the outcomes of these trials have been variable and somewhat disappointing. Tregs have been identified in dogs[39-43] and in cats in the context of feline immunodeficiency virus infection,[44-48] but little is known about the role of these cells in the canine and feline GI tract. Oral tolerance is readily induced in the dog, a recent study demonstrating that the ingestion of ovalbumin ameliorated conjunctivitis, clinicopathologic markers of asthma, and serum titers of ovalbumin-specific IgE and IgG elicited by ocular and airway provocation of presensitized beagles.[49]

Microbiota and Dysbiosis

The full complexity of the GI microbiota and its profound influence on local and systemic immune responses is now well recognized (see Chapter 2). The majority of bacterial species populating the GI tract cannot be cultured, leading in the past to gross underestimates of the number of organisms and the composition of this population. The total microbial load of the human GI tract (10^{13} to 10^{14} microorganisms) contains more than 100 times as many genes (the "microbiome") as the human genome. People may thus be considered "metaorganisms" with a vast, integrated community of prokaryotic symbionts, commensals, and pathobionts,

which in health remains finely balanced. Absolute numbers of organisms vary from 10^{11} cells/g content in the ascending colon to 10^7 to 10^8 cells/g in the distal ileum and 10^2 to 10^3 cells/g in the proximal ileum and jejunum. Anaerobes are several orders of magnitude more abundant than aerobes and eukaryotic fungal organisms have also been identified as components of the microbiota. More than 99% of the human GI microbiota comprises species within four bacterial phyla (*Firmicutes*, *Bacteroidetes*, *Proteobacteria*, and *Actinobacteria*). Most members of the microbial community are indigenous and stable (autochthonous), but some (e.g., the majority of pathogens) may be transient (allochthonous). General functions of the microbiota in health include the following: (a) the provision of short-chain fatty acids as an energy source and the synthesis of vitamins; (b) the maintenance of local and systemic immune regulation by effects on both the innate and adaptive immune system, including the induction of Tregs; (c) stimulatory and cytoprotective effects on the epithelium, helping to preserve the barrier function of the GI tract; and (d) the competitive exclusion of pathogens. Disturbances in the composition of the microbiota (dysbiosis) that favor pathobionts at the expense of symbionts and commensals are thought to promote intestinal inflammation, leading to IBD in individuals with an appropriate genetic background. Factors that are thought to contribute to dysbiosis include host genetic factors (e.g., mutations in the *NOD2* gene), lifestyle issues (e.g., psychological or physical stress and a poor diet), and medical practices (e.g., excessive antibiotic use and overly stringent sanitation). Whether dysbiosis directly causes disease or merely represents an epiphenomenon of an altered intestinal microenvironment remains unclear, but several lines of evidence point to its pathogenic significance. For example, most studies of human IBD show decreased microbial diversity in active disease, associated with increased relative abundance of the *Enterobacteriaceae* and decreased representation of the *Firmicutes*, with selectively diminished *Clostridium* spp. Some patients with Crohn disease have decreased numbers of *Faecalibacterium prausnitzii*, and the same organism is known to increase the synthesis of IL-10 by human peripheral blood mononuclear cells in culture, decrease the activation of NF-κB and the synthesis of IL-8 by Caco-2 cells, and ameliorate the severity of trinitrobenzene sulfonic acid–induced colitis in mice.

The GI microbiota of dogs and cats in health and disease has now been examined (Fig. 3-3). Interactions of the duodenal microflora with the underlying mucosa were recently investigated in a cohort of 17 client-owned cats with IBD, making comparisons with 10 healthy colony cats.[50] The number of mucosa-associated *Enterobacteriaceae* as determined by fluorescence in-situ hybridization (FISH) with probes to 16S rDNA was higher in cats with GI disease than healthy cats. Furthermore, total numbers of mucosal bacteria were strongly associated with changes in mucosal architecture and the density of macrophage and T-cell infiltrates.[50] The number of *Enterobacteriaceae*, *E. coli*, and *Clostridium* spp. correlated with abnormalities in mucosal architecture, upregulation of mRNA encoding IL-1, IL-8, and IL-12, and severity of clinical signs, raising the possibility that the bacteria contributed to the pathogenesis of IBD in these cats.[50] FISH was also used to explore the fecal microflora in 11 individually housed colony cats with IBD, making comparisons with 34 healthy colony cats. Total bacteria, *Bifidobacterium* spp. and *Bacteroides* spp. were all more abundant in the healthy cats, whereas *Desulfovibrio* spp. (which produce toxic sulfide moieties that may elicit mucosal inflammation) were more abundant in the colitic cats, supporting the notion of dysbiosis in IBD and raising the possibility that bacterial metabolites may directly injure the feline intestinal mucosa.[51]

Similar studies have also been performed in the dog. The first suggestion that the enteric flora could be implicated in the pathogenesis of chronic intestinal inflammation in the dog came with the association of adherent and invasive *E. coli* with histiocytic ulcerative colitis in Boxers,[52] a disease that was previously thought to represent an unregulated, idiopathic immune-mediated response. Moreover, antibiotic therapy was effective in eliciting remission of disease and was associated with the eradication of invasive intramucosal *E. coli*, supporting the notion that the bacteria were involved in its pathogenesis. The microbiota of the duodenum in 10 dogs with IBD was defined by means of 16S ribosomal RNA (rRNA) gene sequencing of brush samples collected during diagnostic endoscopy, making comparisons to nine healthy control dogs.[53] Species richness was significantly lower in dogs with IBD, and was enriched in sequences from the families *Enterobacteriaceae* (the majority classified as *E. coli*–type sequences) and *Clostridiaceae*. Moreover, there was a positive correlation between the number of clones belonging to the family *Clostridiaceae* and clinical severity score, and a trend between the number of clones belonging to the family *Enterobacteriaceae* and histopathologic severity.[53] These data suggest that imbalances of the intestinal microbial community may occur in canine IBD; however, remaining questions include the following: (a) What is the impact of breed on determinations of microbial diversity? (b) What are the specific organisms associated with IBD versus other intestinal diseases? and (c) What is the primary or secondary pathogenic significance of dysbiosis in canine IBD?

Increasing awareness of the role of dysbiosis in the pathogenesis of intestinal and extraintestinal diseases has driven a globally concerted effort to manipulate the GI microflora for therapeutic gain, by means of antibiotics, prebiotics, probiotics, and synbiotics (mixtures of pre- and probiotics). Among these strategies, probiotics have attracted considerable commercial interest in human and veterinary medicine, despite often sparse research substantiating their benefit. Proposed mechanisms of probiosis include remodeling of microbial communities and suppression of pathogens; upregulation of antiinflammatory factors such as TGF-β and IL-10 produced by mononuclear cells; downregulation of proinflammatory factors such as TNF-α and IL-8 produced by epithelial cells; promotion of tolerogenic DCs and induction of Tregs; and preservation of intestinal barrier function. Human GI diseases in which probiotics have elicited beneficial responses include acute gastroenteritis, antibiotic-associated diarrhea and colitis, IBD, irritable bowel syndrome, and necrotizing enterocolitis. Various organisms with potential probiotic qualities (e.g., species specificity, nonpathogenicity, resistance to digestion by gastric acid and intestinal enzymes, and ability to adhere to the intestinal epithelium and influence host immune responses) have been identified in dogs[54-58] and cats,[59-61] offering promise in the treatment of GI diseases in these species.[62] For example, a probiotic cocktail of *Lactobacillus acidophilus* (strains NCC2628 and NCC2766) and *Lactobacillus johnsonii* (NCC2767), originally derived from fecal isolates of dogs without GI signs, was able to increase tissue mRNA and supernatant protein concentration of IL-10, and to decrease the ratio of TNF-α/IL-10, IFN-γ/IL-10, and IL-12p40/IL-10 tissue mRNA in duodenal biopsies derived from dogs with chronic enteropathies, when cultured with the probiotic cocktail in vitro for 20 hours.[63] However, the same cocktail yielded less-convincing results when administered to dogs with food-responsive diarrhea alongside an elimination diet for 4 weeks. Followup biopsies failed to show an increase in regulatory cytokine mRNA in the dogs treated with probiotics, but the influence of the probiotic might already have occurred by the time the follow up biopsies were collected.[64] Both the probiotic and placebo

Figure 3-3 Granulomatous colitis of Boxer dogs is characterized by a mucosally invasive microflora. Granulomatous colitis (GC) of Boxer dogs, also known as histiocytic ulcerative colitis, typically affects individuals younger than 5 years of age and is characterized by hemorrhagic, mucoid diarrhea, anemia, hypoalbuminemia, weight loss, and thickening and ulceration of the colon with loss of epithelium and goblet cells and the accumulation of periodic acid-Schiff (PAS)–stained macrophages. It has features in common with ulcerative colitis, including its macroscopic appearance, regional distribution, and immunopathology; Crohn's disease, including its predominantly granulomatous nature, the presence of bacteria within macrophages, and the clinical response to fluoroquinolones; and Whipple disease, including the accumulation of PAS-positive macrophages. Recent years have seen significant advances in our understanding of this disease, which is thought to involve adherent and invasive *Escherichia coli*. One of the tools used to explore this disease and others in veterinary gastroenterology is fluorescent in-situ hybridization (FISH) with probes to conserved and variable regions of the ribosomal 16S subunit. **(A)** The eubacterial probe *EUB-338* (GCTGCCTCCCGTAGGAGT) has been applied to examine the distribution of bacteria within colonic biopsies from Boxer dogs with GC. Bacteria within the normal colon, identified by means of epifluorescence microscopy using the probe cyanine (Cy) 3-*EUB-338* (*red; arrows*), are confined to the surface mucus layer and colonic glands; nuclei are stained blue in this section by means of 4′,6-diamidino-2-phenylindole (DAPI) (×400). **(B)** In GC of Boxer dogs, clusters of bacteria hybridizing with Cy3-*EUB-388* (*red*) are scattered throughout the upper third of the mucosa, clumps of small coccobacilli (1 to 3 μm) most commonly observed in areas in which goblet cells and glands are replaced by a cellular infiltrate (×400). **(C)** Bacteria may often be found within cells, identified here with Cy3-*EUB-338* (*red*) and fluorescein isothiocyanate (FITC)–antivimentin (*green*), labeling nuclei with DAPI (*blue*; n = nucleus) (×600). **(D)** Gram staining reveals that the invasive bacteria are Gram-negative coccobacilli within macrophages (*arrows*) (×1000). Further studies, including culture of affected mucosa, 16S sequencing, and FISH with specific probes, suggested that the bacteria incriminated in GC of Boxer dogs are adherent and invasive *E. coli* resembling the *E. coli* associated with Crohn's disease. (The work illustrated in this figure was performed in the laboratory of Dr. K. Simpson, College of Veterinary Medicine, Cornell University; the images have been reproduced from *Infection and Immunity* 74:4778, 2006 with permission from the American Society for Microbiology.)

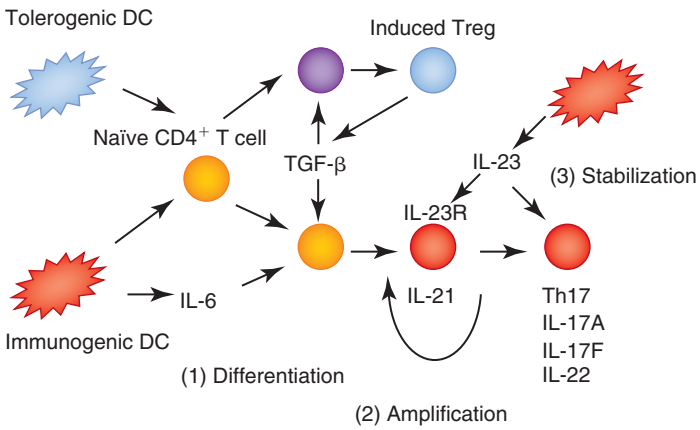

Figure 3-4 Steps in the differentiation of Th17 cells. (1) The activation of naive T cells in the presence of TGF-β and IL-6 initiates the Th17 differentiation pathway; more recently, TGF-β in combination with IL-21 was also shown to induce the differentiation of Th17 cells. The cellular source of these cytokines remains controversial: although IL-6 is produced by activated antigen-presenting cells (e.g., dendritic cells; DCs) on engagement of specific pathogen-recognition receptors (e.g., Toll-like receptors) and IL-21 may be produced by natural killer (NK) and NK T cells in the absence of IL-6, the source of TGF-β could be either Tregs present in the same microenvironment (as illustrated) or the DCs stimulating Th17 differentiation. (2) IL-21 is an important cytokine produced by Th17 cells themselves, amplifying their generation in an autocrine manner and inducing the expression of the IL-23 receptor. IL-23 expands and stabilizes Th17 cells, which express IL-17A, IL-17F, and IL-22, in addition to IL-21. Signal transducer and activator of transcription (STAT) 3 plays a critical role in Th17 differentiation, as IL-6, IL-21, and IL-23 all depend on this factor for intracellular signaling. In contrast to other lymphoid sites, the gastrointestinal immune system is able to support the constitutive differentiation of Th17 cells. Thus, $CD103^-$ ($\alpha_E\beta_7^-$) and $CD103^+$ ($\alpha_E\beta_7^+$) DC subsets in the intestine and mesenteric lymph nodes direct the differentiation of Th17 cells and Tregs respectively, attributed to the ability of $CD103^-$ DCs to produce large amounts of IL-6 but small amounts of TGF-β, and vice versa for $CD103^+$ DCs. While the differentiation of Th17 cells and Tregs is generally thought to proceed in a reciprocal fashion, parallel differentiation in the GI tract may occur.[217] Both Th1 and Th17 cells are implicated in Crohn's disease, but Th17 cells have not yet been explored in dogs and cats. (Image reproduced with permission from the contributing author.)

groups showed a decrease in the number of colony-forming units of *Enterobacteriaceae* per milliliter of fecal material after 4 weeks, concordant with other studies in dogs implicating this family of bacteria in the pathogenesis of chronic enteropathies.[64] Furthermore, a recent study failed to demonstrate any benefit of the immune-enhancing probiotic *Enterococcus faecium* strain SF68 in dogs with chronic, naturally acquired, subclinical giardiasis, in contrast to its ability to decrease giardial cyst shedding and antigen load in rodents.[65] This probiotic has yielded variable results in cats, appearing to ameliorate the morbidity associated with chronic felid herpesvirus-1 infection in experimental, group-housed cats in one study,[61] but failing to alter immune parameters (other than increasing the percentage of peripheral $CD4^+$ lymphocytes) in another.[60] Fewer studies of probiotics have been performed in cats than dogs, but *L. acidophilus* strain DSM13241 has shown promising results in healthy adult cats, increasing the number of beneficial *Lactobacillus* spp. and decreasing the numbers of *Clostridium* spp. and *Enterococcus faecalis* in feces. Furthermore, phagocytic activity of peripheral granulocytes was increased and plasma endotoxin concentration and erythrocyte osmotic fragility were decreased in cats receiving this probiotics.[59] A number of studies have also shown the potential benefit of prebiotics based on the fructan sources inulin and fructooligosaccharides[66] on the intestinal microflora and selected metabolic and immunologic parameters of dogs[67-72] and cats.[73]

Inflammatory Pathomechanisms

In genetically predisposed individuals, tolerance of dietary antigens may break down and lead to the development of Th2-mediated food allergies, characterized by the excessive production of IgE.[74-76] Similarly, defective tolerance of the intestinal microflora contributes to the pathogenesis of IBD, including human Crohn disease (a transmural granulomatous ileocolitis that may be segmental, but which often involves the terminal ileum) and ulcerative colitis (a superficial ulcerative disease of the colon and rectum, with lamina propria infiltration by neutrophils and microabscessation). Crohn disease is generally thought to be driven by Th1 inflammation and ulcerative colitis by Th2, but increasing awareness of the role played by IL-23 and Th17 cytokines in GI homeostasis and inflammation has led to a revision of this simplified viewpoint. IL-23 is a heterodimeric cytokine belonging to the IL-12 family and comprising the subunits IL-12p40 and IL-23p19. IL-23 is an essential component of the mucosal protective immune response, particularly against bacterial infection, but when high concentrations are maintained for extended periods, the associated chronic inflammation may contribute to the pathogenesis of IBD. Produced by DCs in response to microbial stimulation, IL-23 plays a role in the expansion and maintenance of Th17 cells, a novel population of $CD4^+$ T cells whose differentiation is dependent on the presence of IL-6 and TGF-β (Fig. 3-4). The LP is enriched in Th17 cells, which are thought to play both tissue-protective and proinflammatory roles in the GI tract. Th17 cells are somewhat heterogeneous and show a degree of phenotypic plasticity and are capable of producing a range of cytokines including IL-17A, IL-17F, IL-21 and IL-22. IL-17A is thought to mediate a protective role during acute intestinal inflammation (e.g., by stimulating the expression of enterocyte claudin proteins, thereby leading to the formation of tight junctions and augmenting epithelial barrier function), while IL-17F appears to play a pathogenic, proinflammatory role (e.g., $IL\text{-}17F^{-/-}$ mice show reduced susceptibility to dextran sulphate sodium [DSS]-induced colitis compared with wild-type mice). IL-21 amplifies the induction of Th17 cells in an autocrine manner and pathophysiologic functions of IL-21 in the GI tract include the following: (a) enhancement of IFN-γ synthesis by Th1 and natural killer (NK) cells; (b) stimulation of fibroblast synthesis of matrix metalloproteinases (MMPs), which promote tissue damage by cleaving components of the extracellular matrix; (c) enhancement of epithelial synthesis of macrophage

inflammatory protein-3α (CCL20), a chemoattractant that draws T cells into the lamina propria; and (d) mediation of conventional T-cell resistance to the suppressive influence of Tregs. IL-22 is a member of the IL-10 family and has both pro- and antiinflammatory functions in the GI tract. The IL-22 receptor complex is expressed by nonhemopoietic cells (e.g., epithelial cells of the intestine, skin, and lungs) and is thought to have a role in the promotion of innate tissue defenses. This cytokine is also synthesized by DCs, which are thought to be its principal cellular source during the early phase of infection with attaching and effacing bacterial pathogens. IL-22 targets intestinal epithelial cells, inducing their expression of antimicrobial peptides such as members of the RegIII family; S100A8 and S100A9, components of the heterodimeric protein calprotectin; and β-defensin, a cysteine-rich cationic protein. It also increases the proliferation and migration of enterocytes and helps to restore goblet cells, thus enhancing mucus production, all suggesting a role in restitution of the epithelial barrier. However, IL-22 may also have a proinflammatory role in certain contexts, in vitro studies demonstrating that it increases the expression of IL-8 and TNF-α by enterocytes, and proinflammatory cytokines, chemokines, and MMPs by colonic myofibroblasts. Hence, its role in chronic intestinal inflammation remains unclear. Indeed, it is hard to reconcile its antiinflammatory properties in the murine DSS and T-cell receptor $(TCR)^{-/-}$ models of colitis with its high level of expression in murine T-cell transfer colitis and active Crohn disease. Further work needs to be undertaken to define its role in IBD more clearly and to ensure that therapies targeting IL-22 in chronic disease do not result in enhanced susceptibility to mucosal infections.

Oral tolerance has been demonstrated in the dog[49] and similar pathomechanisms to those of human IBD are believed to occur in canine patients with this disease.[77] Although little mechanistic information is currently available in companion animals, several studies have characterized the cells and cytokines expressed within the canine and feline GI tract in both healthy animals and those with IBD (Fig. 3-5).[4,5,78] An immunohistochemical study revealed increased numbers of LP T and B cells, and glandular epithelial T cells, in colonic biopsies of dogs with IBD when compared with sections from control dogs without GI signs.[79] Similarly, increased densities of IgG^+, $IgG3^+$, and $IgG4^+$ plasma cells, T cells, MHC class II^+ cells, and macrophages were observed in the colonic LP of Boxer dogs with histiocytic ulcerative colitis (HUC) when compared with colonic tissue from control animals and nonlesional colon; furthermore, there were fewer goblet cells within the epithelium of HUC patients and increased intensity of MHC class II expression by enterocytes.[80] An immunohistochemical study of duodenal biopsies from dogs with IBD revealed increased densities of LP IgG^+ plasma cells, T cells, macrophages and neutrophils, and increased intraepithelial $CD3^+$ T cells.[81] More subtle changes, limited to the epithelium, were detected in dogs with "nonspecific dietary sensitivity," which showed increased proportions of $CD45^+$ and $CD4^+$ cells, but decreased proportions of $CD8^+$ IELs in the duodenum and increased proportions of $CD45^+$ and $CD3^+$ IELs in the colon.[82] In both regions of the intestine, LP populations were not altered in the dogs with nonspecific dietary sensitivity.[82] Studies interrogating the cytokines expressed by the GI mucosa have yielded variable results: semiquantitative RT-PCR assays of mucosal biopsy homogenates have suggested increased expression of mRNA encoding IL-2, IL-5, IL-12p40, TNF-α, and TGF-β in the duodenum of German Shepherd dogs with IBD or antibiotic-responsive diarrhea (formerly "small intestinal bacterial overgrowth")[83] and increased expression of mRNA encoding IL-2 and TNF-α in the colon of dogs with idiopathic lymphoplasmacytic colitis.[84] However, a more recent quantitative (real-time) RT-PCR approach failed to demonstrate differences in the abundance of transcripts encoding IL-2, IL-4, IL-5, IL-6, IL-10, IL-12, IL-18, IFN-γ, TNF-α, and TGF-β in the duodenum of German Shepherd dogs and other breeds with chronic enteropathies compared with control dogs without diarrhea.[85] Comparable studies have been performed in the cat, revealing a subtle IBD phenotype characterized

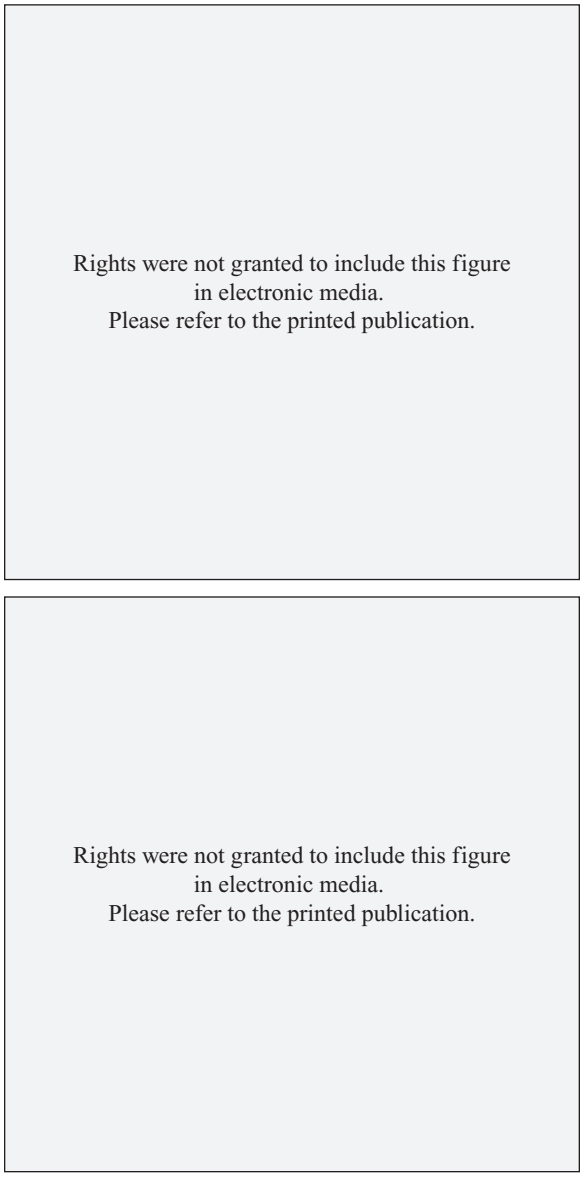

Figure 3-5 "Physiologic inflammation" in the healthy canine small intestine. Expression of mRNA encoding **(A)** IFN-γ and **(B)** IL-10 within the jejunal mucosa of a healthy Irish Setter (i) and Beagle (ii), as detected by in-situ hybridization, is shown. Positive labeling, represented in black, is apparent in the lamina propria (LP) of both breeds, although Beagles tend to show more pronounced labeling for both cytokine mRNA species in this study.[78] Epithelial labeling is also apparent, most clearly observed in the current sections for IL-10 in the Beagle, although other sections in the same study also showed epithelial expression of IFN-γ in both Beagles and Irish Setters.[78] This study and others suggest that healthy canine intestinal mucosa is characterized by the expression of a mixture of both pro- and antiinflammatory cytokines, some of which may be derived from the epithelium, in common with observations made in other species. (Images derived from Garden OA et al., *Vet Immunol Immunopathol* 70:1, 1999 and reproduced with permission from Elsevier.)

by increased density of LP MHC class II$^+$ cells (DCs and macrophages) and more pronounced MHC class II expression by duodenal enterocytes.[86] There were no differences in the LP densities of IgA$^+$ and IgG$^+$ plasma cells, or CD3$^+$ T cells, in the duodenum of enteropathic and control animals.[86] Quantitative RT-PCR revealed greater abundance of mRNA encoding IL-6, IL-10, IL-12p40, TNF-α, and TGF-β in the duodenum of cats with IBD, suggesting a complex phenotype involving the concurrent upregulation of proinflammatory and immunoregulatory cytokines.[87]

In summary, a unifying model of IBD in dogs and cats remains elusive, but recent studies provide some intriguing new clues, including the likely role of the intestinal flora. P-glycoprotein overexpression may also be implicated in the development of steroid-refractory canine IBD[88] and ciclosporin may be a useful immunosuppressive drug in these patients.[89] Significant progress has been made in recent years and the future is likely to yield exciting developments in this dynamic field of clinical research, leading to a greater understanding of the pathogenesis of chronic enteropathies in small animals and in turn novel therapeutic strategies.

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CHAPTER 4

Gastrointestinal Inflammation

Michael J. Day

The fundamental biology of the acute and chronic inflammatory responses is well described in numerous texts.[1,2] Acute inflammation occurs within hours to days of exposure to an inciting trigger and is characterized by changes such as vasodilation, tissue edema and protein exudation, neutrophilic exocytosis, and the release of a wide range of cell-derived preformed or newly synthesized inflammatory mediators. By contrast, the chronic inflammatory response generally occurs subsequent to this acute reaction (over weeks to months) or may have a distinct inciting trigger. Chronic inflammation involves tissue infiltration by mononuclear inflammatory cells (macrophages with formation of multinucleate giant cells, lymphocytes, and plasma cells) with production of a separate range of proinflammatory mediators, cytokines and chemokines. The chronic inflammatory response may incorporate aspects of tissue necrosis and remodeling involving stromal growth factors, matrix metalloproteinases and their inhibitors, and progress to the formation of granulation tissue and organized fibrosis.

These various inflammatory processes may all be recognized in the gastrointestinal tract at all levels from the oral to anorectal mucosa. Alimentary inflammation may be recognized clinically or perendoscopically, but definitive characterization of the inflammatory response requires mucosal biopsy and microscopic assessment of tissue changes. Gastrointestinal inflammation is generally categorized according to the identity of the dominant infiltrating population as neutrophilic, granulomatous, pyogranulomatous, eosinophilic, or lymphoplasmacytic. However, in reality there is a broad spectrum of inflammatory change and mixed inflammatory reactions are often observed. For example, significant elevation in the number of mucosal eosinophils may often accompany lymphoplasmacytic reactions, or foci of neutrophilic inflammation may occur within an otherwise chronic mononuclear cell infiltrate.

The challenge of interpretation of alimentary inflammation is compounded by the intrinsic relationship between the immune and inflammatory responses in these mucosal tissues. The gastrointestinal mucosae are normally populated by large numbers of leukocytes involved in the provision of innate and adaptive immune surveillance.[11,12,15,51] These cells may be diffusely present throughout the lamina propria or marshalled into organized lymphoid structures and their function is described elsewhere in Chapter 3. These immune populations are designed to respond to the plethora of antigenic substances that naturally pass over the mucosal surface, although the outcome of such responses may be immunologic tolerance rather than activation of protective immunity. Many of these lymphoid responses are therefore regarded as physiologic rather than pathologic, so a major complication in interpreting gastrointestinal inflammation is distinguishing between cellular proliferation occurring to maintain homeostasis *versus* proliferation indicating a true inflammatory reaction.

It remains the case that our assessment of alimentary inflammation is largely made by subjective evaluation of a hematoxylin and eosin (H&E)-stained section of biopsy tissue. As is discussed in Chapter 29, this observational process is fraught with potential pitfalls, largely relating to lack of standardized criteria, which define changes consistent with inflammation and distinguish these from baseline physiological infiltration. To that end, the World Small Animal Veterinary Association (WSAVA) Gastrointestinal Standardization Group recently proposed histologic guidelines by which gastrointestinal inflammatory responses may be interpreted in a more standardized fashion.[10]

In the research laboratory, it has become possible to more rigorously define alimentary inflammatory processes by the application of immunohistochemical phenotyping of mucosal leukocyte subpopulations and enumeration of these per unit area of mucosa. Flow cytometric analysis of disaggregated mucosal biopsies has also been employed for the phenotypic characterization of intraepithelial and lamina propria leukocytes.[45,55] Additionally, immunohistochemical, biochemical or molecular tools have been used to characterize the local tissue production of proinflammatory mediators including cytokines, chemokines, and matrix metalloproteinases. Preliminary studies now report the role of "pattern recognition receptors" (PRRs) expressed by antigen-presenting cells (APCs) in the initial interaction between pathogens and the alimentary immune system. For example, cultured canine colonic epithelial cells express both membrane (Toll-like receptors 2 and 4) and intracytoplasmic (nucleotide-binding oligomerization domain [NOD]2) PRRs, and when stimulated by appropriate ligands (lipopolysaccharide or peptidoglycan) display upregulation of genes encoding the cytokines interleukin (IL)-7 and IL-8.[50] These PRRs are also naturally expressed within the canine intestinal mucosa.[24,28] Despite these advances, there remains much to learn about canine and feline alimentary inflammation. For example, the interaction between an array of neuropeptides and the intestinal immune and inflammatory processes remains to be investigated. Dogs and cats appear to lack Paneth cells of the basal crypt region of the intestine that in other species have a major role in the production of assorted bacteriocidal toxins (lysozyme, defensins) and may act to protect the adjacent crypt epithelia. Whether these species have an alternative source of these key inflammatory mediators is also unknown. The application of immunohistochemical and molecular techniques to the study of canine and feline gastrointestinal inflammatory disease are

described using selected clinical examples in the sections that follow.

Oral Inflammation

The oral cavity is an anatomical site predisposed to continual inflammatory change by factors such as high antigenic exposure (to food or microbial flora), physiologic microtrauma related to prehension and mastication of food, and the range of dental pathology to which small companion animals appear susceptible. Underlying systemic pathology (e.g., uremia) may also contribute to the likelihood of clinical expression of oral inflammation.

One of the most severe and clinically challenging examples of oral inflammatory disease is feline chronic gingivostomatitis. This disorder likely has multifactorial etiopathogenesis involving dental disease, feline calicivirus infection, oral bacterial infection, and the exuberant mucosal immune response to assorted antigenic materials. The histopathologic appearance is of a severe, predominantly plasmacytic inflammatory reaction with the presence of distinctive large plasma cells (Mott cells) containing an accumulation of immunoglobulin protein as cytoplasmic Russell bodies (Fig. 4-1). Other cell types may also be part of this mucosal infiltrate, particularly lymphocytes and eosinophils.

Recent immunohistochemical investigations have characterized the normal baseline resident leukocytes in the feline oral mucosa[20] and defined how these alter in this chronic inflammatory process. The mucosal infiltrates in cats with chronic gingivostomatitis are dominated by immunoglobulin (Ig) G plasma cells and recently emigrated myelomonocytic cells expressing the marker MAC387. There are also appreciable numbers of $CD3^+$ T lymphocytes, and of these, $CD8^+$ cells dominate over $CD4^+$ T cells with a median CD4-to-CD8 ratio of 0.22. Surprisingly few IgM or IgA plasma cells, and sparse mast cells, are present in these lesions. APCs expressing class II molecules of the major histocompatibility complex (MHC) are also present, principally forming a subepithelial and perivascular network.[19] This reaction has been functionally categorized as a mixed T-helper 1 (Th1) and Th2 immune response by analysis of tissue cytokine gene expression,[22] and affected cats are also known to have alterations in salivary immunoglobulin concentrations (elevated IgG and IgM with decreased IgA).[21]

Gastric Inflammation

The etiopathogenesis of gastritis has been relatively poorly studied in small companion animals. It is clear that the gastric mucosa has a normal complement of resident leukocytes that maintain immune surveillance and that "gastric lymphoid aggregates" within the lamina propria are a normal feature of the histology of this organ. The follicular microarchitecture and immunophenotype of lymphoid cells within these aggregates has been characterized in the normal dog.[25] As is discussed in Chapter 56, gastritis may be primary in nature, or may occur in association with an inflammatory response in the intestinal tract. Gastritis may have a defined etiology identified from history or clinical examination (e.g., irritant gastritis) or may be classed as idiopathic in nature.

The specific characterization of gastric inflammation relies on examination of biopsy tissue, which is most often collected endoscopically. A thorough histologic examination of the gastric mucosa necessitates collection of biopsy samples from both the fundic and antral-pyloric regions, as lesional change may be recognized in either or both of these sites. The distinct microarchitecture of these anatomical locations means that histologic patterns of inflammatory change may differ, and for this reason the WSAVA Gastrointestinal Standardization Group (see previous discussion) defined specific criteria related to the assessment of inflammatory change in the gastric fundus and antrum.[10]

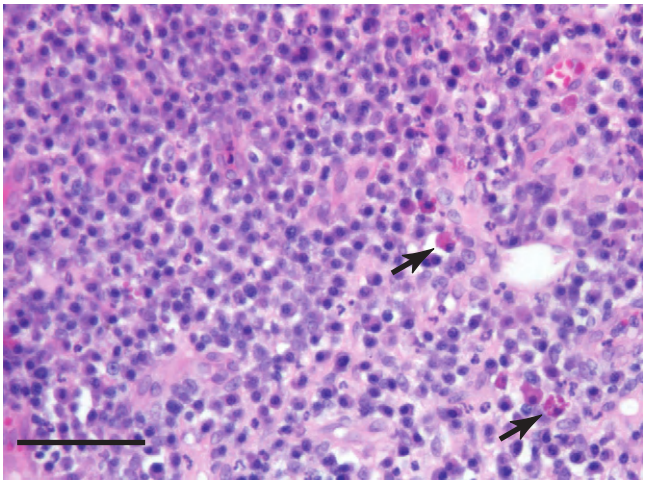

Figure 4-1 Feline gingivostomatitis. Biopsy of gingival mucosa showing an intense inflammatory infiltration dominated by plasma cells. Examples of Mott cells containing cytoplasmic Russell bodies are arrowed. H&E, Bar = 100 μm.

All forms of acute and chronic inflammatory change may be recognized within the gastric mucosa, although lymphoplasmacytic or mixed lymphoplasmacytic and eosinophilic inflammation is probably more commonly noted than neutrophilic, granulomatous, pyogranulomatous, or pure eosinophilic gastritis.[49] Leukocyte infiltration of the lamina propria may be accompanied by microarchitectural disturbances involving the surface epithelium (subtle degenerative change through to ulceration), deep epithelium (degenerative change within the fundus or hyperplasia within the antrum) or glandular tissue ("mucosal atrophy" characterized by fibrosis or "glandular nesting").

Lymphoplasmacytic inflammation is characterized by infiltration of these cell types into the lamina propria and is often accompanied by distinct increases in the number of intraepithelial lymphocytes (IELs) within both surface and deep epithelial structures (Fig. 4-2). In the fundic mucosa, lymphocytes also often infiltrate and apparently disrupt the glandular tissue. It is likely that the majority of these epitheliotropic lymphocytes are $CD3^+$ T cells and probably $CD8^+$ cytotoxic cells, although immunohistochemical characterization has not been widely reported. In humans, this histologic pattern characterizes the autoimmune disease "atrophic gastritis," and although the similarity has been noted, there is no proposal at this time that the canine or feline reaction pattern represents an equivalent disorder. Another distinctive feature of gastric inflammation (particularly lymphoplasmacytic gastritis) in dogs and cats is hyperplasia of the gastric lymphoid aggregates, which may sometimes be extreme and occupy up to 50% of the tissue area of any one biopsy.[35]

One of the most contentious areas in small animal gastroenterology is the debate concerning the role of *Helicobacter* spp. in the induction of gastritis.[37] These distinctive bacteria are frequently noted associated with the surface epithelium and gastric pits of canine and feline tissue biopsies with entirely normal microarchitecture (Fig. 4-3); however, there have been clinical and experimental research studies that have proposed them as an etiologic factor in gastric mucosal inflammation and lymphoid aggregate hyperplasia.[36,41,44] By contrast, other experimental infection studies have not

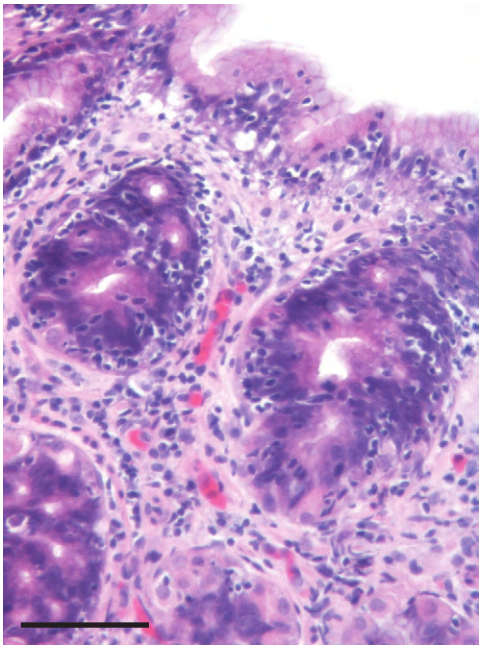

Figure 4-2 Lymphoplasmacytic gastritis. Biopsy of superficial fundic mucosa from a dog with lymphoplasmacytic gastritis. There is mild to moderate infiltration of the lamina propria by a mixed population of lymphocytes and plasma cells. Prominent lymphocytic infiltration of the superficial and glandular epithelium is also seen. H&E, Bar = 200 μm.

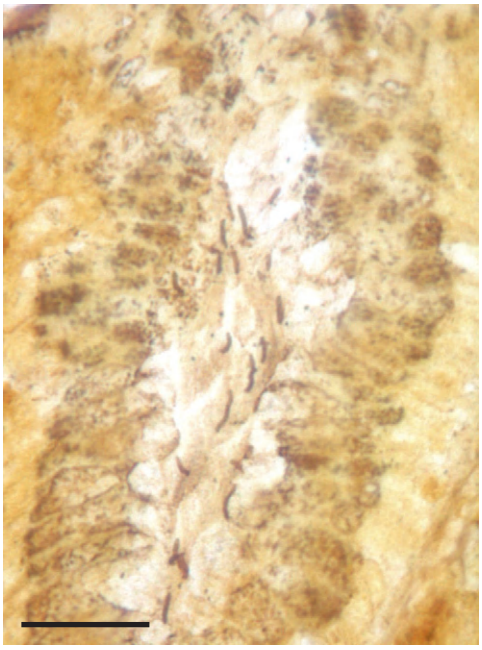

Figure 4-3 Gastric *Helicobacter*. Biopsy of normal canine gastric mucosa showing numerous elongate, spiral-shaped bacteria within the lumen of this gastric pit. There is no association with an inflammatory response in this case. Warthin Starry silver stain, Bar = 50 μm.

shown an association between infection and gastric pathology.[43] A recent investigation of 30 dogs with lymphoplasmacytic gastritis identified *Helicobacter* in 77%, but there was no correlation between infection and the severity of inflammatory change. The same study quantified cytokine gene expression within these mucosal biopsies and identified a Th1-skewed profile with expression of IL-1β, IL-8, IL-10, transforming growth factor (TGF)-β, and interferon (IFN)-γ, but lack of IL-4 transcription. Expression of IL-10 and IFN-γ was most closely associated with the presence of lymphoplasmacytic infiltration.[53] There remains little definitive evidence that *Helicobacter* have a significant role in the development of canine and feline gastritis.

Small Intestinal Inflammation

Small intestinal inflammation in dogs and cats may involve any level of this structure (duodenum, jejunum, or ileum) or may be a diffuse change that can also affect the stomach and colon concurrently. As above, inflammatory change in this organ is generally assessed by microscopic examination of tissue biopsies and these are most often collected endoscopically. For this reason, in many patients only the duodenal mucosa is assessed, despite the fact that it is possible to collect perendoscopic tissue samples from the ileum. Recent investigations have examined the correlation between duodenal and ileal pathology within the same patient, and suggested that duodenal samples may not be an adequate reflection of pathologic change that may be occurring in the distal small intestine.

Small intestinal inflammation in these species is most often lymphoplasmacytic or mixed lymphoplasmacytic and eosinophilic in nature, but eosinophilic, neutrophilic, or pyogranulomatous enteritis is also recognized.[23,31,54] Inflammatory infiltration of the villus or pericryptal lamina propria and elevation in the number of IELs is generally accompanied by a range of microarchitectural changes. These are described in greater detail elsewhere (see Chapter 29), but include villus stunting and fusion, epithelial degeneration to ulceration, cryptal dilation, distortion or crypt abscessation, or mucosal fibrosis.

The nature of the inflammatory infiltration provides guidance on the possible etiology of the intestinal disease. Superficial neutrophilic enteritis is most consistent with an infectious causation whereas eosinophilic enteritis is generally interpreted to suggest parasitic infestation or disease involving a type I hypersensitivity reaction (dietary hypersensitivity). Pyogranulomatous inflammation may trigger a search for particular classes of pathogen or discrete microgranulomata may be associated with blockage of lacteal outflow and the development of lymphangiectasia. Lymphoplasmacytic inflammation (Fig. 4-4) is the hallmark of idiopathic inflammatory bowel disease (IBD), but may also occur in dietary hypersensitivity or in dogs with antibiotic responsive diarrhea (ARD; also small intestinal bacterial overgrowth, SIBO). In the cat, lymphoplasmacytic inflammation of the small intestine may be associated with similar inflammatory disease of the liver and pancreas (colloquially "triaditis").[6]

The recognition of small intestinal inflammation, and particularly lymphoplasmacytic inflammation, is problematic. This relates to the concept discussed above—that the normal small intestinal mucosa is an immunologically active site populated by significant numbers of lymphocytes, plasma cells, and APC that are involved in mediating either tolerogenic or immunogenic responses to luminal antigen. Because of this, it can often be difficult to distinguish between a physiologically reactive mucosa and one undergoing inflammatory change, particularly in the absence of clear evidence of morphologic abnormality. Many clinicians are frustrated by biopsy reports detailing "normal mucosa" in animals with clinical and endoscopic evidence of inflammatory disease. The application of the WSAVA Gastrointestinal Standardization Group criteria for the characterization of duodenal intestinal inflammation[10] may go some

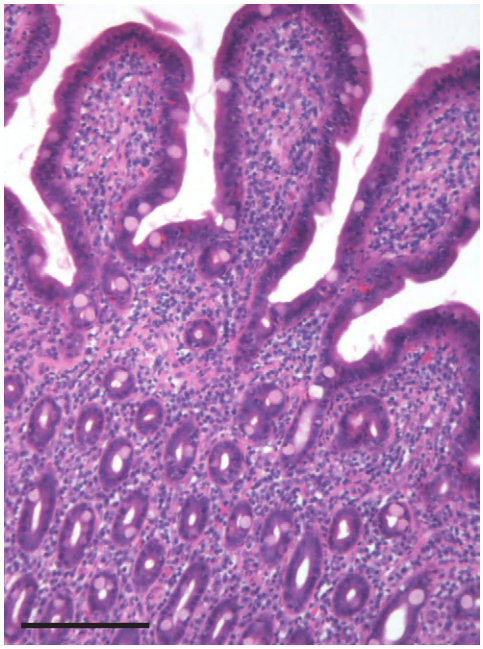

Figure 4-4 Lymphoplasmacytic enteritis. Biopsy from a dog with lymphoplasmacytic enteritis of moderate severity. There is mild to moderate villus stunting without significant epithelial damage. There is prominent infiltration of the villous and pericryptal lamina propria by a mixed population of lymphocytes and plasma cells. The crypts are cut in cross-section as a consequence of the orientation of the biopsy, but are more widely separated than normal by the inflammatory infiltration. H&E, Bar = 500 μm.

way toward providing a more consistent approach to microscopic diagnosis.

At the research level, many recent advances have been made in further understanding the nature of lymphoplasmacytic inflammation in the small intestine of the dog and cat. Even where H&E-stained sections of tissue biopsies may appear morphologically normal, immunohistochemical evaluation of cellular subpopulations has revealed subtle changes. The lamina propria of dogs with IBD is characterized by an elevation in IgG plasma cells, $CD4^+$ T lymphocytes bearing the αβ T-cell receptor (TCR) and myelomonocytic cells expressing MHC class II or MAC387. Additionally, there is an elevation in intraepithelial T cells and a reduction in mucosal mast cells in canine IBD. By contrast, in dogs with ARD the dominant changes are an elevation in IgA plasma cells and $CD4^+$ T cells.[13] Such findings are not always consistent between different studies; for example, one investigation failed to demonstrate increases in villus T cells, IgA, and IgG plasma cells in dogs with IBD, and in fact showed that the number of villus T cells was lower in dogs with IBD than in healthy animals.[32]

Assessment of functional aspects of the immune and inflammatory response by measurement of cytokine gene expression has proven more challenging in these canine diseases. Early investigations using conventional reverse transcriptase polymerase chain reaction (RT-PCR) technology suggested a mixed Th1 and Th2 cytokine profile in both canine enteropathies,[16] but subsequent studies employing more sensitive real-time RT-PCR failed to distinguish between samples from clinically normal and diseased dogs.[39] Genes encoding some types of nuclear transcriptional receptors are upregulated in some dogs with inflammatory enteropathy.[17] Expression of the epithelial drug efflux pump protein P-glycoprotein has been examined in the mucosa of dogs with IBD. Those animals that make a clinical response to prednisolone therapy have low baseline expression of P-glycoprotein, and this is seen to be upregulated in biopsies from these dogs taken posttreatment.[3] Expression of candidate genes involved in postinflammatory repair processes has also been examined in dogs with inflammatory enteropathies. In the duodenum of dogs with food-responsive diarrhea or IBD there is upregulation of messenger RNA (mRNA) expression encoding the growth hormone receptor and insulin-like growth factors-1 and -2.[46]

Recent studies also have evaluated systemic markers of inflammation in dogs with IBD (both small and large intestinal). Assessment of a range of serum acute-phase proteins (C-reactive protein, haptoglobin, α_1-acid glycoprotein, and serum amyloid A) revealed elevation of C-reactive protein in patients with IBD,[33] although this was not replicated in a second study.[5] Similarly, an association between canine IBD and the presence of serum perinuclear antineutrophil cytoplasmic antibody (pANCA) has been demonstrated.[4,5] Measurement of serum neutrophil elastase concentration also is being examined as a potential marker for intestinal inflammation in the dog.[47]

Similar investigations have occurred with samples from cats with idiopathic IBD. In this instance there were no significant differences between normal and diseased cats with respect to the numbers of lamina propria IgG or IgA plasma cells, $CD3^+$, $CD4^+$, or $CD8^+$ T cells or leukocytes expressing the MAC387 antigen. The most striking distinction was marked elevation in MHC class II expression in diseased cats—particularly by enterocytes.[52] A unique difference between the small intestine of dogs and cats is the constitutive expression of MHC class II by canine enterocytes versus induced expression of this molecule in inflammatory or neoplastic disease of the cat. Also in contrast to the dog, studies of cytokine gene expression by real-time RT-PCR in small intestinal biopsies from cats with lymphoplasmacytic inflammation revealed elevations in transcription of genes encoding IL-6, IL-10, IL-12p40, tumor necrosis factor (TNF)-α and TGF-β. These findings are consistent with a mixed Th1-proinflammatory and immunoregulatory phenotype.[38]

A recent investigation directly addressed the hypothesis that feline IBD involves an interaction between luminal flora and the mucosal immune system. Using fluorescence in-situ hybridization (FISH) to identify and localize various bacterial species within lesional mucosa (n = 17 cats with IBD vs. n = 10 healthy cats), clear associations have been found between bacterial load and location (particularly numbers of *Enterobacteriaceae*, *Escherichia coli*, and *Clostridium* spp.) and clinical signs, histopathologic severity of mucosal lesions, numbers of T cells and macrophages infiltrating the lamina propria, and cytokine gene expression (IL-1, IL-8, and IL-12).[29]

Colonic Inflammation

Colitis in small companion animals may be primary or one part of a diffuse gastrointestinal inflammatory disease. The major microarchitectural changes accompanying colonic inflammation have been defined by the WSAVA Gastrointestinal Standardization Group and include surface epithelial degeneration to ulceration, crypt hyperplasia, dilation, and distortion, and mucosal atrophy and fibrosis.[10] Colitis is most frequently lymphoplasmacytic in nature, but eosinophilic, neutrophilic and pyogranuzlomatous forms are also seen (Fig. 4-5).

Some studies have further investigated the immunologic features of lymphoplasmacytic colitis in the dog. Mucosal biopsies from dogs with lymphoplasmacytic colitis have been reported to have more $CD3^+$ T cells and IgA and IgG plasma cells than those from the colonic mucosa of healthy dogs.[30] However, these findings are inconsistent as another group has reported elevated numbers of mucosal

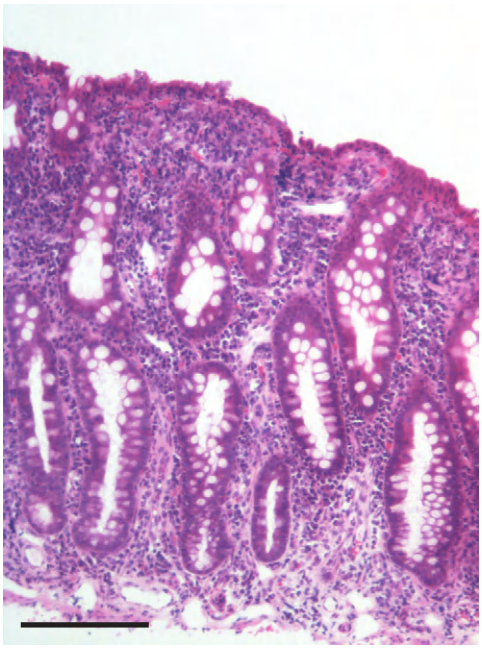

Figure 4-5 Lymphoplasmacytic colitis. Biopsy from a dog with lymphoplasmacytic colitis of moderate severity. The surface epithelium is attenuated and devoid of goblet cells. The crypts are mildly dilated and distorted and there is infiltration of the lamina propria by a mixed population of lymphocytes and plasma cells. The inflammatory infiltrate extends from the superficial lamina propria to the level of the muscularis mucosa. H&E, Bar = 500 μm.

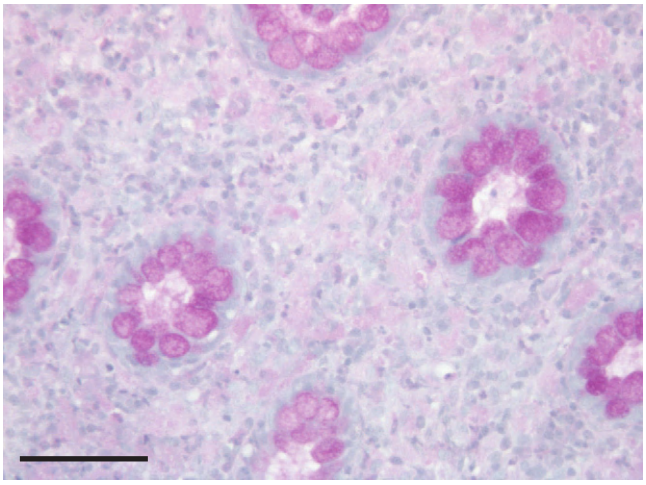

Figure 4-6 Histiocytic ulcerative colitis. Biopsy from the colon of a 3-year-old, female Boxer dog with severe granulomatous inflammation of the mucosa. The section is stained by periodic acid-Schiff, which stains goblet cells in residual crypts and the cytoplasm of macrophages within the lamina propria. PAS, Bar = 100 μm.

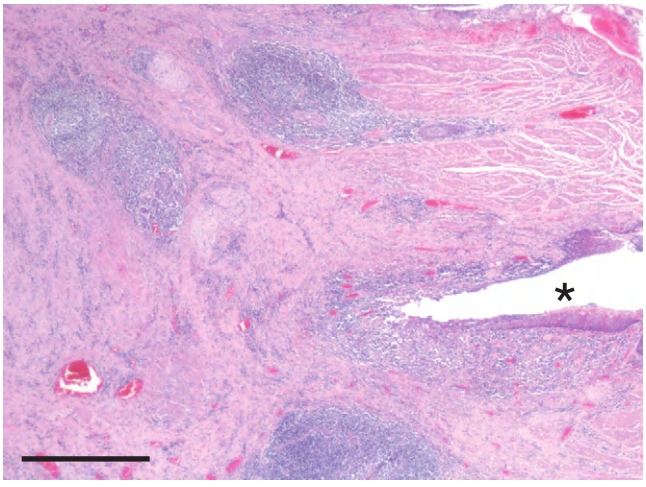

Figure 4-7 Anal furunculosis. Surgical resection of a region of perianal ulceration and sinus tract formation in a 6-year-old, neutered female, German Shepherd dog. Normal perianal structure is replaced by an extensive zone of fibrosis containing series of perivascular lymphoplasmacytic aggregates. At one margin of the image is the termination of a sinus tract (*asterisk*) extending from the perianal surface. This tract is partially lined by degenerate squamous epithelium and there is an intense local mononuclear inflammatory response. H&E, Bar = 1 mm.

T and B cells, but no increase in total plasma cells.[48] Colonic lavage fluids collected from dogs with lymphoplasmacytic colitis have been shown to contain an increased concentration of IgG and nitrite. The latter is a metabolite of nitric oxide, a key inflammatory mediator.[18] Molecular studies have shown upregulation of expression of genes encoding Th1 and proinflammatory cytokines (IL-2, TNF-α) in the mucosa of dogs with lymphoplasmacytic colitis.[40]

Canine pyogranulomatous colitis may be related to specific etiologic agents such as *Histoplasma*. One specific form of canine colitis, histiocytic ulcerative colitis (HUC), has attracted much interest because of the distinct breed association for the disorder (Boxer dogs). Characterized by granulomatous colitis with distinctive macrophages filled with periodic acid-Schiff (PAS)–positive material, this disease was for many years considered to be an idiopathic immune-mediated disorder (Fig. 4-6). Immunohistochemical characterization of lesional colon revealed the presence of infiltrating IgG plasma cells (of the IgG3 and IgG4 subclasses), $CD3^+$ T lymphocytes, $MAC387^+$ myelomonocytic cells, and MHC class II^+ macrophages. There was additional elevation of MHC class II expression by enterocytes.[14] More recent studies have defined HUC as an infectious, rather than immune-mediated, disorder. The clinical responsiveness of these patients to appropriate antimicrobial therapy[7,25] correlates well with the identification of lesion-associated *E. coli* bacteria by FISH.[42]

Rectoanal Inflammation

The most investigated example of inflammatory disease affecting this portion of the canine gastrointestinal tract is anal furunculosis. This enigmatic disorder has long intrigued investigators due to the strong breed predisposition for the German Shepherd dog. This association in a breed also susceptible to the enteropathies described previously, led to early suggestions that a mucosal immunodeficiency might account for the occurrence of this range of disorders. Despite many biochemical and, more recently, molecular studies of the IgA secretion pathway in this breed, there is still little clear evidence for an inherited immunodeficiency related to mucosal IgA production. However, a genetic association between anal furunculosis and a particular allele of an MHC class II gene has been shown.[34]

The inflammatory lesion in canine anal furunculosis is distinctive. Microscopically, there are complex, deep-running sinus tracts (which very rarely fistulate) with a central core of neutrophilic inflammation lined by an intense lymphoplasmacytic infiltration (Fig. 4-7). These tracts often run through extensive zones of fibrosis,

within which may be scattered ectopic (inflammatory) lymphoid follicles.[9] Immunohistochemical characterization of these infiltrates has demonstrated large numbers of IgG, IgM, and IgA plasma cells together with a significant population of $CD3^+$ T lymphocytes.[8] At the functional level, there is molecular evidence for activation of cytokine genes (encoding IL-1, IL-2, IL-6, TNF-α, and IFN-γ) compatible with a proinflammatory and Th1 immune response,[27] and expression of matrix metalloproteinases[26] (MMP-9 and MMP-13) that are likely involved in the tissue remodeling and fibrosis that is a feature of the lesions. These collective observations have led to the hypothesis that inappropriate T-cell activation underlies the pathology of anal furunculosis—and this would certainly be borne out given the dramatic success of systemic cyclosporine therapy in the medical management of this disease. What remains to be definitively shown is the pathogenesis by which these lesions develop. There is little evidence to support the theory that the initiating lesion is anal sacculitis, but histologic and serologic examination does suggest that dermal furunculosis (deep staphylococcal pyoderma) of the haired perianal skin may progress to severe perianal furunculosis.[9]

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CHAPTER 5

Cellular Growth/Neoplasia

Alexandra Sahora and Chand Khanna

The balance between cell growth and death is essential in maintaining tissue and organ homeostasis, even in simple biologic systems. This is of particular importance in specialized organs of high cell turnover such as the gastrointestinal (GI) tract of larger mammals. Several mechanisms of control have evolved within these organs to maintain this balance, including regulators of cell-cycle progression, proliferation, and death. These regulators are influenced by both local (paracrine and autocrine) and systemic (endocrine) signals.[1] Derangements in any of these control mechanisms can result in a disruption of the balance between proliferation and death, often leading to abnormal proliferation and potentially to cancer. The effectiveness of the control mechanisms is evidenced by the relatively infrequent development of cancer of the GI tract despite the extraordinary and diverse requirements for cellular turnover and differentiation of this tissue. This chapter reviews the pathways and processes that control cell growth and proliferation, with specific focus on those that when dysregulated result in cancer of the GI tract.

Overview of Normal Cell Growth and Proliferation

For most cell types, regulation of cell division and replication is a highly conserved continuum with cells traversing through the stages of interphase, mitosis, and cytokinesis (Fig. 5-1). Interphase is defined as the period prior to cell division where the cell grows and replicates its chromosomes in preparation for division by mitosis. For somatic cells, cellular replication is accomplished during mitosis and cytokinesis. The result of mitosis is the generation of two daughter cells (cytokinesis) each with a diploid (2n) genetic constitution. For germline cells that are committed to cellular reproduction, cells exit interphase and enter meiosis. In meiosis, chromosomal numbers within a nucleus are halved (1n) after two cell divisions. Following cytokinesis, two haploid germ cells are available for reproduction.[2]

Interphase

During interphase, cells undergo DNA duplication and a period of extensive RNA, protein, and lipid synthesis. This stage is composed of three signal dependent phases: growth-1 (G_1), synthesis (S), and growth-2 (G_2), that is then followed by mitosis (M) (see Fig. 5-1). Cells that have reached terminal differentiation or the nonreplicating phase, exit from the cycle toward the end of the G_1 phase and arrest in a phase called G_0. Several mechanisms control cell growth and proliferation during the transitions between G_1 and S and between G_2 and M in the cell cycle (also termed *checkpoints*). The key players that are involved in the regulation of these transitions are cyclins and cyclin-dependent kinases (CDKs).[3]

Cyclins and Cyclin-Dependent Kinases

The entry of cells from the phase of mitosis to G_1 involves the presence of progrowth external factors and appropriate internal mitogenic signals. Under circumstances that favor proliferation, the cell cycle progresses as CDKs associate with small intracellular regulatory subunits called cyclins. Cyclins, unlike CDK proteins, have variable expression patterns depending on the cell-cycle phase, acting as a primary level of control for CDK activation. For instance, expression of cyclins A and B is highest at the S/G_2 phase transition, whereas expression of cyclins D and E are highest at G_1/S.[4]

Prior to becoming functional, the cyclin–CDK complexes must become phosphorylated by cyclin-activating kinases (CAKs). This process is site-dependent, meaning that phosphorylation may result in either suppression or activation of the complex, depending on the specific phosphorylated residue.[5] Once activated, the cyclin–CDK complexes can then exert their regulatory control via the phosphorylation of target proteins.

During G_1, cyclin D activates either CDK4 or CDK6, resulting in a functional cyclin–CDK complex. When activated, this complex results in the phosphorylation of several target proteins, including the retinoblastoma protein (Rb).[6] Once the Rb is phosphorylated, the transcription factor E2F is liberated and enables not only the transcription of a variety of genes but also the induction of cyclin E. Cyclin E, in association with CDK2, maintains the Rb in a phosphorylated state. It is the phosphorylation of the Rb that is considered the quintessential final guardian of the transition from G_1 to S phase, and is the critical point at which a cell will move into S phase or into G_0, otherwise known as the *restriction point*. Elevated levels of phosphorylated Rb allow for the accumulation of free E2F, which increases the level of cyclin A and enables the cell to progress into DNA synthesis, or S phase. Cyclin A then plays a critical role in S phase as it interacts with CDK2 and CDK1 while cyclins D and E are concurrently degraded. CDK2 and CDK1 are key for the transition through S phase into M phase, or mitosis. In particular, CDK1, in association with cyclins A and B, is required for the phosphorylation of cytoskeletal proteins necessary for mitosis.[3,7]

In addition to the cell-cycle dependent expression of cyclins, and the regulatory control of the CAKs, the cell cycle is also regulated by the activity of antagonistic cyclin-dependent kinase inhibitors

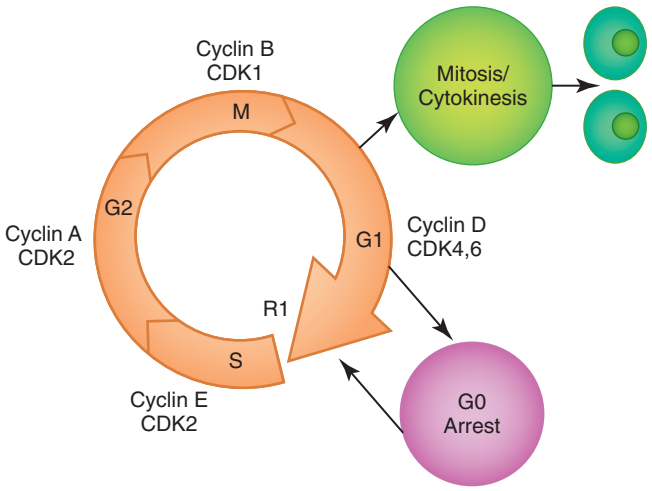

Figure 5-1 The cell cycle. The cell cycle consists of four phases: M (mitosis), G_1 (protein synthesis to prepare for S phase), S (synthesis), and G_2 (protein synthesis to prepare for mitosis). Movement through the cell cycle is tightly regulated by cyclins and cyclin-dependent kinases (CDKs). Retinoblastoma protein (RB) in its active phosphorylated state prevents movement of cells from G_1 to S phase (restriction point; R1) controlling individual cell division. Cells may move out of the cell cycle and arrest (G_0). Following mitosis, the division of cells yielding two progeny results from cytokinesis.

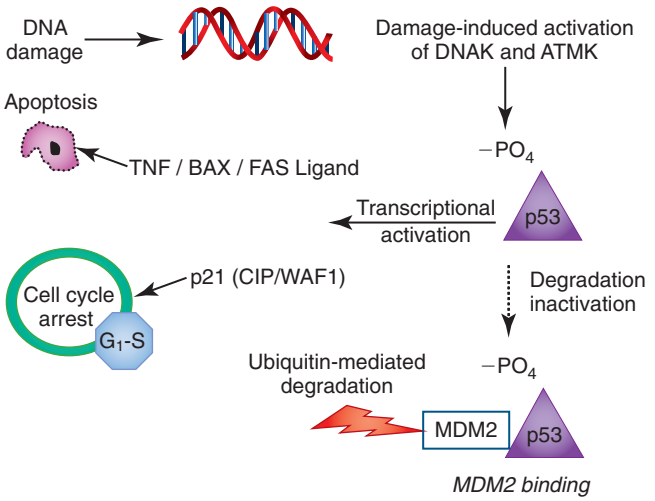

Figure 5-2 p53 regulation and function. In response to DNA damage, the DNA-kinase (DNAK) or ATM kinase (ATMK) phosphorylate p53. This activation step allows p53 to act as a transcriptional activator of genes involved in cell-cycle arrest (p21) and apoptosis (tumor necrosis factor, bax, or Fas ligand). p53 also transcriptionally activates the expression of MDM2, which binds p53, resulting in p53 inactivation and then targets p53 for degradation.

(CDKIs). These proteins block progression of the cell from G_1 to S phase by binding cyclin–CDK complexes and blocking the activation of downstream proteins. Three types of CDKIs are recognized and include the INK4 family, CIP, and KIP.[8] The INK4 family of CDKIs exhibits high specificity for CDK4 and CDK6 complexes, preventing the association of these proteins with cyclin D. CIP (WAF1/p21) is regarded as a general CDK inhibitor, whereas KIP (p27) functions via activation of transforming growth factor (TGF)-β that subsequently prevents the activation of cyclin E/CDK2 and arrests the cell in G_1.[9]

Ligands and Transmembrane Receptors

The internal regulation of the cell cycle is modulated by external and extracellular environmental cues. There are four recognized pathways that play a part in conveying these extracellular messages into the cell: tyrosine phosphorylation; serine and threonine phosphorylation; generation of signaling nucleotides via G-protein-coupled receptors; and production of calcium phosphoinositol through stimulation of phospholipase C.[10] Signaling through these pathways provides a connection between the cell cycle and the environment in which a cell resides. In the presence of growth factors, cells may more easily transition between cellular checkpoints, and in some cases will by influenced toward cellular survival rather than death (discussed below in "Overview of Cellular Death and Apoptosis: The Response to DNA Damage").[11]

Mitosis and Cytokinesis

Once a cell has committed to replicate and surpasses the checkpoints at G_1/S and then G_2/M, it enters mitosis. Mitosis is characterized by cellular DNA replication and segregation, organized in four different phases.[2] Prophase, the first phase of mitosis, involves the replication of chromosomes (4n) and the division of chromosomes into two sister chromatids. These chromatids are joined by a central centromere. In the cytoplasm, centrioles and asters develop and then align at either pole of the nucleus. The nuclear membrane disintegrates at the end of prophase while the centromeres form spindle fibers that will become the organizational scaffolds for chromosomal assembly. In metaphase, the chromosomes are aligned via centriole-spindle fiber interactions on the middle of the spindle, or the metaphase plate. Once aligned, the centromeres split and individual chromatids are segregated to either centriole by the regressing spindle fibers (anaphase). The final phase of mitosis, or telophase, involves the reappearance of the nuclear envelope around each centriole and its associated chromatids. The shared cytoplasm between these two new nuclei is then split (cytokinesis). The maintenance of DNA ploidy, or normal diploid genotype, is critical in mitosis. Aneuploidy, or aberrations in the normal 2n chromosomal number, often resulting from dysregulated mitosis, is a frequent change noted in cancer.[10,12]

Overview of Cellular Death and Apoptosis: The Response to DNA Damage

Exposure to cellular stressors, hypoxia, and toxins can result in damage or changes in the genetic material (DNA) of a cell. In a preserved checks-and-balances system, these changes are identified by a cell and result in its arrest within the cell cycle, most often at a cellular checkpoint. During cellular arrest the damaged DNA is surveyed and repaired. If the damage is determined to be extreme or nonrepairable the cell undergoes controlled cell death (apoptosis). This process of arrest, survey, repair, or death ensures high-quality, mutation-free replication needed for optimal organ homeostasis. Cell-cycle control genes function at each of the cell-cycle cellular checkpoints in a nonmutually exclusive manner. The best-characterized checkpoint gene is the tumor-suppressor gene p53 (Fig. 5-2).[13] The activation of p53 relies upon phosphorylation by either DNA-dependent protein kinase or by ATM kinase in response to cellular damage. Once phosphorylated, p53 functions as a transcriptional activator of multiple cell-cycle regulator genes, including p21 (CIP1/WAF1).[14,15] p53 mediates cell death in part by downregulating the expression of the oncogene bcl2, an inhibitor of apoptosis, which shifts the balance toward cell death. Accumulations in

proapoptotic signals, such as bax, tissue necrosis factor, Fas ligand, and the activation of other oncogenes, also promote cellular apoptosis through p53 regulation.

p53 is also modulated by a variety of proteins to ensure proper function. The gene MDM2 (mouse double minute 2 oncogene) functions as an antagonist to p53.[16] MDM2 can target p53 for degradation by binding the protein and tagging for proteosome-mediated degradation. Conversely, p53 also has a defined binding site in the MDM2 internal promoter that competitively binds free p53. Significant MDM2-p53 binding results in decreased circulating p53, suppressing p53 transcriptional activity.[17] The collective result is that the p53 available for phosphorylation and subsequent transcription of proapoptotic/proarrest proteins drops, favoring cell survival.

The "Cancer Genes": Oncogenes and Tumor-Suppressor Genes

When mutated, certain genes confer malignant characteristics across multiple tumor types. Many of these "cancer genes" have functions related to control of the cell cycle or apoptosis. Two broad categories of cancer genes are known to exist. Oncogenes represent normal genes (protooncogenes) that undergo "gain-of-function" in cancer that contribute to cell proliferation or reduced cell death. Conversely tumor-suppressor genes normally restrain cell proliferation or promote appropriate cell death and undergo "loss-of-function" in cancer.[18]

Oncogenes

Studies of RNA tumor viruses (retroviruses) provided the first evidence that genetic factors play a role in the development of cancer. Rous demonstrated that a retrovirus, now known as avian leukosis virus, was capable of producing lymphoid tumors in chickens.[19] Retroviral sequences that are responsible for transforming properties are called *viral oncogenes* (v-onc). The names of these genes are derived from the tumors in which they were first described (e.g., v-ras from rat sarcoma virus). Subsequently, viral oncogenes were shown to have cellular homologues called *cellular oncogenes* (c-onc).[20] The term *protooncogene* was later used to describe cellular oncogenes that do not have transforming potential to form tumors in their native state but which can be altered to lead to malignancy. Most protooncogenes are complex genes involved in the control of cell growth and proliferation. These genes, when transcribed, represent a variety of proteins, including signaling growth factors, growth factor receptors, protein kinases, signal transducers, and nuclear proteins and transcription factors. Abnormal function/expression of any of these proteins can result in changes that lead to aberrant proliferation.

Growth factors act through transmembrane receptors on the cell surface and trigger the intracellular cascades that ultimately result in cellular proliferation. Overexpression of a growth factor and the abnormal expression of a growth factor by a cell that typically does not produce it represent two ways in which a cellular environment can contribute toward carcinogenesis. Examples of growth factors that are typically expressed by tumor cells are epidermal growth factor (EGF) and fibroblast growth factor (FGF).[21]

The growth factor receptor can be another target for change. Several receptor proteins are formed for protooncogenes. Overexpression or disturbances (mutation) in the structure of these proteins can result in aberrant regulation of signal transduction that may tip the scale toward tumorigenesis.

Protein kinases function in signal transduction on the inner side of the cell membrane. These proteins transmit signals through cytoplasmic intermediaries through phosphate group transfer. Structural changes in these genes and proteins lead to increased kinase activity that can have profound effects on signal transduction pathways.

Signal transduction through the cell involves a variety of second messengers, such as guanosine triphosphate (GTP), adenosine triphosphate (ATP), and intracellular calcium. If mutated, the genes that transcribe these proteins may alter the response of these second messengers to inhibitory or activation signals. A common signal transducer that is altered in malignancies is GTP. GTP is converted to guanosine diphosphate (GDP) via the guanosine triphosphatase (GTPase) activity of G proteins as part of the signaling cascade. This cascade is modulated by the expression of the ras family of genes, where the resultant proteins police GTPase and GTP binding activity. When mutated, the ras oncogene allows for continual expression of GTP, reduced numbers of the CDKI p21 (CIP), and reduced GTPase activity. These changes together favor tumor formation.[22]

Alterations in the level and activity of intranuclear transcription factors may allow for aberrant gene expression and induce a malignant phenotype. An example of a key nuclear oncogene is that of the myc family and in particular c-myc. c-myc plays a significant role in modulating cellular proliferation, differentiation, and apoptosis amongst other functions. Mutations in c-myc are frequently encountered across tumor types, including those in the GI tract.[23]

In general, oncogenes require mutation of only one allele in order for phenotypic change to occur. This is known as a dominant gain-of-function. The conversion from protooncogene, the normal phenotype, to oncogene, the mutated form, can involve a variety of mechanisms, commonly relying upon abnormal gene amplification. Other mechanisms of mutation include chromosomal translocation, point/frameshift mutations, and viral insertions.[24]

Table 5-1 lists the oncogenes associated with the development of GI cancer. The oncogene β-catenin (and alternations in the Wnt [wingless]–β-catenin pathway) has been specifically incriminated in the development of GI cancers. This pathway involves the regulation of cytoplasmic free β-catenin and conformational changes in the APC–axin–GSK-3B complex. Nuclear translocation of this β-catenin and subsequent interactions with nuclear proteins result in the active transcription of a variety of genes including c-myc, cyclin D_1, MMP-7, and ITF-2, most of which are progrowth proteins that have been implicated in cancer development.[25]

Tumor-Suppressor Genes

Tumor-suppressor genes differ from oncogenes in that both alleles encoding a gene must be converted in order for a phenotype to be seen. Maintenance of a single allele is sufficient for protein expression to maintain cellular phenotype. When tumor-suppressor genes are mutated, the result is a loss of inhibitory function and the promotion of cellular growth and proliferation.[26] Two common tumor-suppressor genes that have been studied extensively and implicated in a variety of human and animal tumors include the Rb and the p53 tumor-suppressor genes.

As illustrated previously, the Rb plays a crucial role in the decision of a cell to proceed from G_1 to S phase.[6] Disruption of the Rb or other proteins that work in concert with the Rb can lead to unwanted cellular proliferation. Observations of the familial inheritance patterns of certain cancers, like that of the inherited form of retinoblastoma led to the formation of Knudson's two-hit model. This hypothesis suggests that two separate mutations must occur in a tumor-suppressor gene prior to tumor development. Mutations or dysregulation in the Rb pathway are common in many different forms of cancer in both man and animals.[27-33] The inherited form of retinoblastoma results from a germline mutation in one allele of a

Table 5-1 Cancer Genes and Gastrointestinal Cancers

Gene Class	Specific Examples	Normal Function	Abnormal Function	Association with Human Gastrointestinal Cancers
Oncogenes	β-Catenin in the canonical Wnt pathway	Pathway that regulates cellular growth and proliferation	Increased nuclear β-catenin activity	Attributed to the development of multiple GI cancers
	c-myc	Nuclear transcription factor involved in cellular growth, proliferation, and apoptotic pathways	Overexpression of c-myc favors cellular proliferation and growth by inducing cyclins and CDKs	Colorectal cancer
	ras	Oncogenes that encode for proteins similar to the G proteins	Alterations in the cell cycle that favor cell proliferation by specifically keeping p21/CIP/WAF1 inactivated	Attributed to the development of multiple GI cancers
Tumor-suppressor genes	p53	Key gene that controls cell-cycle progression, regulation of genetic expression, and responses to DNA damage	p53 inactivation either by mutation or overexpression of MDM2 oncogene favors cellular growth and proliferation	Attributed to the development of multiple GI cancers
	Rb	Critical component of regulation of the cell cycle, particularly at the G_1/S phase	Rb mutations result in abnormal cellular growth and proliferation	Familial/somatic retinoblastoma Attributed to the development of multiple GI cancers
	APC	Tumor-suppressor gene regulating multiple pathways for cellular growth and proliferation	Mutations in both alleles resulting in dysregulation of growth signals	Colorectal cancer and familial adenomatous polyposis (FAP) coli Intestinal cancer Hepatic cancer
	Smad4 (DPC-4)	Functions through the TGF-β signaling pathway that negatively regulates epithelial cell growth	Biallelic mutation results in disruption of the TGF-β pathway	Pancreatic cancer Familial juvenile polyposis Colorectal cancer
DNA mismatch repair	hMSH2	High affinity for correcting single base mispairs and structural anomalies	Dysfunctions enable the accumulation of mutations that may confer growth advantages that result in malignancy	Hereditary nonpolyposis colorectal cancer (HNPCC) syndromes
	hMLH1	Molecular coupling between recognition factors and downstream proteins that are key for excision and replacement of base pairs		Attributed to the development of multiple GI cancers
Hormonal regulation via G-coupled-protein receptors and mitogen-activated protein kinase (MAPK)	Gastrin	Regulator of gastric acid secretion	Hypergastrinemia (especially with concurrent *Helicobacter pylori* infection)	Gastric cancer Colorectal cancer
			Achlorhydria (lack of gastrin)	Gastric cancer related to bacterial overgrowth
	Cholecystokinin (CCK)	Regulates contraction of the gall bladder and secretion of pancreatic enzymes	Elevations in CCK	Pancreatic cancer
	Neurotensin (NT)	Released in response to intraluminal fats	Elevations in NT	Attributed to the development of multiple GI cancers
	Gastrin-releasing peptide (GRP)	Stimulates release of multiple GI hormones	Elevations in GRP/mutations in GRP receptor	Gastric cancer Pancreatic cancer

APC, antigen-presenting cell; MLH, mutL homolog 1; MSH, malignant hyperthermia sensitivity; Rb, retinoblastoma protein.

gene that exists in all cells that derive from that altered cell. This loss is referred to as the *loss of heterozygosity* or *allelic deletion*. A secondary somatic mutation (second hit) occurs in the other normal allele of that same gene, resulting in the so-called two-hit knockout of tumor-suppressor function.[34] In the sporadic form of retinoblastoma, two distinct somatic mutations are needed in both the Rb alleles to eliminate tumor-suppressor function and lead to cancer development. Not surprisingly, the sporadic form of retinoblastoma occurs in older patients and is less commonly bilateral at presentation.

The tumor-suppressor gene p53, sometimes known as the "guardian of the genome," controls cellular arrest, apoptosis, and proliferation, and is essential in mitigating DNA damage. The policing activity of p53 prevents the accumulation of mutations that would favor genomic instability and subsequent malignancy.[14] Inactivation of p53 by mutation plays a critical role in tumorigenesis in many human and animal cancers.[35-39] For the most part, dysregulation of p53 protein is associated with its stabilization and overexpression in cancer tissues. Germline mutations that affect p53 also have been documented and associated with familial cancer risk (Li-Fraumeni syndrome).[40] The activity of p53 can also be affected by nonmutational means. Overexpression of the p53 inhibitor MDM2, a cellular oncogene, reduces the amount of active p53, shifting the cell balance away from apoptosis.[17]

Another key tumor-suppressor gene linked to the development of several GI neoplasms is Smad4 (DPC4). Smad4, a member of the Smad family, plays a critical role in the mediation of the TGF-β pathway by acting as signal transducer. Wild-type expression of this gene results in suppression of epithelial cell growth via regulation of transcription of target genes inside the nucleus.[10] Germline mutations in Smad4 have been implicated in the development of familial juvenile polyposis, a precancerous condition of the GI tract. Somatic mutations in this same tumor-suppressor gene have also been linked to the development of pancreatic and colorectal cancers.[41]

DNA Mismatch Repair and the Prevention of Mutations

DNA mismatch repair is a cellular process that monitors and corrects DNA replication errors and thereby limits mutation risk. In this process, mismatch correction recognition enzymes bind to the DNA at the site of mismatch. After identifying the marred region, additional enzymes excise the aberrant DNA. This step is then followed by DNA polymerase-mediated reconstruction of the strand and DNA ligase activity to seal the nicks. In people, many mismatch repair enzymes have been identified including the hMSH, hMLH, and hPMS families.[10] Of these enzymes, hMSH2 and hMSH1 are the most implicated in tumorigenesis when mutated. Germline or somatic mutations in either of these enzymes is correlated with the development of hereditary nonpolyposis colorectal cancer (HNPCC) syndromes in humans. Additionally, alterations in mismatch repair that confer tolerance to DNA mutations may also result in carcinogenesis by allowing mutations to exist without addressing them.[42]

Mechanisms of Oncogenesis: Transformation from Normal to Malignant State

Understanding of normal cell biology and the processes that lead to malignancy has increased dramatically in recent years. We now recognize that the transformation of a normal cell into a malignant cell requires molecular, biochemical, and cellular changes that incrementally contribute to the process. Furthermore, despite the wide diversity of cancer types, these acquired capabilities appear to be common to all types of cancer. An optimistic view of increasing simplicity in cancer biology is further endorsed by the fact that all normal cells—irrespective of origin and phenotype—carry similar molecular machineries that regulate cell proliferation, differentiation, aging, and cell death.

The continuum from a normal cellular phenotype to malignancy includes metaplasia (particularly in the GI tract), benign tumors, in-situ tumors, and cancer. Each step in this continuum is the result of genetic dysregulation (involving cancer-associated genes) within the tumor and in the surrounding tumor stroma. Metaplasia is defined as the conversion of a mature differentiated cell into another form of a mature cell type, often following injury or insult. Typically, this occurs secondary to a chronic disease such as inflammatory bowel disease (IBD).[43] These changes often result from mutations in committed adult tissue-specific stem cells or secondary to transdifferentiation of lineage-committed cells.[44] Although metaplasia involves alterations in genotype and phenotype, once the inciting stimulus is removed, the change can revert, leading to a normal phenotype. In contrast, phenotypic changes noted in benign tumors, in-situ tumors, and malignancy are irreversible.[45] Benign tumors may be locally invasive, but do not metastasize. Although in-situ tumors are true malignancies of the epithelium, these tumors have not gained the ability to penetrate through basement membranes. These tumors are small and are often the precursor to malignancy, where a tumor has the capability of explicit local invasion and metastasis.

The model of cancer progression that involves cancer cells moving through multiple stochastic events, leading from the normal state to malignancy is not equally applied to all cancer types. Cancers of the GI tract are well matched to this model where distinctive precancerous lesions have been identified within the continuum.[46] This stepwise association of genetic dysregulation coupled to a specific disease entity in this continuum has been best defined in human colon cancer by Vogelstein et al. and is affectionately referred to as the "Vogel-gram of multistep carcinogenesis."[47,48] In tumors where such precancerous lesions are not identified (e.g., osteosarcoma), a similarly complex set of genetic changes are nonetheless believed to be necessary.

In 2000, Hanahan and Weinberg proposed that the cancer phenotype is defined by five to six defining hallmarks.[49] These cancer hallmarks include (a) self-sufficient growth, (b) insensitivity to antigrowth signals, (c) evasion of programmed cell death (apoptosis), (d) limitless replicative potential, (e) sustained angiogenesis, and (f) tissue invasion and metastasis. One appealing feature of these hallmarks of cancer is that the complexity and diversity of genetic dysregulation known to exist in and between cancers can be unified by the phenotypic effects associated with these genetic events. Some genetic events may be responsible for the acquisition of one or more of the hallmarks, whereas other genetic events may contribute to part of a single hallmark. Each of the acquired capabilities described previously represent a dysregulation in a homeostatic mechanism. The process of metastasis requires angiogenesis and invasion, as such the traits of sustained angiogenesis, and tissue invasion and metastasis may be collectively considered to represent a single hallmark of metastasis.

The hallmark of autonomy in cellular growth allows cancer cells to be free from dependency on external mitogenic signals. This hallmark is often attained following genetic dysregulation of one or more of the cell-cycle control mechanisms. The ability to evade the attempts of the body to arrest abnormal proliferation is then required for the development of malignancy. The normal cell responds to cell–cell interactions, intracellular signals, and other environmental information when deciding whether to divide, differentiate, or die.

These intricate signals and clear cell–cell communications are key to maintaining the harmony of homeostasis. In the event of malignancy, cells no longer appropriately respond to signals for cytostasis and shirk the postmitotic state (G_0). A common pathway of eluding differentiation involves the oncogene c-myc, a nuclear transcription factor for cellular growth. In yet another example of cellular yin and yang, c-myc function is restrained by the MAD–MAX transcription factor complex. When c-myc associates with the protein MAX, the resultant effect is cellular growth and proliferation. However, if MAX is conjoined with a MAD transcription factor, the balance is shifted toward terminal differentiation. If a genetic alteration occurs, resulting in an exuberant dominance of c-myc expression, the scales are tipped and prevention of proliferation or arrest is not possible.[23]

Cancer cells must also gain the ability to avoid death, or apoptosis. The minimization of the number of cells that perish allows tumors to grow and invade locally, a hallmark of all types of benign or malignant tumors. As discussed previously, this often involves loss of the recessive p53 tumor-suppressor gene or aberrant overexpression of anti-p53 genes such as MDM2.[50] Failure of tumor cells to appropriately undergo apoptosis following DNA damage progressively contributes to the hallmarks of cancer by allowing growth disrupting mutations to persist in cells without death. An innate mechanism created to stop aberrant cellular proliferation exists in the chromosomes themselves. Aging somatic cells are allowed only a finite number of replications limited by their chromosomal ends (telomeres). Because of the inaccuracy of 5′ to 3′ DNA synthesis at the terminal regions of chromosomes, an average of 50 to 200 repeated noncoding DNA nucleotides are lost during each cell division, a phenomenon termed *telomere attrition*.[2] Once the telomeric region has been sufficiently compromised, the cell enters a period of senescence, defined by continued cell functioning but the loss of replicative capabilities. In time, the aged cell enters crisis, the terminal cell stage where morphologic alterations and chromosomal instability result in ultimate cell death.[51,52] By recruiting the enzyme, telomerase, cancer cells retaliate against this mechanism and maintain the lengths of their telomeres. In so doing, the cancer cell achieves immortality, unrestrained in the number of replications it can undergo.[53-55]

Once a tumor establishes itself, it must ensure the survival of its increasing mass. This is accomplished primarily via the recruitment of new blood vessels to bring essential nutrients, oxygen, and facilitate the elimination of waste products.[56] This process is known as *angiogenesis* or *vasculogenesis*. Just as a tumor may enlist the aid of neighboring normal cells to help it grow, it may also elicit normal cells to produce angiogenic signals. At least 20 angiogenic growth factors have been identified and described, including vascular endothelial growth factor (VEGF) and basic fibroblastic growth factor (bFGF). As with any controlled system, antiangiogenic substances also exist (e.g., angiostatin and thrombospondin).[57] In normal adult cells, the switch controlling angiogenesis favors antiangiogenic control. In cancer, the angiogenic signals prevail resulting in new blood vessel formation. Angiogenesis begins with the activation of the endothelial cells by binding of an angiogenic signal (e.g., VEGF) to a surface endothelial receptor. In concert with angiogenic stimulation, proteins called *matrix metalloproteinases* (MMPs) help the activated endothelial cells invade the extracellular matrix by breaking down the surrounding tissues.[58-60] The activated endothelial cells then mature, forming hollow networks that coalesce into blood vessels. The importance of new blood-vessel formation in neoplastic cells is not restricted to just feeding the primary tumor. Metastasis, or the spread of cancer cells to other areas of the body distant from the primary site, relies upon tumor emboli being able to access blood and lymphatic vessels. Metastases are not a direct extension of the primary tumor and are not dependent upon the route of spread (i.e., hematogenous versus lymphatic versus peritoneal seeding).[61] The process of metastasis is believed to occur through the completion of a series of stepwise events. For this process to occur, a cancer cell must leave the site of the primary tumor, pass through the tumor basement membrane, and then pass through or between endothelial cells to enter the circulation (extravasation). While in the circulation, tumor cells must be able to resist anoikis (programmed cell death associated with loss of cellular contact), evade immune recognition and physical stress, and eventually arrest at distant organs. At that distant site the cell must leave the circulation and survive in the hostile microenvironment of the foreign tissue. This distant site may be the eventual target organ for metastasis or may be a temporary site. In either case the cancer cell is thought to lie dormant for a protracted period of time before moving to its final location. Following dormancy, cells receive signals to proliferate, create new blood vessels (angiogenesis) or coopt existing blood vessels, and then successfully grow into a measurable metastatic lesion. It is likely that further progression is associated with the repetition of this process and the development of metastases from metastases; as such the steps outlined above continue not only after the detection of the primary tumor but also after the detection of metastases. The basic tenets of this model of metastasis have been intact for more than 40 years; however, a greater understanding of biologic principles associated with each metastasis process is emerging and has been reviewed.[62-64] The opportunity provided by this emerging understanding is the development of novel strategies for the management of metastases in pet animals.

Risk Factors Contributing to the Hallmarks of Gastrointestinal Cancers

We have reviewed the mechanisms of normal cell proliferation and apoptosis, the genes and pathways involved in these mechanisms that when dysregulated contribute to cancer, and the necessary and defining features (hallmarks) of the cancer phenotype. The factors that contribute to the dysregulation of gene and gene function are complex and include host genetics, environmental exposures, cellular aging, and the interplay among these factors. Some cancer risks contribute to cancer development in all organ systems, whereas others are organ and cell-type specific. The following sections review specific cancer risks that may contribute to the development of cancers of the GI tract.

Inflammation as a Precursor to Cancer

Chronic inflammation, particularly in the GI tract, can mediate changes that, if left unaddressed, can progress to cancer. In examples such as gastroesophageal reflux disease (GERD) and IBD, derangements in mucosal host defenses and dysregulation of immune responses result in chronic inflammatory changes. In human patients, these diseases have been shown to progress from reversible metaplastic disease through dysplasia to cancer.[65,66] Inflammatory mediators, cytokines, and reactive oxygen and nitrogen species are often elevated in these conditions. Signal transduction pathways are activated including the arachidonic acid–cyclooxygenase (COX) and the canonical Wnt pathways to promote cellular proliferation, mounting the risk of acquiring somatic mutations that may result in a malignant phenotype.[67] Additionally, oxidative stress may result in mismatch repair and p53 dysfunction allowing for higher numbers of mutations and the evasion of apoptosis.[68] With this selection toward mutability, long-term inflammation can easily expedite the

normally slow transition toward malignancy and facilitates tumorigenesis. Direct correlations between gastric infection with *Helicobacter pylori* and the development of gastritis that matures into gastric cancer are well established in both humans and animals.[69-71] The same pathophysiology may be involved in diseases such as esophageal osteosarcoma–fibrosarcoma secondary to *Spirocerca lupi* infestation in dogs. It is interesting to speculate that intestinal lymphoma may develop as a sequel to prolonged severe lymphocytic-plasmacytic IBD.[72,73] In dogs or cats, no direct correlations have been established between these disease states.

Chemical Carcinogenesis and Dietary Factors

The GI tract is exposed to a variety of factors that may act as carcinogens/procarcinogens, including dietary substances or by-products. Correlations between the consumption of certain compounds and the development of cancer are well documented in humans and animals.[74] Procarcinogens that are ingested are either activated or detoxified, typically through the liver, and can exert DNA damage that may result in a somatic mutation. When paired with other protumor factors, these mutations can result in malignancy.[10] Other connections between the fiber and fat content in foods are implicated in tumor regulation.[75]

Hormonal Control over Gastrointestinal Proliferation

GI hormones play a significant role in the proliferation and maintenance of GI tissues via tightly regulated G-protein-coupled receptors (GPCRs) and the downstream activation of mitogen-activated protein kinases (MAPKs).[76] The primary function of GI hormones is the endocrine control of secretion, absorption, motility, and digestion mediated through the GI tract. However, when dysregulated, these hormones and their associated GPCRs are integral to the development of neoplastic conditions in locations such as the stomach, colon, and pancreas.[77] The primary GI hormones that have been investigated in cancer development include gastrin, a hormone that is responsible for gastric acid secretion; cholecystokinin (CCK), a mediator of gallbladder and pancreatic function; neurotensin (NT), a hormone released in response to intraluminal fats; and gastrin-releasing peptide (GRP), the universal switch for GI hormone release. These hormones act synergistically with and antagonistically to each other and are also influenced by external factors. These intimate interactions ultimately maintain a delicate balance favoring homeostasis.[78]

Once disrupted, either via hormonal or receptor dysregulation, cellular proliferation is favored and the risk of malignancy increases. Cancers that originate in the stomach and colon are particularly sensitive to the abnormal expressions of gastrin and of gastrin receptors. In conditions that favor hypergastrinemia, such as infection with *H. pylori*, metaplastic changes are noted in the GI mucosa.[77] When chronic, these changes can become irreversible, resulting in the formation of carcinomas.[79] In conditions where gastrin is insufficiently produced, tumorigenesis is also possible as a sequel to bacterial overgrowth, inflammation, and the activation of pathways that shift toward abnormal cell growth (e.g., STAT3, interferon [IFN]-γ).[78]

Gastrointestinal Cancer Stem Cells

A recent hypothesis in solid and hematopoietic tumor cancer biology involves a specialized subset of tumor cells that are endowed with unique abilities to replicate. These progenitor cells, otherwise known as *cancer stem cells*, account for a very small population of the cells within a mass. These cells are believed to retain the tumorigenicity of a cancer and are responsible for the emergence of cellular heterogeneity within a cancer. In studies that examined the clonogenicity of several tumor types (i.e., leukemia, multiple myeloma, lung, and breast cancer), a range of 1 in 10,000 to 1 in 100 tumor cells was capable of producing new tumor colonies when transplanted to naive environments.[80,81] These percentages mimic the prevalence of normal stem cells within the body, and this suggests that only a small percentage of cancer cells are truly tumorigenic.[82] From the cancer stem cell hypothesis emerges the possibility that tissue-specific stem cells (e.g., GI stem cells) may be a receptive or permissive cellular target for the genetic events that lead to the cancer phenotype. The "stemness" of these cells may then contribute to their ability to act as cancer stem cells once transformed. GI stem cells have high replicating and differentiating capabilities that are required to maintain tissue homeostasis, as well as the ability to restore a multitude of cells within the GI system.[44] The implication that a finite group of cells controls the growth of a given tumor has widespread significance in cancer biology, diagnosis, and therapy. As with tissue and embryonic stem cells (i.e., bone marrow), cancer stem cells may be more chemoresistant than the remainder of the tumor population. Elevated expression of cell survival proteins as well as upregulation of transmembrane receptors that promote chemotherapy export (i.e., multidrug resistance genes) may all play a role in the invisibility of cancer stem cells.[83] By discovering targets that specifically lead to the destruction of the progenitor cells, treatment responses and remission times may be dramatically improved.[84,85]

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CHAPTER 6

Abdominal Pain

Jean A. Hall

Definition

Abdominal pain is pain that originates from within the abdominal cavity. *Acute abdomen* is a term used to designate acute onset of abdominal pain, sepsis, or shock caused by abdominal disorders.

Pathophysiology and Mechanisms

Based on its origin, pain can be divided into visceral, somatic, and neuropathic. Abdominal pain is visceral in origin. Visceral pain differs from somatic pain in several ways.[1] First, visceral pain is not evoked in all visceral organs because peripheral receptors behave differently. Hepatic and renal parenchyma, for example, are not sensitive to pain; therefore activation of their receptors does not reach the level of consciousness. Second, visceral pain is not always associated with injury. Stimuli producing pain include distention, ischemia, and inflammation. Third, visceral pain is diffuse and poorly localized because there are fewer sensory visceral afferent fibers relative to afferent innervations of somatic tissues. Moreover, these visceral afferent fibers terminate diffusely in the spinal cord on neurons receiving input from both somatic and visceral receptors. Fourth, visceral pain is referred to the body wall because somatic (e.g., skin and muscle) and visceral afferents terminate on the same dorsal horn neurons in the spinal cord. This viscera–somatic convergence may give rise to referred pain in areas remote from the original lesion. Fifth, visceral pain is accompanied by motor and automatic reflexes such as nausea and vomiting. Visceral afferents travel together with afferents of the autonomic nervous system, and crosstalk occurs between nerves at local and central levels.[1] Thus sensory stimulation of the chemoreceptor trigger zone may initiate nausea and vomiting in addition to abdominal pain. Intense or long-lasting pain stimuli or inflammation can lead to plastic changes in the nervous system both in the periphery and at the spinal and supraspinal level. This results in enhanced visceral input, increased central neuronal activity and excitability, referred to as sensitization, and may ultimately lead to central plasticity, hyperexcitability, and pain memory.[1]

The visceral pain system consists of afferent peripheral fibers that synapse in the dorsal horn of the spinal cord and transmit information to a second order neuron, which than transmits information to the brain where information is further distributed to different supraspinal centers for processing.[1] Visceral afferent fibers are thinly myelinated Aδ-fibers or unmyelinated C-fibers with free nerve endings that respond to mechanical, thermal, and chemical stimulation. Visceral afferents converge with neurons in the dorsal root that receive input from superficial and deep somatic tissue as well as other viscera. Thus a group of neurons become hyperexcitable in an area of the dorsal horn as a result of a visceral pain signal. This is perceived as pain in somatic tissues innervated by afferents projecting to this same area in the dorsal horn. Afferent signals in second order neurons travel in spinothalamic tracts to reach thalamus and cortex. These neurons are subject to descending control from higher brain centers, which can be inhibitory or excitatory. Descending inhibition, via endogenous opioid release on afferent fibers in the spinal cord, appears to be the major way by which brain controls pain perception. The brain can also undergo cortical reorganization by enlarging and involving neighboring areas. Central sensitization results in allodynia (i.e., pain caused by a visceral stimulus that does not normally provoke pain), hyperalgesia (i.e., decreased pain threshold), and a significant increase in the size of the referred pain area together with hyperalgesia of muscle and skin.[1]

Differential Diagnosis

Abdominal pain is associated with a number of disorders (Table 6-1).[2,3] Differential diagnoses can be categorized based on disorders of body systems. These include disorders of the gastrointestinal system (stomach, small intestine, and large intestine), hepatobiliary system and pancreas, urologic system (renal, ureter, bladder, and urethra), hemolymphatic (spleen and lymph nodes), reproductive systems (prostate and testicles; uterus and ovaries), peritoneum and retroperitoneum, vascular and mesentery, and body wall including skin and subcutaneous tissues.

Extraabdominal disorders should also be considered because they may be mistakenly interpreted as causing abdominal pain. Skeletal or thoracolumbar pain from intervertebral disk disease, diskospondylitis, spinal neoplasia, sublumbar or retroperitoneal abscesses, fractures, and pelvic trauma can mimic abdominal pain. Other extraabdominal sources of pain include meningitis, polymyositis, steatitis, heavy metal toxicities, and black widow or brown recluse spider envenomation.[4] Poor abdominal palpation technique in a normal dog or cat also can elicit abdominal rigidity that may be erroneously interpreted as abdominal pain.

Table 6-1 Causes of Abdominal Pain[2,3]

Gastrointestinal System

Stomach
Gastric-dilation volvulus (GDV)*
Gastric dilation (GD)*
Obstruction*
Foreign body*
Ulceration or perforation
Neoplasia
Acute gastritis
Ischemia
Gastroesophageal reflux
Gastroduodenal intussusception

Small Intestine
Obstruction*
Foreign body*
Ulceration or perforation
Neoplasia
Enteritis*
Ischemia
Intussusception

Large Intestine
Torsion
Obstruction
Obstipation
Ulceration or perforation
Neoplasia
Colitis; typhlitis
Ischemia
Ileocecocolic intussusception
Cecal inversion

Hepatobiliary and Pancreas

Hepatic
Hepatitis; cholangiohepatitis
Abscess
Hematoma
Laceration
Lobar torsion
Neoplasia

Biliary
Cholecystitis
Cholelithiasis
Gallbladder mucocele
Rupture
Obstruction

Pancreas
Pancreatitis*
Abscess
Pseudocyst
Neoplasia
Ischemia; necrosis

Urologic

Kidney
Infection (pyelonephritis)
Urolithiasis
Obstruction
Rupture
Neoplasia
Renal ischemia
Acute nephritis
Toxicosis

Bladder
Nonseptic cystitis; infection*
Urolithiasis
Obstruction*
Rupture*
Neoplasia

Ureters and Urethra
Urolithiasis
Obstruction*
Rupture*
Neoplasia

Hemolymphatic

Spleen
Neoplasia*
Splenitis
Torsion
Infarction
Abscess
Hematoma
Laceration; rupture

Lymph nodes
Neoplastic infiltrate
Lymphadenitis
Reactive lymphadenopathy

Vascular
Mesenteric avulsion
Mesenteric volvulus
Mesenteric artery thrombosis
Portal vein thrombosis

Mesentery
Rent with herniation
Neoplasia

Reproductive System

Male
Prostatitis*
Prostatic abscess
Prostatic cyst
Prostatic neoplasia
Intraabdominal testicular torsion

Female
Pyometra; ruptured uterus*
Uterine torsion
Acute metritis
Uterine neoplasia
Dystocia
Ovarian neoplasia
Ovarian cyst

Body Wall
Penetrating injury
Abscess
Hematoma
Hernia
Neoplasia
Prepubic tendon avulsion

Skin and Subcutaneous Tissue
Penetrating injury
Abscess
Mastitis

Peritoneum
Peritonitis*
Septic (bacterial, viral)*
Chemical
Uroabdomen*
Bilious abdomen
Pancreatitis*
Hemoperitoneum*
Disseminated neoplasia
Adhesions

Retroperitoneum
Hemoretroperitoneum

*Common.

Evaluation of the Patient

History

A complete and detailed history should be obtained as for any other serious disease process. The history should start with the presenting complaint (abdominal pain) and include a chronologic description of progression of illness. When was the patient last normal? The focus should be on the previous six months, but be sure to include all previous medical conditions. Ask about clinical signs involving other body systems, for example, vomiting, diarrhea, appetite, fecal consistency, polyuria, polydipsia, urination behavior, coughing, and sneezing. Discuss current and previous medications, including routine medications like heartworm and flea and tick treatments. Ask about current diet as well as feeding behavior. Inquire about travel history and vaccination status. Ask about exposure to toxins, missing sewing thread and needles, chew toys, and the possibility of trauma.

Physical Examination

The initial physical examination is focused on the identification and treatment of immediately life-threatening problems (e.g., shock and gastric dilation volvulus [GDV] syndrome). This includes a quick assessment of cardiovascular, respiratory, and central nervous systems, and abdominal palpation to determine if GDV is present. If the patient is stable, a more thorough physical exam is performed. Abdominal palpation may reveal focal pain (e.g., caused by an intestinal foreign body), regional pain (e.g., caused by pyometra), or diffuse pain (e.g., caused by peritonitis).[2] Size of liver, spleen, kidneys, and bladder should be noted. Intestines and colon should be assessed for pain, thickening, gas, or a foreign body. The spine should be palpated for the presence of skeletal pain masquerading as abdominal pain. The abdominal wall should be inspected for traumatic wounds or bruising.

Digital rectal exam should be performed to assess fecal color and the size and morphology of the prostate gland. Peripheral lymph nodes should be inspected for signs of systemic disease. An oral examination should be performed to look for a linear foreign body wrapped around the base of the tongue.

Laboratory Evaluation and Tests

In addition to a thorough history and physical examination, the diagnostic workup for the patient with abdominal pain may include imaging, abdominal fluid analysis, clinical laboratory tests, and if needed, exploratory abdominal surgery (Fig. 6-1).[3] If the problem cannot be localized following thorough physical exam, abdominal imaging should be performed. If an obvious reason for surgery is identified on abdominal radiographs, then surgery should be performed after initial stabilization. If not, samples should be collected for a minimum data base (e.g., complete blood count, serum

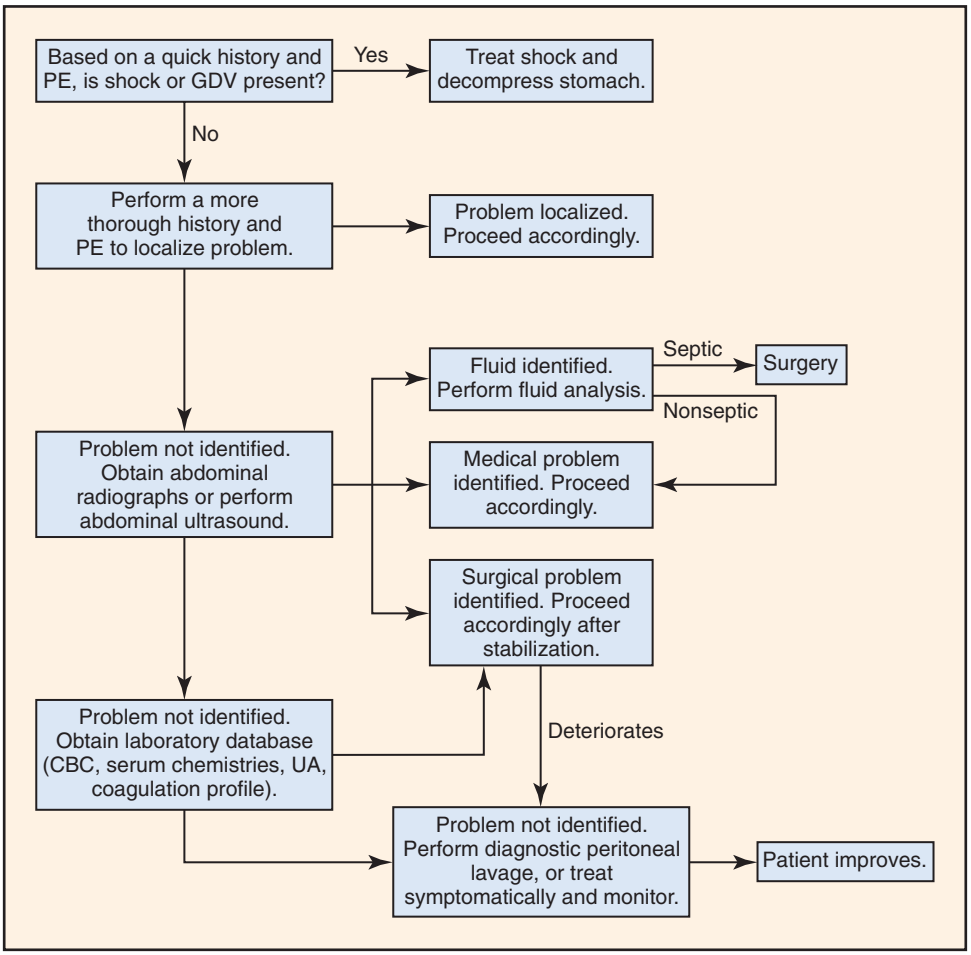

Figure 6-1 Diagnostic approach to the painful abdomen.[3]

chemistry, coagulation profile, urinalysis, fecal analysis). If abdominal pain persists and a cause has not been determined, abdominocentesis and diagnostic peritoneal lavage should be performed.

Radiography is a familiar and available modality for evaluating patients with painful abdomen.[5] If gastrointestinal (GI) perforation is suspected, an iodinated contrast agent should be used (e.g., diatrizoate sodium as a 30% solution at a dose of 2 to 20 mL/kg). Iodinated contrast agents decrease small intestinal transit time. Remember that some pain medications (e.g., opioids) prolong gastric emptying time.[6] Contrast procedures that are used to evaluate patients with urologic disorders include positive contrast cystography, urethrography, and excretory urography. Ultrasound is widely available and can support radiographic findings.[7] In addition, ultrasound may be helpful for collecting peritoneal or retroperitoneal fluid, as well as for aspirating or biopsying various abdominal structures. Radiographs should be obtained before performing diagnostic peritoneal lavage. Computed tomography (CT) and magnetic resonance imaging (MRI) may aid in identification of underlying conditions.

Abdominal paracentesis (i.e., percutaneous removal of abdominal fluid for diagnostic purposes) provides a rapid, easy, and safe method of diagnosing disease associated with abdominal effusion.[8] This can be performed by simple- or four-quadrant abdominal paracentesis. Four-quadrant abdominal paracentesis is performed by dividing the abdomen into four quadrants by bisecting the linea alba through the umbilicus. Each site is prepared aseptically and all four sites are aspirated in sequence until 5 to 10 mL of fluid is collected. Ultrasound guidance of the needle is used if fluid is not easily retrieved. Diagnostic peritoneal lavage is indicated when the other techniques have failed to provide a diagnostic sample. A dialysis catheter or other catheter with numerous side holes provides more opportunities for retrieval of a fluid sample; it is directed into the abdominal cavity just caudal to the umbilicus. (The animal is encouraged to empty its urinary bladder, a surgical preparation is performed, and local anesthetic instilled.) Warm 0.9% sodium chloride (20 to 22 mL/kg) is infused and the animal is gently rolled from side to side to disperse the fluid prior to aspiration and fluid collection. Fluid should be collected for cytologic analysis, chemical analysis, and culture.

Abdominal fluid can be classified as a pure transudate, modified transudate, or exudate (see Chapter 8), depending on the fluid's total nucleated cell count and protein concentration.[9] Modified transudates and exudates are further classified as neoplastic, inflammatory (nonseptic), hemorrhagic, or septic. Chemical analyses may include blood urea nitrogen (BUN), creatinine, amylase, lipase, glucose, potassium, or bilirubin. In many cases, comparison of abdominal fluid content with that of serum can support or even make a definitive diagnosis.[9] Abdominal fluid creatinine concentration greater than two times serum creatinine concentration, and abdominal fluid (potassium) greater than 1.4 times (dogs) or 1.9 times (cats) serum (potassium) suggests uroabdomen. Lipase and amylase concentrations greater than that of serum suggest pancreatitis. Abdominal fluid (bilirubin) that is greater than serum concentrations indicates bile peritonitis.

Treatment and Management

General Principles

Abdominal pain is approached on the basis of the severity of clinical signs. Initially the patient must be treated for shock and stabilized. Subsequent diagnostic steps are used to determine whether surgery or medical therapy is more appropriate.

Stabilization should be the primary objective in dogs or cats with shock and abdominal pain. Ventilation and/or perfusion abnormalities should be managed by providing oxygen therapy and intravenous fluids. If possible, diagnostic blood and urine samples should be collected prior to fluid therapy for later submission, if indicated. Choice of fluids and rate of administration are based on underlying clinical disorders (see Chapter 48). The goal is to restore heart rate, capillary refill time, mucous membrane color, blood pressure, urine output, bicarbonate or base excess, and lactate to normal.[2]

Treating abdominal pain does not necessarily compromise timely diagnosis or treatment of a surgical abdomen.[10] A literature review of studies published from 1996 through 2007 on the timing and frequency of assessment, and on the use of patient-controlled analgesia for nonsurgical pain in inpatients on medical wards showed that opioid administration has a negligible impact on successful clinical management of acute abdominal pain.[10]

Medical

Conditions treated medically include gastroenteritis (bacterial, viral, and toxic causes), pancreatitis, nonseptic cystitis, pyelonephritis, acute prostatitis, and cholecystitis. Medical treatment should be directed at the underlying disorder as well as supportive of normal body functions. Pain management should be a part of medical therapy. Analgesic agents should be administered to all patients, whether medical or surgical, in which immediate relief of abdominal pain cannot be accomplished.[4] Opioid agents (e.g., morphine) may induce vomiting and thus may not be as appropriate as other drugs. Phenothiazine tranquilizers should not be used in pain management. Suggested drugs include butorphanol at 0.1 mg/kg intravenously (cats) and 0.2 to 0.4 mg/kg intramuscularly, intravenously, subcutaneously every 2 to 4 hours (dogs); buprenorphine 0.005 to 0.02 mg/kg intramuscularly, intravenously, or subcutaneously every 6 to 12 hours (dogs) and 0.01 to 0.03 mg/kg intramuscularly every 12 hours (cats); fentanyl at 3 µg/kg intravenous bolus followed by 1 to 5 µg/kg/h given intravenously by constant rate infusion (dogs and cats); or hydromorphone at 0.1 to 0.2 mg/kg intramuscularly, intravenously, or subcutaneously (dogs and cats).

Early antibiotic therapy within one hour of recognition of severe sepsis improves survival in humans.[2] Therefore if septic peritonitis is suspected based on abdominal fluid cytology (the presence of phagocytosed bacteria), empirical antibiotic therapy should be initiated according to Gram staining characteristics of the bacteria. Additional therapeutics that should be considered include antiemetic agents (see Chapter 35).[4]

Surgical

Patients with a diagnosed surgical condition, evidence of sepsis, evidence of free abdominal gas, intractable hemorrhage, or who fail to stabilize with aggressive medical therapy are candidates for emergency surgery.[11] If medical therapy is ineffective, the animal's condition is deteriorating or does not improve after two to five days of therapy, or if severe abdominal pain persists, it is appropriate to recommend exploratory surgery.[3] The owner should be advised that a nonsurgical problem may be found or that a definitive diagnosis might not be possible, in which case biopsies should be taken from multiple organ systems.[3] Examples of conditions requiring surgical intervention include gastrointestinal obstruction, gastric rupture, and GDV; urinary obstruction, calculi, and ruptured bladder; pyometra, uterine torsion, and prostatic abscess; hepatic abscess, obstruction of the common bile duct, and ruptured gallbladder; pancreatic abscess; splenic torsion; abdominal hernia with

strangulated viscera; penetrating abdominal wound; ruptured abdominal neoplasia; and septic peritonitis. Anesthesia and abdominal surgery offer the opportunity to initiate nutritional support through early enteral feeding via esophagostomy, gastrostomy, or jejunostomy feeding tubes (see Chapter 33).[2]

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CHAPTER 7

Anorexia

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Definition

Anorexia is the lack or loss of appetite for food. It is a common and nonspecific finding in sick or injured patients and a frequent reason people seek medical attention for their pets. Anorexia can be partial or complete, depending on its underlying cause and severity. Resolution of this condition can be relatively simple in patients if its etiology is readily treatable. However, when anorexia is due to a chronic or incurable condition (which occurs with certain gastrointestinal diseases), management of anorexia becomes more challenging and more critical because of the negative consequences of long-term inadequate food intake.

Pathophysiology and Mechanisms

Control of Food Intake

Regulation of initiation, maintenance, and termination of food intake is complex and involves integration of numerous internal and external stimuli by different areas of the central nervous system (CNS). In addition to signals for hunger and satiety, there are other factors influencing initiation and maintenance of food intake. Understanding these various stimuli will help clinicians assess which factors may be involved when evaluating anorexic patients.

Sensory Signals

Sensory signals affecting feeding behavior fall into two categories: orosensory and postingestive. When one thinks of orosensory stimuli, the concept of flavor immediately comes to mind; however, olfaction and perception of physical attributes of a food (e.g., temperature, texture, consistency) contribute to the relative appeal of that food. Sense of smell is more highly developed in dogs and cats than in humans; consequently, it is likely to have a greater role in influencing food intake in these species. Warming food often enhances its aroma, and this may explain why dogs and cats prefer foods that are warmed to approximately their body temperature. Food acceptance drops off sharply, however, when the food is perceptibly warmer than normal body temperature.[1]

Although olfaction is involved in initiation of food intake and contributes to what is perceived as the flavor of food, the way foods taste is important for maintaining food consumption. Dogs and cats are believed to be able to taste salty, bitter, acidic, and meaty (*umami*) flavors. Dogs, but not cats, can also taste sweet flavors.[2] Increasing fat and protein content of foods generally improves palatability for dogs and cats, as will adding natural sweeteners for dogs. Cats, on the other hand, seem to have a preference for slightly acidic flavors. Texture and consistency of a food can be an important aspect of palatability for companion animals. Dogs and cats generally dislike sticky or powdery foods, while increasing moisture content correlates with enhanced appeal. However, individuals can develop strong preferences for a particulate texture or kibble shape and refuse foods of higher moisture content.

Postingestive sensory signals come from the gastrointestinal tract and prompt termination of a meal. Mechanoreceptors located in the stomach, for example, detect gastric distention and provide feedback signals to the brain via vagal stimulation.

Metabolic Signals

There are several orexigenic factors that are produced in the CNS; however, neuropeptide Y (NPY) plays the central role in regulating appetite in the hypothalamus. A variety of signals that influence NPY production will increase or decrease food intake.[3] Decreased circulating insulin concentration can increase NPY levels while postprandial elevations in serum insulin concentration decreases NPY. Leptin, a peptide secreted by adipocytes, plays a key role in maintaining energy balance. Leptin levels increase as fat reserves increase, which reduces NPY production. The polyphagic effect of glucocorticoids is believed to be due to these substances increasing NPY while there is evidence that certain cytokines have the opposite effect on NPY production.

Digestion and absorption of nutrients from a meal also trigger release of factors that feedback to the CNS. Cholecystokinin release by the gut in response to arrival of fat and certain amino acids in the duodenum suppresses food consumption. Peptide YY is another factor believed to inhibit food intake; it is released by the gut after food ingestion.

Environmental Signals and Learned Behavior

Although food itself and the physiologic response to ingestion of a meal are major factors influencing food intake, the environment in which food is offered may override any preexisting positive or negative sensory and metabolic signals. Companion animals usually become accustomed to some kind of routine associated with meals. Timing and location of meals, ambient noise level, type of feeding bowls, the person offering the food, and positive or negative associations of these environmental cues can influence patient appetite. Past experiences have some degree of impact on what types of food an animal find acceptable. Although cats in particular tend to be

neophilic in their food preferences, individual animals may develop fixed food preferences with partiality to particular flavors or textures.[4]

Differential Diagnosis

Any condition or circumstance interfering with initiation of food intake or triggering negative stimuli during food consumption can lead to anorexia. Inciting causes can include pathologic conditions, drug therapy, and alterations in the patient's diet, environment, and psychological status.

Reduced food intake is common in patients with organ failure, neoplasia, and conditions producing inflammation or hyperthermia. Underlying mechanism can be one or more circulating factors that act on appetite and satiety centers in the brain, including certain cytokines (e.g., tumor necrosis factor [TNF]-α, interleukin [IL]-1, interferon) or substances that would normally be metabolized by affected organs (e.g., uremic toxins). Chronic pain may directly cause negative stimuli that discourage food ingestion or may generate factors that trigger a reduction in appetite. Gastrointestinal tract diseases are often associated with anorexia. The cause of reduced food consumption may be pain or discomfort in conjunction with the act of eating (e.g., severe periodontal disease, stomatitis, dysphagia, pancreatitis, gastroenteritis). Another significant negative stimulus for food intake is nausea, a frequent clinical sign in gastrointestinal disorders including gastroenteritis, inflammatory bowel disease, pancreatitis, and hepatic diseases. Anorexia is a frequent consequence of conditions leading to hypokalemia and gastrointestinal ileus.

Anorexia may be iatrogenic in some patients. Factors that disrupt a patient's normal routine (e.g., stress of hospitalization and treatment, change in diet or feeding management) can interfere with learned feeding behaviors. Many pharmaceutical agents affect appetite through the same mechanisms at work in gastrointestinal disorders (Box 7-1). Nausea and vomiting are common side effects of many classes of drugs, including antibiotics, cardiac glycosides, and chemotherapeutic agents. Nonsteroidal antiinflammatory drugs, corticosteroids, and chemotherapeutic agents can cause gastrointestinal tract pathology. Adynamic ileus is a side effect of some analgesic agents, particularly the narcotic analgesic agents.

One consequence of a patient experiencing noxious stimuli when it eats is that it may come to associate pain, nausea, or indisposition with the diet being fed or even with the act of eating. This phenomenon is called *learned food aversion* and can be a contributing factor in development and persistence of anorexia for many companion animals.

Box 7-1 Medications Causing Anorexia in Cats and Dogs

- Antibiotics (including amoxicillin, ampicillin, cephalexin, chloramphenicol, erythromycin, tetracycline, trimethoprim/sulfadiazine)
- Cardiac glycosides
- Nonsteroidal antiinflammatory drugs
- Corticosteroids
- Chemotherapeutic agents (including cisplatin, doxorubicin, methotrexate)
- Narcotic analgesic agents
- Chelating agents (penicillamine)

Evaluation of the Patient

Because anorexia is nonspecific and associated with a broad spectrum of conditions, the diagnostic plan is initially predicated on the medical history and physical examination. There are two specific aspects of the history and physical examination, however, that should receive special attention: the patient's dietary history and the assessment of body condition.

History

Historical findings in anorexic patients are variable and depend upon the underlying condition. Key information is obtained by conducting a thorough dietary history, including magnitude and duration of the patient's reduction in food intake, details of the patient's normal diet with attention to feeding management plus recent changes that may have occurred, a description of normal feeding behavior and whether this has altered, and any other aspects of the patient's household environment that can affect the patient's routine, psychological status, or access to food (e.g., move to a new residence, changes in the household makeup) (Box 7-2).

To assess the patient's food intake for adequacy of calories and essential nutrients, it is necessary to obtain a detailed account of what the pet is consuming. To acquire this information, the pet's caregiver may have to keep a food diary for a few days, documenting the types and amounts of foods the patient consumes, including commercial pet foods, home-prepared diets, table foods and scraps, treats, and dietary supplements. Many people will try a variety of pet foods and offer table foods when they perceive their pet has a decreased appetite or shows disinterest in its usual diet. This dietary change is usually unsuccessful, although it sometimes produces an overall improvement in meeting calorie needs, but at the expense of complete and balanced nutrient intake.

The patient's maintenance energy requirement (MER) can be estimated from an accounting of its "normal" diet and food intake. If this information is not available, MER can be calculated using body weight and surface area (Box 7-3). Comparing patient's MER with an estimate of its current energy intake based on dietary history will reveal the magnitude of the caloric deficit. Patients receiving significant amounts of their calories (>25%) from foods other than complete and balanced pet foods should have an assessment of the overall nutritional adequacy of the diet (Box 7-4). Although short-term intake (1 to 2 weeks) of an unbalanced diet

Box 7-2 Conducting a Dietary History

- What is the pet normally fed?
- What is the pet currently being fed?
- Be certain to inquire about specific varieties and amounts of:
  - commercial pet foods
  - home-prepared diets
  - table foods or scraps
  - treats
  - dietary supplements
- Who lives in the household and have there been any recent changes including people and other pets?
- How is the pet fed and have there been any recent changes including:
  - who feeds the pet
  - timing
  - free choice versus meals
- What is the pet's feeding behavior

Box 7-3 Calculating Maintenance Energy Requirement (MER) for Dogs and Cats

1. Calculate resting energy requirement (RER) using one of the following equations:
   - $RER = 70WT_{kg}^{0.75}$
   - $RER = 30WT_{kg} + 70$*
2. MER is a multiple of RER based on the pet's level of physical activity.
   - Adult dogs: MER = 1.2 to 2.0 × RER
   - Adult cats: MER = 1.0 to 1.5 × RER

*Only for animals weighing between 2 and 30 kg.

Box 7-4 Assessing the Nutrient Adequacy of a Diet for a Dog or a Cat*

- What is the protein source? Ideally the protein source should be of animal origin (especially for cats) and lean rather than fatty.
- What is the fat source?
- What is the carbohydrate source? Cooked cereal grains provide one of the more digestible forms of carbohydrate.
- Is there a source of macrominerals (particularly calcium)?
- Is there a source of vitamins and trace elements?

*This checklist provides a quick overall assessment of the nutritional adequacy of a diet but does not ensure that it is nutritionally complete and balanced.

is unlikely to lead to significant nutrient deficiencies, some patients can become depleted in certain essential nutrients in a matter of weeks, depending upon the underlying disease. Expert nutritional advice should be sought for a patient who is eating an unbalanced diet and is anticipated to continue to do so for longer than a few weeks.

In addition to allowing an assessment of caloric and nutritional adequacy of the patient's food intake, dietary history should reveal any changes in that individual's household environment, including overall feeding management. This information will help differentiate between anorexia resulting from external factors that have caused psychological stress, fear, or competition with another animal versus anorexia secondary to an underlying physical condition (Fig. 7-1).

Obtaining information about the patient's normal feeding behavior and how it has changed can help pinpoint causes of anorexia. Patients with a normal or increased interest in food but reluctance to eat or that abruptly stop eating may be experiencing pain or dysfunction associated with prehending or swallowing. In contrast, patients with systemic diseases often show little, if any, interest in food.

Physical Examination

Careful examination of the oral cavity and cranial nerve function will help to identify decreased food intake due to sensory abnormalities or conditions leading to pain or dysfunction associated with eating and swallowing. Ideally the examination should include

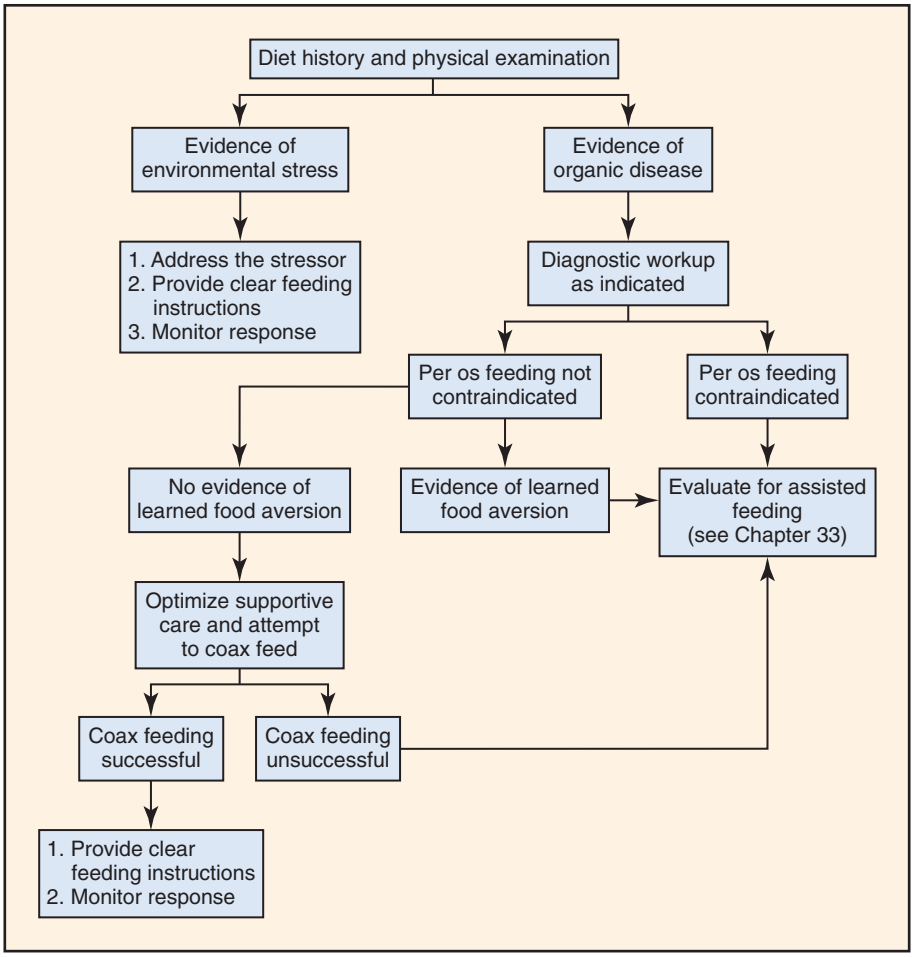

Figure 7-1 Algorithm for basic approach to anorexia.

observation of prehension, mastication, formation of a bolus, and swallowing.

The impact of anorexia on a patient's nutritional status can be assessed in part by evaluating its body condition. Body condition should be evaluated in terms of both the patient's energy reserves (body fat) and lean body mass (muscle mass). When weight loss is a consequence of simple starvation, metabolic adaptations occur that spare the catabolism of endogenous proteins and lean tissue. However, when weight loss is a result of a reduction in food intake secondary to a pathologic condition, a catabolic state ensues with the magnitude tending to mirror the severity of underlying disease processes. In such circumstances a disproportionate amount of weight loss is a consequence of breakdown of lean body mass. Thus it is common to see patients with significant muscle wasting despite excessive body fat. Simply assigning a body condition score based on body silhouette and palpation of adipose tissue is insufficient because patients that are significantly protein-depleted and therefore at risk for nutritionally associated complications will be overlooked.

Diagnostic Tests

Diagnostic workup of anorexic patients usually includes hematology, serum biochemistry, urinalysis, and fecal parasitologic examinations. Feline leukemia virus (FeLV) and feline immunodeficiency virus (FIV) status should be determined in cats. Based on the patient's signalment, history, physical examination, and results of the preliminary laboratory tests, further diagnostic testing and imaging may be indicated.

Treatment and Management

General Principles

Anorexia is usually secondary to some underlying condition; therefore the principal goals of therapy are to diagnose and address primary problems. Every effort should be made to optimize the patient's overall comfort and well-being through supportive care, as this will improve likelihood of adequate voluntary food consumption (see Fig. 7-1).

Attention should be given first to ensuring the patient is properly hydrated and has normal electrolyte concentrations. Hypokalemia is common in inappetent patients and can produce gastrointestinal ileus. Consideration should be given to intravenous administration of vitamin B complex. B vitamins are water soluble and are rapidly eliminated from the body. Patients with poor food intake or who are consuming an unbalanced diet may become deficient in one or more of the B vitamins, which can produce anorexia.

One should also address conditions causing discomfort or distress. Efforts should be made to normalize body temperature as febrile patients are unlikely to eat, and hypothermia causes poor gut perfusion. Effective pain management will improve a patient's comfort, although this must be balanced with the fact that some pain medications may reduce appetite either by decreasing gut motility or causing gastrointestinal tract pathology. It is essential to recognize and treat nausea by addressing underlying etiology or administering antiemetic drugs (see Chapters 23 and 35). It should also be remembered that drugs being given to a patient to treat the primary complaint may be affecting appetite. Adjusting the dosage or switching to another route of administration or a different drug may improve the patient's food intake.

Optimizing environment and timing of meals can be important. One should try to maintain the patient's normal routine and minimize stressful conditions at mealtimes. For example, treatments or procedures that frighten or otherwise upset the patient should not be scheduled to coincide with feeding times. If the patient is hospitalized, offering food in a location other than a busy hospital ward may improve food acceptance.

Box 7-5 Tips for Coax Feeding a Dog or a Cat

- Minimize stress at mealtimes.
- Approximate the patient's routine feeding management as much as possible.
- Recognize the signs of food aversion.
- Try to choose complete and balanced, and energy dense foods that are appropriate for the patient's medical condition.
- When medically appropriate, choose foods which with the patient is familiar.
- Try novel foods if the patient seems averse to its typical diet.
- Warm the food slightly.
- Offer modest portions of fresh foods frequently.
- Offer one food item at a time.
- Do not leave food with the patient for extended periods of time.
- Give clear feeding instructions that include the specific diet to be fed, portion size, and meal frequency.

Dietary

Enteral or parenteral nutrition may be needed in anorexic patients with concurrent conditions in which it is anticipated that voluntary food intake will be insufficient during initial stages of treatment or where feeding is contraindicated (see Chapter 33). Patients who are judged able to achieve adequate voluntary intake are candidates for coax feeding.

Coax feeding is not force feeding. With few exceptions, companion animals will experience stress and resist when food is forcibly placed in their mouths. It is rare that a force-fed patient achieves sufficient food intake, and this type of maneuver can put it at risk of both aspiration pneumonia and development of learned food aversion. The goal of coax feeding is to persuade the patient to consume adequate amounts of food on a voluntarily basis.

Several strategies can be employed for successful coax feeding (Box 7-5). First, assess whether the patient is showing signs of learned food aversion. Observe the patient's behavior when food is offered. Does the patient show interest or does it turn its head, back off, or actively try to push the food away? If food is placed in or near the patient's mouth does it show signs of nausea (e.g., salivation or swallowing)? If the patient does not appear averse to food, then different types of food can be used to tempt it. There are several considerations to bear in mind when choosing a food for coax feeding. The goal is to find a complete and balanced diet that will be suitable for nutritional management of any concurrent conditions and of which the patient will consume sufficient amounts to meet its caloric needs. Ideally, the diet will be energy dense so as to minimize the quantity the patient needs to consume. Sometimes the only food that a patient will accept is one which is not nutritionally complete or which is not entirely appropriate given the patient's underlying disease. Depending upon circumstances, this may be innocuous in the short-term. In other cases, however, it may worsen the patient's condition or lead to new problems.

Finding a diet the patient accepts often involves empirically trying a variety of foods. Knowing what the patient typically ate before becoming ill can aid in making choices (e.g., if it is clear that an individual previously only ate a dry commercial diet or had a

Table 7-1 Appetite Stimulants

Drug	Dosage	Side effects
Benzodiazepine derivatives		Sedation, idiosyncratic hepatic necrosis, effects wane with time when used in sick animals
Diazepam	0.2 mg/kg intravenously (cats)	
Oxazepam	2.5 mg/cat PO (cats)	
Cyproheptadine	2-4 mg/cat PO q12-24h 0.2 mg/kg PO q12h (dog)	Can cause excitability, aggression, and vomiting
Mirtazapine	3.75-7.5 mg/dog, daily PO; 1.9 mg/cat q24h to 72h	Serotonin antagonist; should not be administered to patients receiving monoamine oxidase (MAO) inhibitors
Megestrol acetate	0.25-0.5 mg/kg q24h PO for 3-5 days, then q48-72h (cats)	Polyuria-polydipsia, diabetes mellitus, adrenocortical suppression, hepatotoxicity

fixed preference for a certain flavoring). A patient may develop an aversion to the type of food it used to eat; in such cases the patient may find a novel food more appealing. Knowledge of attributes of food that enhance palatability for dogs and cats (i.e., aroma, moisture, fat, protein, sweetness, acidity, and mouth feel) should be employed when making a food selection.

When a food is offered for the first time, the portion should be modest and the food should be fresh and at room temperature or slightly warmer. Avoid leaving food with the patient for extended periods of time (particularly moist foods that will dry out and lose their appeal). Offering multiple varieties of food simultaneously can make it difficult to discern which foods the patient prefers, will make keeping track of the patient's calorie intake more complicated, and could increase the risk of developing a learned food aversion.

If an acceptable food is found, the next steps are to estimate how much of that food the patient should consume on a daily basis to meet its energy needs and translate that into clear feeding instructions for nursing staff and pet owners when it is discharged from the hospital. If the patient appears to be developing a food aversion or if repeated attempts at coax feeding fail, assisted feeding should be considered to prevent further deterioration of the patient's nutritional status.

Medical

Several drug classifications (benzodiazepines, 5-hydroxytryptamine [5-HT_2] antagonists, tricyclic antidepressants, progesterone derivatives) are believed to have appetite-stimulant properties (Table 7-1). None of these drugs is without side effects, and none will be efficacious if the underlying condition is not addressed and the patient's comfort and well-being has not been optimized through appropriate supportive care. Even under best conditions, appetite stimulants are often ineffective, and the effects will be short term when they do work. Appetite stimulants are most likely to be successful in patients who may have developed a food aversion during an illness from which they have recovered. Most patients in which coax feed fails should be evaluated as candidates for assisted feeding.

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CHAPTER 8

Ascites

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Definition

Ascites is defined as fluid accumulation within the peritoneal cavity. Although any peritoneal fluid accumulation could be classified as ascites, the term is more often used to refer to pure and modified transudates. Pure transudates are clear, colorless fluids, with low nucleated cell count (< 1.0 to 1.5 × 10^9 cells/L or <1000 to 1500 cells/μL), specific gravity ≤1.013 to 1.018, and total protein <2.5 g/dL (<25 g/L). Modified transudates may be clear, straw colored, or cloudy in appearance. The protein count of a modified transudate is slightly higher (2.5 to 5.0 g/dL or 25 to 50 g/L) as is the total nucleated cell count (<5.0 to 7.0 × 10^9 cells /L or 5000 to 7000 cells/μL) and specific gravity (>1.013 to 1.018).[1] Exudates are viscous and/or serosanguineous in appearance, have a high protein content (>5.0 g/dL) and cellularity (>10,000 cells/μL), and have a relatively high specific gravity (>1.018). Ascites generally indicates serious disease and warrants prompt investigation.

Pathophysiology and Mechanisms

Ascites forms because of disruption of Starling forces in local capillary beds, with diffusion of fluid across the serosa into the peritoneal cavity. Under normal circumstances, portal pressure gradient decreases (from 6.5 to 13 cm H_2O to 3 to 3.5 cm H_2O) as it progresses from the hepatic triads through to the sinusoids, central vein, hepatic veins, and the caudal vena cava.[2] The changing pressure gradient pushes fluid from sinusoids into protein-rich perisinusoidal spaces (spaces of Disse) which are covered by a thin membrane.[3,4] The balance between oncotic and hydrostatic pressures is maintained by lymphatic system (much of it located in the diaphragm) returning tissue fluid to the vascular system.[5,6]

Portal hypertension is a sustained increase in blood pressure of portal vasculature. Portal hypertension can be caused by capillarization of hepatic sinusoidal endothelium, increased portal blood volume, or increased resistance to normal flow.[3,6,7] Diseases that lead to *portal hypertension* are divided anatomically into prehepatic, intrahepatic (presinusoidal, sinusoidal, or postsinusoidal), and posthepatic causes.[7-9] Ascites in *posthepatic* and *sinusoidal* or *postsinusoidal intrahepatic* portal hypertension develops when sinusoidal pressure increases so that fluid leaving sinusoids exceeds the capacity of lymphatics to return it to circulation.[8] The fluid that leaves the surface of the liver has percolated through the spaces of Disse where hepatic lymph has a high protein content, resulting in formation of a modified transudate.[6,10,11] Acquired portosystemic shunts do not develop in *posthepatic portal hypertension* because caval pressure also increases significantly.[7,8]

Ascites caused by *presinusoidal intrahepatic* and *prehepatic portal hypertension* is uncommon because the rate of fluid production rarely exceeds rate of lymphatic absorption.[6,7,9] When accumulation exceeds absorption, a pure transudate develops because there is transudation of intestinal lymph which has a much lower protein content than hepatic lymph.[9,12]

Regardless of cause or anatomic site of portal hypertension, the renin–angiotensin–aldosterone system (RAAS) contributes to ascites formation.[13] Circulating blood volume may be initially increased by development of extrahepatic portosystemic shunts and shunting of blood to systemic circulation.[14-16] When *portal hypertension* exceeds this capacity, there may be a decrease in circulating intravascular blood volume detected by volume receptors,[3,8,13,17] and the RAAS becomes activated. Decreased renal prostaglandins and natriuretic factor result in water and sodium retention.[6,7,18] Further increases in blood volume perpetuates the tendency toward ascites formation.[19-22] If portal pressures are already elevated, altered renal sodium handling may be a precipitating (rather than a perpetuating) factor for ascites formation.[23-25]

Increases in capillary hydrostatic pressure resulting from intravenous fluid overload or reduced cardiac output may occasionally be severe enough to induce ascites, although pulmonary edema is often the predominant clinical sign particularly in cats.[1] Vasculitis is another potential cause of fluid accumulation in abdominal and thoracic body cavities.

Decreases in plasma colloidal osmotic (oncotic) pressure represent another disruption to Starling forces. This circumstance arises when serum albumin decreases to <10 to 15 g/L (1.0 to 1.5 g/dL) and is often accompanied by fluid accumulation in pleural space and subcutaneous tissues. Fluid that develops in this instance is a pure transudate.

Differential Diagnosis

Posthepatic portal hypertension occurs when there is obstruction of flow from hepatic veins and caudal vena cava to the right side of the heart. Pericardial disease (e.g., pericardial effusion or pericarditis causing cardiac tamponade) is the most common cause in dogs.[26-28] Other possible causes include right-sided cardiac disease (e.g., intracardiac masses, tricuspid valve insufficiency, cor triatrium dexter, pulmonic stenosis) and pulmonary hypertension (e.g., primary or caused by chronic respiratory disease, left-sided congestive heart

failure, pulmonary thromboembolism and dirofilariasis).[29-33] Obstruction of the caudal vena cava because of congenital abnormalities, thrombi formation, dirofilariasis ("caval syndrome"), neoplasia, or trauma may also occur.[34-37] Budd-Chiari–like syndrome refers to obstruction of hepatic venous flow to the right atrium.[38] Posthepatic portal hypertension is uncommon in cats.[1]

Hepatic (sinusoidal or postsinusoidal) portal hypertension generally results from chronic hepatic disease that either increases resistance to portal blood flow or increases hepatic arterial blood flow. The most common cause of sinusoidal or postsinusoidal portal hypertension is diffuse parenchymal disease such as cirrhosis (an end-stage disease in breed-specific hepatopathies), drug-related hepatopathies, fibrosis, diffuse neoplasia, chronic diffuse hepatitis, and chronic cholangiohepatitis.[6,15,39,40] In rare cases, severe hepatocyte swelling due to vacuolar hepatopathy (e.g., hepatic lipidosis) may cause portal hypertension, but rarely does it cause fluid accumulation.[1]

Prehepatic or presinusoidal hepatic portal hypertension results from intraluminal occlusion of the portal vein (thrombosis, neoplasia), abnormal developmental anomalies of the portal vein (stenosis, atresia, hypoplasia) or extraluminal compression of the portal vein by neoplasia or other abdominal masses.[41-44] It may also develop as a consequence of surgical ligation of a congenital portosystemic shunt.[1] Congenital arterioportal fistula is a direct communication between a portal venous branch and a hepatic arterial branch, representing another presinusoidal portal hypertension.[45,46]

Hypoalbuminemia is another cause of ascites formation, when serum albumin concentration falls below 1.5 g/L. Albumin may be decreased because of excessive losses, decreased production, or protein-calorie malnutrition. Albumin is a small protein (molecular weight 66,000 daltons) easily lost in severe *glomerular* disease (*protein-losing nephropathy*), as well as *protein-losing enteropathy* and severe exudative cutaneous lesions. Albumin may decrease in other exudative process such as septic or neoplastic peritonitis. The liver is the major site of albumin synthesis and is capable of producing adequate albumin at 33% of maximal capacity.[47] That factor, in addition to the relatively long circulating half-life of albumin (8 to 9 days) means that hepatic disease must be both chronic and severe to cause clinically important hypoalbuminemia.[6,47,48] End-stage acquired hepatic disease, and congenital portosystemic shunting both cause substantially decreased albumin production.[42] Decreased nutritional intake alone is seldom sufficient to cause albumin to decrease to such an important degree, but starvation will contribute to the severity of hypoalbuminemia associated with other causes.

Evaluation of the Patient

History

History is highly dependent upon underlying disease. Congenital diseases would be more likely in young animals, while some breeds are predisposed to specific hepatopathies, congenital portosystemic shunts, portovascular anomalies, or hepatic fibrosis.[46,49,50] Owners may present their animal for "weight gain" caused by abdominal distention. If ascites is caused by primary hepatic disease, the animal may display neurobehavioral signs ranging from changes in temperament to seizures and coma caused by hepatic encephalopathy. Other signs of hepatic dysfunction may be present such as anesthetic or sedative intolerance, dermatoses, polyuria/polydipsia, melena, acholic feces, vomiting, diarrhea, weakness, and lethargy.[47,51] Determination of toxin and drug exposure is important.

Dyspnea, exercise intolerance, and syncope may be present if concurrent pleural effusion is present. Dyspnea could still be a manifestation of ascites if abdominal fluid volume impedes diaphragmatic muscle contractility.[52] Heartworm prophylaxis status should be established in animals from heartworm endemic areas. Losses of albumin through exudative processes are fairly self-evident, but clinical signs associated with loss through glomeruli or intestines may be less obvious. Small bowel diarrhea may be present or absent even in severe small-intestine disease if the large intestine retains sufficient capacity to absorb excess fecal water. Establishment of intestinal parasitic prophylaxis may also be important, especially in young puppies or kittens.

Physical Examination

Expected physical examination findings are also dependent on underlying disease processes. In general, ascites can be detected only when a large volume of fluid is present. This large volume often precludes thorough abdominal palpation and assessment of organ size. Animals with profound abdominal distention may have loss of dorsal musculature and body condition. Assessment of mucous membrane color is often useful and may demonstrate anemia (Chapter 16) or icterus (Chapter 18). Prolonged capillary refill time or skin tenting may be present with dehydration, and rarely there may be signs of a bleeding diathesis because of coagulopathy (Chapter 9). Digital rectal examination may provide evidence of melena, acholic feces, or hematochezia. Abdominal pain may be present with gastrointestinal ulceration or perforation.

Concurrent pleural effusion may be present with posthepatic portal hypertension because of right-sided cardiac disease or pulmonary hypertension. Relevant clinical signs may include tachypnea, muffled heart and lung sounds, jugular distention, cardiac murmur, pulsus paradoxus, and abnormal adventitious lung sounds.

Laboratory Evaluation and Tests

Figure 8-1 outlines an algorithmic approach to diagnostic evaluation of ascites. The first step in diagnostic evaluation is abdominal fluid analysis to allow differentiation of pure and modified transudates, septic and nonseptic exudates, blood, and chyle. Abdominocentesis is readily performed in conscious animals and should be performed in a sterile manner with needle insertion at the level of the umbilicus, just lateral to midline. Peritoneal lavage is rarely required in cases of ascites. If there is a suspicion of concurrent pleural effusion, then thoracocentesis may be performed in preference to abdominocentesis as both a palliative and diagnostic tool.

Ascitic fluid is first characterized according to appearance, specific gravity, total protein, and cellularity. Table 8-1 outlines the basic differences between fluid types. Fluid analysis should include cytologic and chemical evaluation. Additional fluid analysis could include Gram staining and culture (bacterial infection), measurement of blood urea nitrogen (BUN) and creatinine (renal failure), and triglyceride analysis (lymphatic transport disorders). Determination of serum-ascites albumin gradient may be used to differentiate between transudative and exudative processes. A serum-ascites albumin gradient >1.1 g/dL is usually indicative of portal hypertension but may not distinguish between hepatic and posthepatic portal hypertension.[53] Ascitic fluid amino acid profiles (e.g., glutamate-to-glutamine ratio) may help to differentiate cirrhosis and other noncirrhotic causes of ascites.[54]

Interpretation of abdominal fluid characteristics should always be performed in conjunction with serum hematology, serum biochemistry, and urinalysis. Hematology usually shows only nonspecific changes in hepatic disease such as a microcytic anemia, or normocytic, normochromic nonregenerative anemia. Serum enzyme activities that reflect hepatocellular injury or repair such as alanine

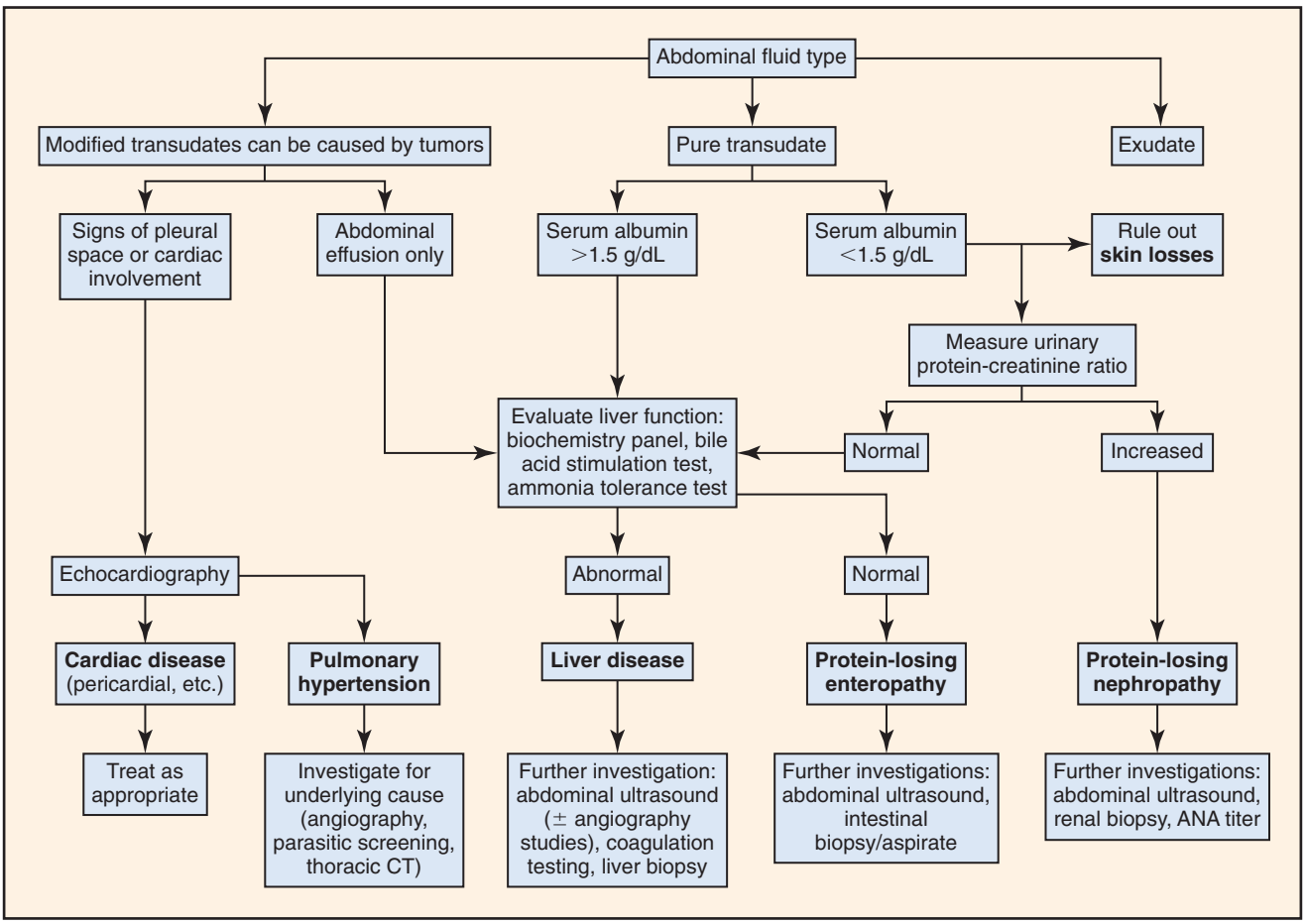

Figure 8-1 Algorithmic approach to diagnostic evaluation of ascites.

Table 8-1 Differentiation Among Fluid Types

Fluid Type	Appearance	Specific Gravity	Total Protein	Nucleated Cell Count	Cell Types
Pure transudate	Clear	≤1.013-1.018	<2.5 g/dL	1000-1500 cells/μL	Occasional mesothelial cells
Modified transudate	Straw-colored, slightly cloudy	>1.013-1.018	2.5-5.0 g/dL	<5000-7000 cells/μL	Mesothelial cells, nondegenerate neutrophils, macrophages, lymphocytes
Nonseptic exudate	Turbid to opaque, blood tinged	>1.018	>2.5 g/dL	>5000 cells/μL	Mesothelial cells, nondegenerate neutrophils, macrophages, lymphocytes, and occasionally neoplastic cells
Septic exudate	Turbid to opaque, blood tinged	>1.018	>2.5 g/dL	>5000 cells/μL	Degenerate neutrophils, intracellular bacteria
Blood	Cloudy and red (clear supernatant after centrifugation)	= Peripheral blood	= Peripheral blood	= Peripheral blood	= Peripheral blood
Bile	Clear to cloudy with green tinge	>1.018	>2.5 g/dL	>5000 cells/μL	Bilirubin crystals evident
Urine	Clear to slightly cloudy and pale yellow	Variable	Variable	>3000 cells/μL	May become septic
Chyle	Opaque and white-pink	Variable	20-70 g/dL	<10,000 cells/μL	Fluid triglyceride > serum triglyceride, large number of small lymphocytes

aminotransferase (ALT) and aspartate amino transferase (AST) are commonly increased in animals with primary hepatic disease, or hepatocellular swelling secondary to congestion (posthepatic portal hypertension).[55] Other serum hepatic enzyme activities may be more useful markers of cholestasis and drug induction. Alkaline phosphatase (ALP) is associated with the canalicular membrane and γ-glutamyltransferase (GGT) with the epithelial cells of the bile ducts.[55] ALP has a half-life of 66 hours in dogs and <6 hours in cats; therefore it is usually the last serum enzyme to return to normal in dogs.[55] In dogs ALP is induced by glucocorticoids (stress or hyperadrenocorticism) and exogenous drugs (phenobarbital or exogenous corticosteroids) while GGT is not affected.[55] There is no stress-induced induction of ALP in cats.[55] This fact plus the short circulating half-life means any increase in ALP in cats must be considered significant. Bone isoenzyme of ALP can be increased in young dogs and cats, as well as in animals with severe bone pathology, and may be increased with congenital portosystemic shunts.

Renal (protein-losing nephropathy [PLN]) and intestinal (protein-losing enteropathy [PLE]) protein losses must also be ruled out as causes of hypoalbuminemia. Hypoglycemia may occur in congenital or end-stage hepatic disease, when <20% hepatic function remains. The urea cycle detoxifies ammonia produced by the gut, and BUN is often decreased when there is decreased hepatic function. Urea is also affected by nonhepatic factors, and it is unusual for low urea to be the sole abnormality in hepatic disease. BUN may also be artifactually increased if there has been recent gastrointestinal hemorrhage. Serum cholesterol may be high if there is impaired excretion of cholesterol (bile duct obstruction, severe cholestasis), normal, or low if there is altered intestinal absorption and hepatic synthesis. Increases in serum bilirubin may be evident on biochemical testing before jaundice is clinically apparent. Differentiation of unconjugated versus conjugated bilirubin is usually of little benefit in companion animal medicine. Measurement of serum bile acids reflects hepatocellular function and efficiency or integrity of enterohepatic circulation with increases often seen before increases in serum bilirubin.[56,57] Ammonia tolerance testing may be performed if portosystemic shunting is suspected, but care must be taken not to precipitate hepatoencephalopathy in susceptible animals. Plasma samples should be analyzed within 20 minutes of collection.

Urinalysis findings may be nonspecific in dogs and cats with ascites. Dogs often have hyposthenuria (urine specific gravity <1.008), and ammonium biurate crystals may be detected in both dogs and cats with congenital portosystemic shunts. Urine protein-to-creatinine ratio determinations may be necessary to exclude PLN as a cause of hypoalbuminemia. In some instances it may be difficult to obtain a cystocentesis sample in an animal with large-volume ascites, and in such patients should be guided by ultrasound.

Coagulation factors should be assessed if liver dysfunction is suspected, particularly before liver sampling is performed. Platelet dysfunction may also result from severe liver disease, so assessment of platelet function via function analyzer or a buccal mucosal bleeding time is warranted. Pretreatment with injectable vitamin K and plasma may be appropriate before hepatic surgery or biopsy.

Conventional survey radiography is of little benefit in assessing abdominal pathology when there is a large-volume effusion. It may, however, be useful for assessing concurrent thoracic cavity disease and vena caval dimensions.[58] Abdominal ultrasound is more useful in investigation of ascites. In some cases, ultrasound may detect small amounts of fluid not detected clinically. Ultrasound of heart and caudal vena cava is the diagnostic test of choice for diagnosing pericardial disease, right-sided heart disease, pulmonary hypertension, and caudal vena caval obstruction. Ultrasonography may also detect extrahepatic and intrahepatic shunting vessels although the sensitivity for detection is less than 100%. Ultrasound evaluation of the liver and biliary tract may permit determination of hepatic parenchymal or cholestatic disease. In some instances, advanced imaging techniques such as scintigraphy or computed tomography (CT) angiography may be necessary, particularly for shunting vessels.[59]

Sampling of the liver for cytologic or histopathologic assessment is important in diagnosing hepatic disease, but there are some limitations in its diagnostic utility. Fine-needle aspiration (FNA) is a relatively easy and safe procedure and can be performed without ultrasound guidance in diseases causing marked hepatomegaly. There is a low risk of hemorrhage, but it is only diagnostic for exfoliative diseases such as lymphoma, lipidosis, glycogen deposition, and vacuolar hepatopathy, all of which are unlikely causes of ascites. Larger tissues samples may be obtained by needle biopsy (ultrasound guided) or tissue wedge (exploratory laparotomy or laparoscopy). This should be performed only if the patient is stable for a general anesthetic agent, has adequate hemostasis, and an adequate sample size can be obtained. If a correctable problem such as a congenital extrahepatic shunt is suspected, potential benefits of a surgical procedure outweigh the risks as long as the patient is medically stable. In general, multiple needle biopsies should be taken to maximize the likelihood of diagnosis, and subcapsular connective tissue should be excluded to avoid the misdiagnosis of fibrosis.

Treatment and Management

General Principles

Treatment of ascites is highly dependent on underlying etiology, and this should be pursued extensively before definitive treatment. Palliative treatment may be necessary, however, to improve respiration, and abdominocentesis may be performed.[60] Care should be taken not to remove too much fluid, as this may worsen hypovolemia and ascites and precipitate hepatic encephalopathy in animals with hepatic disease.[61] If there is concurrent pleural effusion, thoracocentesis is more likely to relieve respiratory distress than abdominocentesis. Furosemide is relatively ineffective as a sole agent in mobilizing ascitic fluid, and an aldosterone antagonist (e.g., spironolactone) may be more effective.[17,61-63] Combined use of a loop diuretic and a low-sodium diet is best in chronic cases, provided there is sufficient oral potassium intake. Hypokalemia and metabolic alkalosis are risk factors for development of hepatic encephalopathy.[17,64,65]

Cardiac Disease

Diuresis is ineffective and probably contraindicated for the mobilization of ascitic fluid caused by pericardial effusion. The preferred treatment of choice for pericardial effusion is pericardiocentesis, and this may be repeated a number of times in individual animals. Pericardiectomy (either via thoracotomy or thoracoscopy) may be necessary for management of recurrent effusions or to differentiate malignant from benign causes.[27,66] Pulmonic stenosis may be treated by balloon valvuloplasty whilst medical management is currently the only realistic option for tricuspid insufficiency.[67,68]

Respiratory Disease

Management of pulmonary hypertension is highly dependent on the underlying cause, and oxygen supplementation may be necessary in the short-term. Vasodilators such as pimobendan and sildenafil also may be beneficial.[69]

Hepatic Disease

Medical management of hepatic disease is aimed at treating underlying disease and managing associated clinical signs (ascites, gastrointestinal hemorrhage, and hepatoencephalopathy). The mainstay of medical management is dietary reduction of protein (in dogs), particularly aromatic amino acids, sufficient to reduce signs of hepatoencephalopathy but not to aggravate protein catabolism.[63] Supplementation of soluble fiber and various water- and fat-soluble vitamins may be beneficial, in addition to moderate sodium reduction.[63]

Treatment of concurrent complications includes lactulose and antibiotics for hepatoencephalopathy, proton-pump inhibitors for gastrointestinal ulceration, and mannitol for cerebral edema.[70]

Specific treatment of the underlying etiology can range from immunosuppressive therapy (e.g., prednisolone, azathioprine) to copper-chelating agents and antifibrotic drugs.[70] Nutraceutical management of liver disease (vitamins C and E, *S*-adenosyl-L-methionine, and silymarin) are receiving increasing attention as supplementary therapy in acquired hepatopathies, although evidence-based data are still lacking in most instances.[71] Ursodeoxycholic acid is also being increasingly used in treatment of cholestatic liver disease.

Surgical correction of symptomatic, single congenital portosystemic shunts is considered the treatment of choice, with a greater success rate seen with extrahepatic shunts using newer modalities such as cellophane banding or ameroid constrictors.[72,73] Although no one contests this statement when discussing the more classic young, symptomatic patient, there are an increasing number of older, asymptomatic patients or middle-aged asymptomatic patients that are fortuitously diagnosed when working up other problems—for these patients, surgery has not been shown to be needed. Intrahepatic shunts are more difficult to correct surgically. Surgical correction of multiple shunts because of portal hypertension is not indicated.

Protein-Losing Enteropathy

Treatment of PLE is dependent upon the underlying cause, such as inflammatory bowel disease, lymphangiectasia, parasitism, infectious disease, intussusception, and neoplasia. Enteral feeding is ideal, but short-term support may need to be provided in the form of total parenteral nutrition. Colloidal fluid support may also be necessary, although plasma transfusions alone does not provide sufficient albumin unless given at a dose approximating 20 mL/kg.[74]

Protein-Losing Nephropathy

Current recommendations for treatment of significant proteinuria are reduced dietary protein, fatty acid (omega-3) supplementation, low-dose aspirin to prevent thromboembolic disease and use of an angiotensin-converting enzyme inhibitor.[75] In some individual cases, uses of immunosuppressive or antihypertensive medication may also be warranted.[76]

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CHAPTER 9

Coagulopathy

Mary Beth Callan

Definition

The hemostatic system (i.e., platelets, vascular endothelial cells, plasma coagulation factors) is a finely controlled mechanism that prevents excessive blood loss following vascular injury. Abnormalities in any part of the hemostatic system may result in bleeding. Hemostatic disorders may be classified as *primary* or *secondary*. Primary hemostasis refers to the platelet–vessel interaction; therefore primary hemostatic disorders include thrombocytopenia, thrombopathia, von Willebrand disease (vWD), and, rarely, vasculopathy. Secondary hemostasis refers to generation of thrombin and formation of a fibrin clot through a series of enzymatic reactions; therefore coagulopathies are secondary hemostatic disorders that typically result from deficiency of one or more plasma coagulation factors. In addition, enhanced fibrinolysis may result in a bleeding tendency.

Pathophysiology and Mechanisms

Following vascular injury, platelets adhere to exposed subendothelial collagen. Under conditions of high shear forces (in arterioles and microcirculation) plasma von Willebrand factor (vWF) is also needed to support platelet adhesion. Once activated, platelets aggregate (i.e., stick to one another via crosslinking by fibrinogen) to form an unstable platelet plug. Stabilization of the platelet plug with a fibrin clot occurs through blood coagulation. The liver is the major site of synthesis for blood coagulation factors that are secreted into circulation as inactive zymogens. Plasma coagulation factors (F) II, VII, IX, and X, as well as anticoagulant protein C and protein S, require vitamin K for carboxylation of their glutamic acid residues, allowing them to bind calcium ions essential to the coagulation process. FVII (extrinsic pathway) plays a pivotal role in the initiation of coagulation, combining with membrane protein tissue factor (TF) following vessel injury. Activated FVII and TF complex (FVIIa–TF) in the presence of calcium cleaves FIX (intrinsic pathway) and FX (common pathway) to their activated forms, ultimately leading to the generation of fibrin. Platelets exert a procoagulant effect with the platelet membrane phospholipid phosphatidylserine (PS) providing a catalytic surface for enzymatic activities known as tenase and prothrombinase, resulting in activation of FX and FII (prothrombin), respectively.

The liver plays a key role in regulating fibrinolysis, synthesizing both plasminogen and the major plasma inhibitor of plasmin, α_2-antiplasmin. Within the fibrinolytic system, plasminogen is converted to plasmin via tissue-type plasminogen activator (t-PA). Plasmin then degrades fibrin into soluble fibrin degradation products (FDPs). Therefore decreased production of plasminogen or α_2-antiplasmin because of severe hepatic dysfunction may cause thrombosis or excessive fibrinolysis and a bleeding tendency, respectively.[1] Patients with hepatic disease may have increased FDPs as a result of enhanced fibrinolysis or decreased hepatic clearance of FDPs from circulation.

Primary and secondary hemostatic disorders may be hereditary or acquired. In the context of hepatobiliary and gastrointestinal disease, there are two main considerations regarding hemostatic defects: (a) development of a hemostatic abnormality secondary to an underlying hepatobiliary or gastrointestinal disease, and (b) a hereditary or acquired hemostatic disorder causing gastrointestinal bleeding. Hepatic failure may cause coagulopathy because of impaired production of plasma coagulation factors. It has been estimated that greater than 70% of functional hepatic mass must be lost to cause clinically important decreases in clotting factors.[2] Consequently, patients with massive hepatocellular necrosis and end-stage chronic hepatic disease are more likely to have a coagulopathy. Severe bleeding may exacerbate hemostatic defects (e.g., secondary to disseminated intravascular coagulation [DIC]). Depending on the cause of the hepatopathy (e.g., infectious disease, neoplasia, heat stroke), DIC may occur and contribute to an acquired hemostatic disorder. A thrombopathia associated with hepatobiliary disease has been documented in dogs with mucosal surface bleeding having normal coagulation profiles and platelet counts but impaired whole-blood platelet aggregation in response to collagen and arachidonic acid.[3] Proposed mechanisms of such an acquired thrombopathia include altered arachidonic acid metabolism and prostaglandin synthesis, disruption of membrane release of calcium into the cell, and defective calcium-initiated platelet granule release.[3]

Extrahepatic biliary obstruction (EHBO) may cause vitamin K–dependent coagulopathy because of impaired absorption of this fat-soluble vitamin from the intestines. Intrahepatic cholestasis has been postulated to decreased vitamin K absorption in some cats with hepatic disease (e.g., cholangiohepatitis, hepatic lipidosis), with a correlation existing between increased serum alkaline phosphatase and coagulation abnormalities.[4] Other rare potential causes of a vitamin K-dependent coagulopathy include severe intestinal disease leading to impaired absorption of vitamin K and oral antibiotic therapy resulting in decreased synthesis of vitamin K by intestinal flora. One study of experimentally induced cholestasis (via ligation of the common bile duct) in dogs resulted in inhibition of adenosine

diphosphate (ADP) and collagen-induced platelet aggregation in vitro, with impaired platelet function attributed to elevated serum bile acids rather than bilirubin.[5]

Differential Diagnosis

Hemostatic disorders in patients with underlying hepatobiliary disease may be noted initially when performing a coagulation screen in preparation for hepatic biopsy or surgery. Alternatively, such patients may be presented for a bleeding, either spontaneous or following surgery or trauma, due to their underlying hepatobiliary disease. In patients presented for gastrointestinal hemorrhage, it may be challenging to determine if a hemostatic disorder has exacerbated mucosal bleeding caused by underlying gastrointestinal disease rather than either condition occurring alone.

Hepatobiliary or Gastrointestinal Disease Causing Hemostatic Disorder

Because severe hepatic dysfunction is required to impair production of blood coagulation factors, acute massive hepatocellular necrosis and cirrhosis are more likely than other hepatopathies to cause clinically significant hemostatic disorders. Toxin ingestion appears to be the most common cause of massive hepatocellular necrosis and subsequent coagulopathy. Chapter 61 discusses hepatotoxins that cause hemostatic disorders.

Coagulation abnormalities in dogs and cats with hepatic disease are common. Sixty-six percent to 93% of dogs[6-8] and 82% of cats[4] have at least one coagulation test abnormality, the most common being prolongation of the activated partial thromboplastin time (aPTT) in 75% of dogs and prothrombin time (PT) in 77% of cats evaluated. Histopathologic diagnoses reported in dogs with coagulation abnormalities include acute hepatitis with necrosis, chronic active hepatitis, cirrhosis, and diffuse hepatocellular carcinoma,[8] whereas diagnoses reported in cats include hepatic lipidosis, cholangiohepatitis, and lymphoma.[4] Approximately 45% of cats with severe hepatic lipidosis have abnormal coagulation profiles.[9] Despite the high prevalence of coagulation test abnormalities in dogs and cats with hepatobiliary disease, few have clinically evident bleeding tendencies.[4,7-9]

Vitamin K–dependent coagulopathies may develop in patients with EHBO, particularly if the obstruction is complete and of several days' duration. The most common causes of EHBO in dogs include necrotizing cholecystitis secondary to cholelithiasis, pancreatitis, and neoplasia.[10-12] The most common causes of feline EHBO fall into two groups: neoplasia of either biliary or pancreatic origin, and inflammatory diseases including pancreatitis, cholangiohepatitis, cholecystitis, and cholelithiasis.[13] The prevalence of coagulation test abnormalities in dogs and cats with extrahepatic biliary disease varies, potentially as a consequence of some patients having EHBOs that are partial or acute. In one retrospective study of cats with EHBO, eight of 18 (44%) cats had a prolonged PT whereas 10 of 18 (56%) had a prolonged aPTT; all cats with prolonged PT also had an aPTT prolongation.[13] However, in a retrospective study of cats with obstructive cholelithiasis, a normal coagulation profile was noted in all eight cats tested.[14] Similar differences have been noted in dogs with EHBO. Nine dogs undergoing choledochal tube stenting had normal PT and aPTT,[11] whereas prolongation of aPTT was associated with mortality among 57 dogs undergoing extrahepatic biliary surgery.[10] In this latter study, the retrospective nature precluded determination of the cause of prolonged aPTT, but DIC and systemic inflammatory response syndrome (SIRS) secondary to septic bile peritonitis and vitamin K malabsorption may have contributed to the coagulopathy.[10] Although coagulation profile results are variable amongst both dogs and cats with EHBO, bleeding is uncommonly observed in such patients with abnormal hemostatic profiles. However, there is a case report of excessive bleeding associated with vitamin K deficiency in a dog with an EHBO.[15]

Exocrine pancreatic insufficiency (EPI) may result in a vitamin K–dependent coagulopathy as a result of lipase deficiency preventing breakdown of dietary triglycerides into monoglycerides and fatty acids, a step in lipid digestion that is needed for adequate solubilization and absorption of fat soluble vitamins.[16]

Hemostatic Disorder Causing Gastrointestinal Bleeding

Primary hemostatic disorders are more likely than coagulopathies to cause gastrointestinal bleeding. Severe thrombocytopenia (platelet count <30,000/μL) is the most common primary hemostatic disorder causing mucosal surface bleeding. Differential diagnoses for severe thrombocytopenia include idiopathic thrombocytopenic purpura (ITP), secondary immune-mediated thrombocytopenia (associated with drugs, neoplasia, or infectious diseases), bone marrow suppression, or various infectious diseases (especially tick-borne diseases). ITP is the most common cause of severe thrombocytopenia in dogs but is rare in cats. vWD and thrombopathia are other primary hemostatic disorders that may cause gastrointestinal bleeding, either spontaneous or associated with underlying gastrointestinal disorders. Dogs and cats with hereditary thrombopathies may present with petechiae, ecchymoses, excessive bleeding following surgery or trauma, or bleeding from various mucosal surfaces including the gastrointestinal tract. Well-characterized canine hereditary thrombopathies include thrombasthenic thrombopathia (also referred to as Glanzmann thrombasthenia), an absence or deficiency of the platelet glycoprotein (GP) IIb/IIIa receptor for fibrinogen (documented in Otterhounds and Great Pyrenees[17]), Basset Hound thrombopathia (a platelet signal transduction defect resulting in abnormal cyclic adenosine monophosphate [cAMP] metabolism[18]), platelet δ-storage pool deficiency (caused by decreased dense granule ADP content, reported in the American Cocker Spaniel[19]), and platelet procoagulant deficiency (also referred to as Scott syndrome, which is a result of abnormal membrane PS exposure and described in the German Shepherd[20]). A thrombopathia caused by a platelet δ-storage pool deficiency has also been documented in blue smoke Persian cats with Chediak-Higashi syndrome.[21] Acquired platelet function defects may occur following ingestion of nonsteroidal anti-inflammatory drugs (NSAIDs) or in association with uremia, cholestatic hepatic disease, and dysproteinemias. In gastrointestinal bleeding following NSAID administration, the cause is more likely gastrointestinal ulceration than an acquired thrombopathia, although concurrent platelet dysfunction could exacerbate bleeding.

Coagulopathies are more often associated with cavity bleeding than mucosal surface bleeding, but secondary hemostatic defects should be considered in patients with gastrointestinal bleeding. Mild to moderate thrombocytopenia has been documented in dogs with anticoagulant rodenticide poisoning, but marked thrombocytopenia (<30,000/μL) has also been reported.[22] Melena, hematochezia, and other surface bleeding (e.g., epistaxis, hematuria, gingival bleeding) have been noted in dogs with anticoagulant rodenticide poisoning and normal platelet counts.[23] A hereditary vitamin K–dependent coagulopathy attributable to defective γ-glutamylcarboxylase has been reported in Devon Rex cats with spontaneous hemorrhage into the thoracic cavity, joint, and urinary bladder.[24,25] Hereditary FVII deficiency is typically considered an asymptomatic defect or a cause

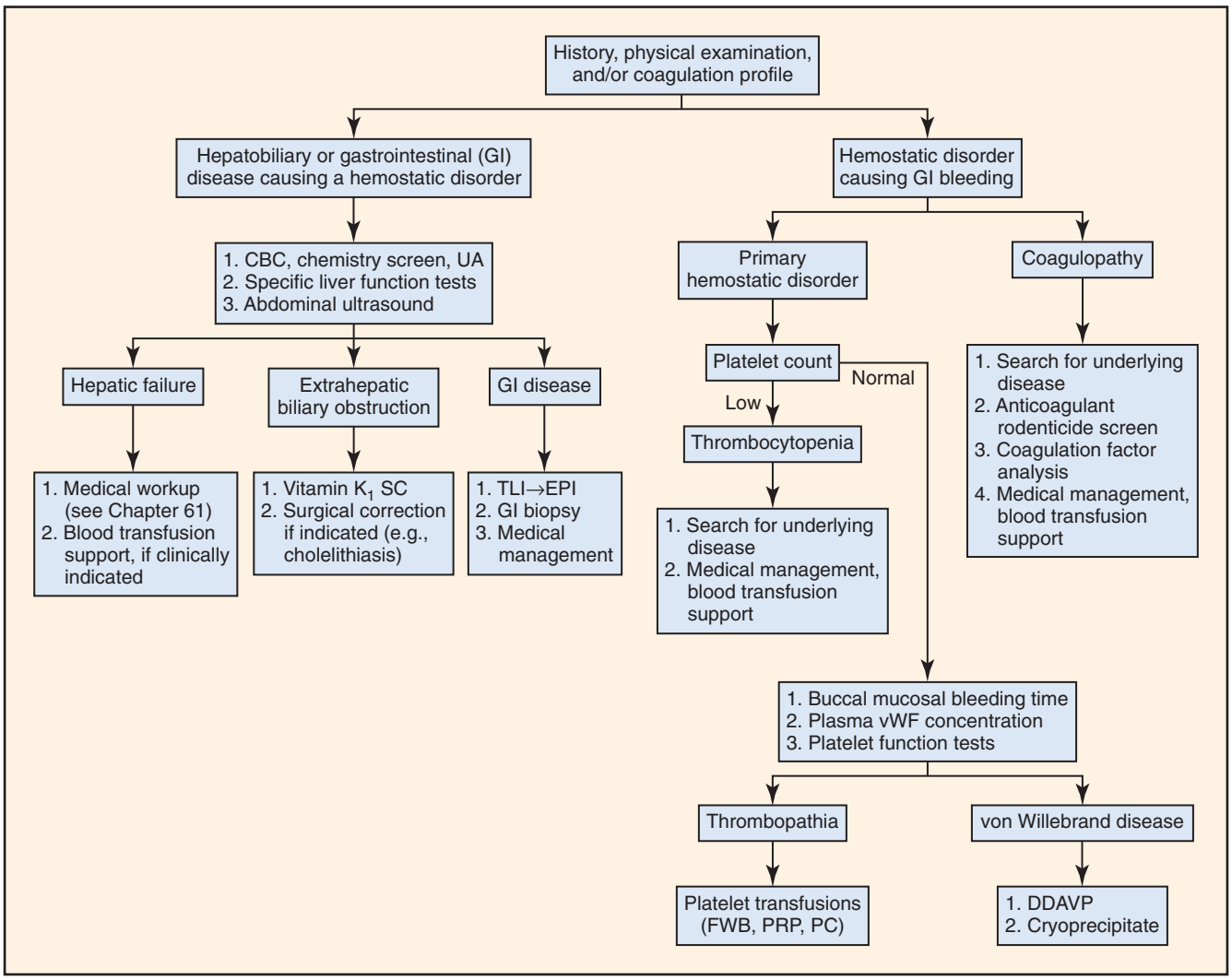

Figure 9-1 Algorithm for diagnostic and therapeutic approach to hemostatic disorders.

of minor bleeding, although severe bleeding has been reported, most often after surgery or trauma.[26] Hematochezia has been noted in FVII-deficient Beagles without other signs of colonic inflammation.[26] Of the intrinsic coagulopathies, hemophilia A (FVIII deficiency) or hemophilia B (FIX deficiency) may be more likely than others to cause bleeding within the gastrointestinal tract; severe gastrointestinal hemorrhage, potentially in association with coccidiosis, has been reported in hemophilic puppies.[27]

Evaluation of the Patient

History

The presence of a hemostatic abnormality should prompt questions about prior bleeding, such as excessive bleeding following neutering, other surgery, or trauma. A complete medication history is essential, as various drugs affect platelet function (e.g., aspirin) or platelet number (e.g., trimethoprim-sulfate–induced immune-mediated thrombocytopenia, or azathioprine-induced bone marrow suppression leading to decreased platelet production) and some potentially cause hepatoxicity (e.g., trimethoprim-sulfate and azathioprine). Similarly, toxin exposure could produce a severe coagulopathy (e.g., brodifacoum) or acute hepatocellular necrosis and resultant coagulopathy (e.g., aflatoxin).

Determining the presenting complaint, time that patient was last normal, progression of clinical signs, and systems review may provide key information for differentiating acquired and hereditary hemostatic disorders, as well as identifying the underlying cause of the gastrointestinal or hepatobiliary disease (Fig. 9-1). For example, in the case of young dog with a recent dietary indiscretion and an acute onset of vomiting, subsequent development of icterus and a coagulopathy may be more likely attributed to pancreatitis and an EHBO than to hepatic failure.

Physical Examination

The type of bleeding may help differentiate primary and secondary hemostatic disorders. As a general rule, primary hemostatic disorders are usually associated with petechia, ecchymosis, and mucosal surface bleeding (e.g., melena, epistaxis, gingival bleeding, hematuria), whereas coagulopathies typically produce cavitary bleeding (e.g., hematoma, hemarthrosis, hemoperitoneum, hemothorax). Melena is not necessarily indicative of a hemostatic disorder as gastrointestinal ulceration, neoplasia, and a variety of other disorders may produce melena. Interestingly, dogs with vWD do not typically present with spontaneous petechia and ecchymosis. Patients with primary and/or secondary hemostatic disorders may both present with excessive bleeding following surgery or trauma.

Icterus in patients with a coagulopathy is suggestive of hepatic disease or EHBO. However, hemolysis from immune-mediated hemolytic anemia or microangiopathic hemolytic anemia and concurrent DIC could also produce icterus and coagulopathy. Pallor may occur in patients secondary to blood loss. Although pallor is not necessarily helpful in identifying a patient's underlying disease process, it may indicate the need for additional oxygen-carrying support (i.e., a red blood cell [RBC] transfusion). Hepatomegaly may be indicative of an acute inflammatory process or infiltrative disease, whereas microhepatia is more suggestive of cirrhosis. Similarly, concurrent splenomegaly, lymphadenopathy, and/or an abdominal fluid wave may help narrow the list of differential diagnoses. Finally, a patient's body condition score may reflect the chronicity of the underlying disease.

Laboratory Evaluation and Tests

Initial hemostatic testing typically includes platelet count, PT, and aPTT. In emergencies, evaluation of a blood smear allows estimation of platelet numbers (e.g., 10 to 20 platelets per oil immersion field is considered adequate). The blood smear should be evaluated in conjunction with automated platelet counts because platelet clumping can cause spuriously decreased automated platelet counts. A bleeding tendency is not typically observed until the platelet count is <30,000 to 40,000/μL. However, platelet counts of 25,000 to 30,000/μL are associated with an autosomal recessive trait of congenital asymptomatic thrombocytopenia in Cavalier King Charles Spaniels.[28] The platelet count is interpreted in light of the complete blood cell count (CBC). Pancytopenia usually indicates a bone marrow aspirate or biopsy. Severe thrombocytopenia (<30,000 platelets/μL), regenerative anemia, and normal PT and aPTT in patients with melena or other surface bleeding may be suggestive of an immune-mediated thrombocytopenia; and, infectious disease screening and radiographic imaging (e.g., thoracic radiographs, abdominal ultrasound) may be indicated to rule out underlying disease. Thrombocytopenia plus prolongation of PT and aPTT would be suggestive of a consumptive coagulopathy, as potentially noted in patients with severe hemorrhage or DIC.

The PT assesses extrinsic and common coagulation pathways while aPTT assesses intrinsic and common pathways. Therefore prolonged PT plus normal aPTT isolates hemostatic defects to the extrinsic pathway (i.e., FVII deficiency), whereas prolonged aPTT plus normal PT indicates an intrinsic coagulopathy. The more commonly seen combination of prolonged PT and aPTT is caused by deficiency of multiple plasma coagulation factors or, less likely, a common pathway factor deficiency (i.e., FX, FII, fibrinogen). If a heritable single factor deficiency is suspected, plasma coagulation factor activity analysis should be performed (Comparative Coagulation Laboratory at Cornell University) to confirm the diagnosis and guide treatment. Anticoagulant rodenticide screening, hepatic function tests, and/or ultrasonographic imaging of the liver and biliary tract may be appropriate in patients with suspected multiple coagulation factor deficiencies.

If the platelet count, PT, and aPTT are normal, then a buccal mucosal bleeding time (BMBT) is used to test platelet function in patients with mucosal surface bleeding. The BMBT is specific for primary hemostatic defects, and reference values are less than 4 and less than 2 minutes for dogs and cats, respectively. Although the effect of anemia on BMBT in dogs and cats has not been evaluated, similar bleeding time tests in humans have been shown to be dependent on RBC number with prolonged bleeding times being corrected following RBC transfusion.[29] The same is expected to be true for dogs and cats although lower cut-offs for packed cell volume (PCV) affecting BMBT results have not yet been determined. Finding prolonged BMBT in a patient with a normal platelet count and PCV is suggestive of vWD, thrombopathia, or, rarely, vasculopathy. Because vWD occurs more commonly than thrombopathia in dogs (both occur rarely in cats), measurement of plasma vWF-to-antigen concentration is indicated in patients with prolonged BMBT before pursuing specific platelet function tests. As genetic mutations causing various hereditary thrombopathies are characterized, diagnosis of a thrombopathia will be greatly simplified as a small ethylenediaminetetraacetic acid (EDTA) blood sample can be submitted for DNA analysis. DNA testing is currently available through Auburn University for diagnosis of Glanzmann thrombasthenia in the Great Pyrenees, Otterhound, and Basset Hound thrombopathies. Screening for other platelet function defects typically requires onsite evaluation of the patient at a university and institution performing platelet aggregation studies.

Complete blood count (CBC), serum chemistry screen, and urinalysis may point toward hepatic failure or EHBO as the cause of a coagulopathy. Finding decreased serum concentrations of glucose, blood urea nitrogen (BUN), albumin, and cholesterol and increased concentration of bilirubin is suggestive of hepatic dysfunction, whereas elevation of serum alkaline phosphate (ALP), γ-glutamyltransferase (GGT), cholesterol, and bilirubin would be more suggestive of a EHBO. Specific hepatic function tests (e.g., blood ammonia, serum bile acid concentrations provided serum bilirubin is not elevated) can support a diagnosis of hepatic failure. Abdominal ultrasound is indicated to evaluate hepatic architecture (hepatic size is better evaluated by radiographs), the biliary tract, and surrounding structures, including the pancreas and duodenum.

The anticoagulant proteins antithrombin (AT) and protein C are synthesized by the liver and have been used to detect hepatobiliary disease and portosystemic shunting in dogs.[30] Dogs with hepatic failure (majority caused by ingestion of hepatotoxins) had substantially reduced plasma AT and protein C activities compared with dogs with chronic hepatitis or miscellaneous hepatobiliary disease (including neoplasia and vacuolar hepatopathy). Ninety-five percent and 85% of dogs with acute hepatic failure had decreased protein C and AT activities, respectively.[30] In dogs with portosystemic vascular anomalies, low protein C and AT activities were noted in 88% and 53% of dogs, respectively.[30] Interestingly, dogs with hepatobiliary disease and portosystemic vascular anomalies had low protein C activity more frequently than prolongation of either PT or aPTT.[30] Measurement of plasma protein C activity may be useful in assessing both hepatic function and perfusion. However, in contrast to decreased plasma coagulation factor activity, low AT and protein C activities may be associated with thrombotic disorders rather than a hemorrhagic tendency.

Treatment and Management

Hepatobiliary or Gastrointestinal Disease Causing Hemostatic Disorder

Identification and correction of underlying hepatobiliary or gastrointestinal disorders is necessary to resolve acquired hemostatic disorders. However, some underlying conditions (e.g., hepatic cirrhosis) cannot be reversed. Patients with hepatic dysfunction causing coagulopathy and bleeding may benefit from fresh-frozen plasma (FFP) (6 to 12 mL/kg intravenously q12h) as a way to improve hemostasis

prior to hepatic biopsy or in actively bleeding patients. Citrate is rapidly metabolized by the liver, but administration of large volumes of FFP or whole blood can cause ionized hypocalcemia secondary to impaired citrate metabolism in patients with severe hepatic dysfunction, particularly if anesthetized and hypothermic. It is prudent to determine blood type and perform a blood crossmatch for dogs transfused more than 4 days prior and for all cats in case the patient has significant bleeding following a hepatic biopsy. Packed red blood cells (PRBCs) (10 mL/kg intravenously initially, and then given to effect) can provide additional oxygen-carrying support. Alternatively, fresh whole blood (i.e., less than 8 hours old from the time of collection and stored at room temperature) (20 mL/kg intravenously) may be administered to provide plasma coagulation factors, RBCs, and platelets to patients thrombocytopenic from increased consumption.

Vitamin K_1, also called phytonadione, (1 mg/kg subcutaneously q24h) is indicated in patients with coagulopathy secondary to EHBO or potentially severe intestinal disease causing malabsorption of vitamin K. Administration of vitamin K typically corrects such coagulopathies within 24 hours because the liver continues producing coagulation factors in their inactive form despite the cholestasis. One may administer vitamin K to patients with hepatic dysfunction to optimize hepatic carboxylation of vitamin K–dependent factors. If a patient with a vitamin K–dependent coagulopathy presents with severe or life-threatening bleeding, FFP will improve hemostasis more rapidly than administering vitamin K alone.

Hemostatic Disorder Causing Gastrointestinal Bleeding

It is essential that underlying causes of acquired hemostatic disorders causing gastrointestinal bleeding be identified so as to institute specific treatment. For example, corticosteroids would be appropriate for a dog with melena caused by immune-mediated thrombocytopenia, whereas doxycycline would be indicated in a dog with melena and severe thrombocytopenia secondary to ehrlichiosis. Similarly, oral vitamin K would be the most appropriate treatment for a dog with anticoagulant rodenticide poisoning.

In patients with hereditary bleeding disorders causing gastrointestinal bleeding, the hemorrhagic tendency is a lifelong problem that may require intermittent blood transfusions to control bleeding. Although there are few indications for platelet transfusions in small animal medicine, patients with hereditary thrombopathies experiencing severe mucosal surface bleeding may require platelet transfusions. In such patients, fresh whole blood is typically administered to provide functional platelets and RBCs because they often develop blood loss anemia. Platelet-rich plasma and platelet concentrate are other options for transfusion support, although these products are not available in clinical practice. Administration of cryoprecipitate (1 unit/10 kg body weight intravenously, q8-12h), a plasma product containing a high concentration of vWF in addition to FVIII, fibrinogen, and fibronectin is recommended to control severe bleeding in vWD patients. Desmopressin (DDAVP) (1 µg/kg subcutaneously) is another option improving hemostasis in vWD dogs. DDAVP has also been shown to exert beneficial hemostatic effects in human patients with acquired and hereditary thrombopathias,[31] although similar data is not available for dogs and cats. Administration of FFP can be used to help control bleeding from any coagulopathy, and type-compatible RBC transfusion support should be available, regardless of the underlying cause of the gastrointestinal or other bleeding.

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CHAPTER 10

Constipation

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Definition

Reviews of idiopathic megacolon have emphasized the importance of considering an extensive list of differential diagnoses (e.g., neuromuscular, mechanical, inflammatory, metabolic/endocrine, pharmacologic, environmental, and behavioral causes) for the obstipated cat (Box 10-1; reviewed in reference 1). One review of published cases suggests that 96% of cases of obstipation are accounted for by idiopathic megacolon (62%), pelvic canal stenosis (23%), nerve injury (6%), or Manx sacral spinal cord deformity (5%).[2] A smaller number of cases are accounted for by complications of colopexy (1%), and colonic neoplasia (1%); colonic hypo- or aganglionosis was suspected in another 2% of cases. Inflammatory, pharmacologic, and environmental/behavioral causes were not cited as predisposing factors in any of the original case reports. Endocrine factors (e.g., obesity and hypothyroidism) were cited in several cases, but were not necessarily impugned as part of the pathogenesis of megacolon. It is important to consider an extensive list of differential diagnoses in an individual animal, but it should be kept in mind that most cases are idiopathic, orthopedic, or neurologic in origin. Behavioral (e.g., stress) and/or environmental (e.g., competition for the litter box) factors may play an important role in the development of the disorder, but haven't been very well characterized in retrospective or prospective studies.

Pathophysiology and Mechanisms

Megacolon develops through two pathologic mechanisms: *dilation* and *hypertrophy*. *Dilated megacolon* is the end stage of colonic dysfunction in idiopathic cases. Cats affected with idiopathic dilated megacolon have permanent loss of colonic structure and function. Medical therapy may be attempted in such cases, but most affected cats eventually require colectomy. *Hypertrophic megacolon*, on the other hand, develops as a consequence of obstructive lesions (e.g., malunion of pelvic fractures, tumors, foreign bodies). Hypertrophic megacolon may be reversible with early pelvic osteotomy or it may progress to irreversible dilated megacolon if appropriate therapy is not instituted.[3]

Constipation and *obstipation* are earlier manifestations of the same problem. Constipation is defined as infrequent, difficult, painful evacuation of feces but does not necessarily imply a permanent loss of function. Many cats experience one or two episodes of constipation without further progression. Intractable constipation that has become refractory to cure or control is referred to as *obstipation*. Obstipation implies a permanent loss of function. A cat is assumed to be obstipated only after several consecutive treatment failures. Recurring episodes of constipation or obstipation may culminate in the syndrome of *megacolon*.

The pathogenesis of idiopathic dilated megacolon involves functional disturbances of colonic smooth muscle. Megacolonic smooth muscle develops less isometric stress in response to neurotransmitter (acetylcholine, substance P, cholecystokinin), membrane depolarization (potassium chloride), or electrical field stimulation, when compared to healthy controls.[4,5] Differences have been observed in longitudinal and circular smooth muscle from descending and ascending colon. No significant abnormalities of smooth muscle cells or of myenteric neurons have been observed on histologic evaluation. Feline idiopathic megacolon is a generalized dysfunction of colonic smooth muscle, and treatments aimed at stimulating colonic smooth muscle contraction generally improve colonic motility. The lesion may begin in the descending colon and progress to involve the ascending colon over time.[6]

Differential Diagnosis

Neoplasia

In dogs, colonic tumors are more common than gastric or small intestinal tumors. The mean age of dogs affected with colonic neoplasia is variably reported between 7 and 11 years of age.[7] Most colonic tumors of dogs are malignant and include adenocarcinomas, lymphosarcomas, and gastrointestinal stromal tumors (leiomyosarcoma, neurofibrosarcoma, fibrosarcoma, and ganglioneuroma).[8-17] Leiomyosarcomas are the most common (91%) of the gastrointestinal stromal tumors.[10-13] Most colonic neoplasia develop in the descending colon and rectum, although leiomyosarcomas more frequently develop in the cecum.[10,12] Local tumor invasion apparently occurs at a slower rate with canine colonic neoplasia, and metastasis to distant sites is relatively uncommon. Benign colonic neoplasia (e.g., adenomas, adenomatous polyps, and leiomyomas) also occur, although they are less common than malignant tumors. Malignant transformation of adenomatous polyps to carcinoma in situ and invasive adenocarcinoma has been demonstrated in the dog just as it has in humans.[7,18,19] Extramedullary plasmacytomas are an uncommon tumor of the gastrointestinal tract, but many of these occur in the large intestine and rectum.[20,21] All of the aforementioned tumors are associated with signs of inflammation and obstruction (e.g., hematochezia, tenesmus, and dyschezia). Carcinoids (rare 5-hydroxytryptamine [5-HT] secreting tumors) are occasionally associated with diarrhea because of the effects of 5-HT on secretion and motility.

Box 10-1 Differential Diagnosis of Constipation in the Cat

Neuromuscular Dysfunction
Colonic smooth muscle: idiopathic megacolon, aging
Spinal cord disease: lumbosacral disease, cauda equine syndrome, sacral spinal cord deformities (Manx cat)
Hypogastric or pelvic nerve disorders: traumatic injury, malignancy, dysautonomia
Submucosal or myenteric plexus neuropathy: dysautonomia, aging

Mechanical Obstruction
Intraluminal: foreign material (bones, plant material, hair), neoplasia, rectal diverticula, perineal hernia, anorectal strictures
Intramural: neoplasia
Extraluminal: pelvic fractures, neoplasia

Inflammation
Perianal fistula, proctitis, anal sac abscess, anorectal foreign bodies, perianal bite wounds

Metabolic and Endocrine
Metabolic: dehydration, hypokalemia, hypercalcemia
Endocrine: hypothyroidism, obesity, nutritional secondary hyperparathyroidism

Pharmacologic
Opioid agonists, cholinergic antagonists, β agonists, diuretics, phenothiazines

Environmental and Behavioral
Soiled litter box, inactivity, hospitalization, change in environment

In cats, adenocarcinoma (46%) is the most common large intestinal tumor, followed by lymphosarcoma (41%) and mast cell tumors (9%).[22-24] The mean age of cats affected with colonic neoplasia is 12.5 years. The descending colon (39%) and the ileocolic sphincter (28%) are the most common sites of colonic neoplasia in the cat. Unlike colonic tumors in dogs, feline colonic tumors have a high rate (63%) of metastasis and, of course, metastasis is associated with decreased survival time. Metastatic sites include colonic lymph nodes, mesenteric lymph nodes, liver, spleen, bladder, urethra, omentum, mesocolon, lungs, duodenum, and peritoneum.

Intussusception

Intussusception is an invagination of one segment of the gastrointestinal tract into the lumen of an adjoining segment. The intussusceptum is the invaginated segment of the alimentary tract, whereas the intussuscipiens is the enveloping segment. Invagination may occur in an antegrade (aborad) or retrograde (orad) direction, but is most commonly in the antegrade direction. Any portion of the alimentary tract may be involved, but enterocolic intussusceptions account for almost two-thirds of published cases in dogs and cats. Enterocolic intussusceptions can be further divided into three types: cecocolic (or cecal inversion), with the inverted cecum forming the apex[25]; ileocolic, with the ileum forming the apex; and ileocecal, with the ileocecal junction forming the apex.[26] Of these three forms of enterocolic intussusception, the ileocolic intussusception is most frequently encountered in clinical practice. A number of conditions are reported to predispose to intussusception, including intestinal parasitism, viral enteritis, foreign bodies, and masses, but in dogs and cats most intussusceptions are idiopathic.[27-29]

Evaluation of the Patient

History

Constipation, obstipation, and megacolon may be observed in cats of any age, sex, or breed; however, most cases are observed in middle aged (mean = 5.8 years) male cats (70% male, 30% female) of Domestic Shorthair (46%), Domestic Longhair (15%), or Siamese (12%) breeding.[2] Affected cats are usually presented for reduced, absent, or painful defecation for a period of time ranging from days to weeks or months. Some cats are observed making multiple, unproductive attempts to defecate in the litter box, while other cats may sit in the litter box for prolonged periods of time without assuming a defecation posture. Dry, hardened feces are observed inside and outside of the litter box. Occasionally, chronically constipated cats have intermittent episodes of hematochezia or diarrhea caused by the mucosal irritant effect of fecal concretions. This may give the pet owner the erroneous impression that diarrhea is the primary problem. Prolonged inability to defecate may result in other systemic signs, including anorexia, lethargy, weight loss, and vomiting.

Physical Examination

Colonic impaction is a consistent physical examination finding in affected cats. Other findings will depend upon the severity and pathogenesis of constipation. Dehydration, weight loss, debilitation, abdominal pain, and mild to moderate mesenteric lymphadenopathy may be observed in cats with severe idiopathic megacolon. Colonic impaction may be so severe in such cases as to render it difficult to differentiate impaction from colonic, mesenteric, or other abdominal neoplasia. Cats with constipation as a consequence of dysautonomia may have other signs of autonomic nervous system failure, such as urinary and fecal incontinence, regurgitation because of megaesophagus, mydriasis, decreased lacrimation, prolapse of the nictitating membrane, and bradycardia. Digital rectal examination should be carefully performed with sedation or anesthesia in all cats. Pelvic fracture malunion may be detected on rectal examination in cats with pelvic trauma. Rectal examination might also identify other unusual causes of constipation, such as foreign bodies, rectal diverticula, stricture, inflammation, or neoplasia. Chronic tenesmus may be associated with perineal herniation in some cases. A complete neurologic examination with special emphasis on caudal spinal cord function should be performed to identify neurologic causes of constipation, for example, spinal cord injury, pelvic nerve trauma, and Manx sacral spinal cord deformity.

Laboratory Evaluation and Tests

Although most cases of obstipation and megacolon are unlikely to have significant changes in laboratory data (e.g., complete blood count, serum chemistry, urinalysis), nonetheless these tests should be performed in all cats presented for constipation. Metabolic causes of constipation, such as dehydration, hypokalemia, and hypercalcemia, may be detected in some cases. Basal serum T_4 concentration and other thyroid function tests should also be considered in cats with recurrent constipation and other signs consistent with hypothyroidism. Although hypothyroidism was documented in only one case of obstipation and megacolon, obstipation is a frequent clinical sign in kittens affected with congenital or juvenile-onset hypothyroidism.[2] Constipation could also theoretically develop following successful treatment of feline hyperthyroidism.

Abdominal radiography should be performed in all constipated cats to characterize the severity of colonic impaction, and to identify predisposing factors such as intraluminal radiopaque foreign material (e.g., bone chips), intraluminal or extraluminal mass lesions,

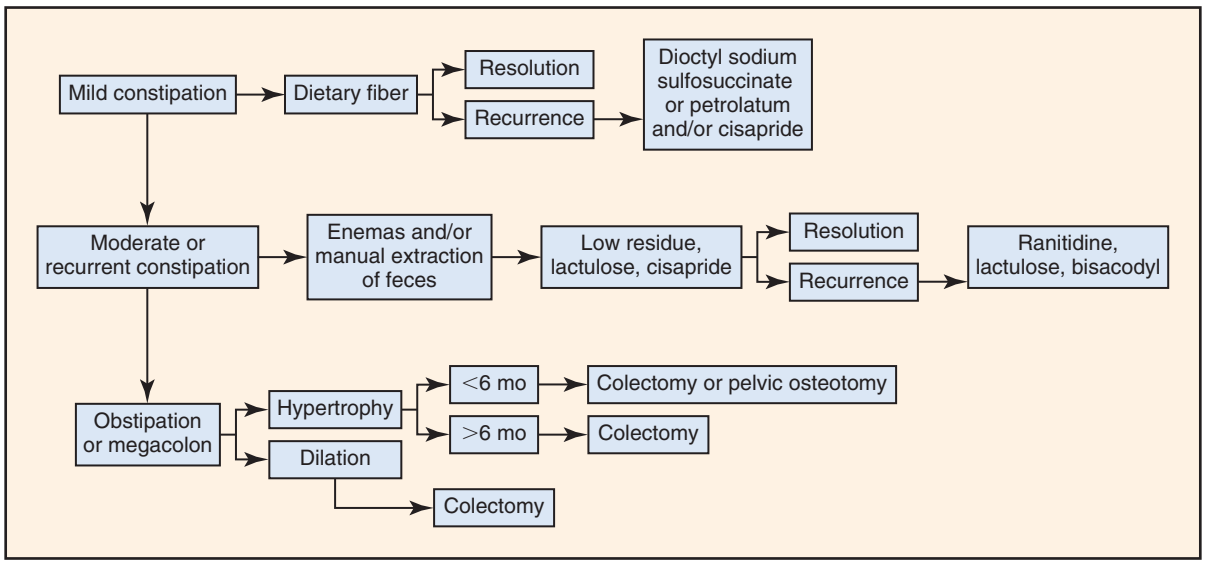

Figure 10-1 Medical management of cats affected with mild constipation, moderate or recurrent constipation, and obstipation or megacolon.

pelvic fractures, and spinal cord abnormalities. Radiographic findings of colonic impaction cannot be used to distinguish between constipation, obstipation, and megacolon in idiopathic cases. First or second episodes of constipation in some cats may be severe and generalized but may still resolve with appropriate treatment.

Ancillary studies may be indicated in some cases. Extraluminal mass lesions may be further evaluated by abdominal ultrasonography and guided biopsy, whereas intraluminal mass lesions are best evaluated by endoscopy. Colonoscopy may also be used to evaluate the colon and anorectum for suspected inflammatory lesions, strictures, sacculations, and diverticula. Barium enema contrast radiography may be used if colonoscopy is not possible. Both colonoscopy and barium enema contrast radiography will require general anesthesia and evacuation of impacted feces. Cerebrospinal fluid analysis, computed tomography (CT) or magnetic resonance imaging (MRI), and electrophysiologic studies should be considered in animals with evidence of neurologic impairment. Finally, colonic biopsy or anorectal manometry is necessary to diagnose suspected cases of aganglionic megacolon.

Treatment and Management

Specific therapeutic plans depend upon severity of constipation and underlying causes.[1] Medical therapy may not be necessary with first episodes of constipation. First episodes are often transient and resolve without therapy. Mild to moderate or recurrent episodes of constipation, on the other hand, usually require some medical intervention. These cases may be managed, often on an outpatient basis, with rehydration, dietary modification, water enemas, oral or suppository laxatives, and/or colonic prokinetic agents. Severe cases of constipation usually require brief periods of hospitalization to correct metabolic abnormalities and to evacuate impacted feces using water enemas, manual extraction of retained feces, or both. Followup therapy in such cases is directed at correcting predisposing factors and preventing recurrence. Subtotal colectomy will become necessary in cats suffering from obstipation or idiopathic dilated megacolon. These cats, by definition, are unresponsive to medical therapy. Pelvic osteotomy without colectomy may be sufficient for some cats suffering from pelvic canal stenosis and hypertrophic megacolon.[30]

Figure 10-1 is an algorithm for the therapeutic approach to the constipated, obstipated, and megacolonic cat.

Removal of Impacted Feces

Removal of impacted feces may be accomplished through the use of rectal suppositories, enemas, or manual extraction.

Rectal Suppositories

Numerous pediatric rectal suppositories are available for management of mild constipation. These include dioctyl sodium sulfosuccinate (emollient laxative), glycerin (lubricant laxative), and bisacodyl (stimulant laxative). Use of rectal suppositories requires a compliant pet and pet owner. Suppositories can be used alone or in conjunction with oral laxative therapy.

Enemas

Mild to moderate or recurrent episodes of constipation may require administration of enemas and/or manual extraction of impacted feces. Several types of enema solutions may be administered, such as warm tap water (5 to 10 mL/kg), warm isotonic saline (5 to 10 mL/kg), dioctyl sodium sulfosuccinate (5 to 10 mL/cat), mineral oil (5 to 10 mL/cat), or lactulose (5 to 10 mL/cat). Enema solutions should be administered slowly with a well-lubricated 10 to 12 Fr rubber catheter or feeding tube. Enemas containing sodium phosphate are contraindicated in cats because of their propensity for inducing severe hypernatremia, hyperphosphatemia, and hypocalcemia in this species.[31]

Manual Extraction

Cases unresponsive to enemas may require manual extraction of impacted feces. Cats should be adequately rehydrated and then anesthetized with an endotracheal tube in place to prevent aspiration should colonic manipulation induce vomiting. Water or saline is infused into the colon while the fecal mass is manually reduced by abdominal palpation. Sponge forceps may also be introduced rectally (with caution) to break down the fecal mass. It may be advisable to evacuate the fecal mass over a period of several days to reduce risks of prolonged anesthesia and perforation of a devitalized colon. If this approach fails, colotomy may be necessary to remove

the fecal mass. Laxative and/or prokinetic therapy may then be instituted once the fecal mass has been removed.

Laxative Therapy

Laxatives promote evacuation of the bowel through stimulation of fluid and electrolyte transport or increases in propulsive motility. They are classified as bulk-forming, emollient, lubricant, hyperosmotic, or stimulant laxatives according to their mechanism of action. There are literally hundreds of products available for treatment of constipation.

Bulk-Forming Laxatives

Most bulk-forming laxatives are dietary fiber supplements of poorly digestible polysaccharides and celluloses derived principally from cereal grains, wheat bran, and psyllium. Some constipated cats will respond to supplementation of the diet with one of these products, but many require adjunctive therapy (e.g., other types of laxatives or colonic prokinetic agents). Dietary fiber is preferable because it is well tolerated, more effective, and more physiologic than other laxatives. Fiber is a classified as a bulk-forming laxative, although it has many other properties. Beneficial effects of fiber in constipation include increased fecal water content, decreased intestinal transit time, and increased frequency of defecation.[32,33] Fiber-supplemented diets are available commercially, or the pet owner may wish to add psyllium (1 to 4 tsp. per meal), wheat bran (1 to 2 tbsp. per meal), or pumpkin (1 to 4 tbsp. per meal) to canned cat food. Cats should be well hydrated before commencing fiber supplementation to maximize therapeutic effect. Fiber supplementation is most beneficial in mildly constipated cats prior to development of obstipation and megacolon. In obstipated and megacolon cats, fiber may, in fact, be detrimental. Low-residue diets may be more beneficial in obstipated and megacolonic cats.

Emollient Laxatives

Emollient laxatives, or stool softeners, are anionic detergents that increase the miscibility of water and lipid in digesta, thereby enhancing lipid absorption and impairing water absorption. Dioctyl sodium sulfosuccinate and dioctyl calcium sulfosuccinate are examples of emollient laxatives available in oral and enema form. Anecdotal experience suggests that dioctyl sodium sulfosuccinate therapy may be most useful in animals with acute but not chronic constipation. As with bulk-forming laxatives, animals should be well-hydrated before emollient laxatives are administered. It should be noted that clinical efficacy has not been definitively established for the emollient laxatives. Dioctyl sodium sulfosuccinate, for example, inhibits water absorption in isolated colonic segments in vitro, but it may be impossible to achieve tissue concentrations great enough to inhibit colonic water absorption in vivo. Dioctyl sodium sulfosuccinate at a dosage of 30 mg/kg/day had no effect on fecal consistency in Beagle dogs.[34] Further studies are required to determine clinical efficacy and therapeutic role of dioctyl sodium sulfosuccinate in management of constipated cats.

Lubricant Laxatives

Mineral oil and white petrolatum are two major lubricant laxatives available for treatment of constipation. Lubricating properties of these agents impede colonic water absorption, as well as permit greater ease of fecal passage. These effects are usually moderate, however, and lubricants are generally beneficial only in mild cases of constipation. Mineral oil usage should probably be limited to rectal administration because of risk of aspiration pneumonia with oral administration, especially in depressed or debilitated cats.

Hyperosmotic Laxatives

This group of laxatives consists of poorly absorbed polysaccharides (e.g. lactose, lactulose), magnesium salts (e.g., magnesium citrate, magnesium hydroxide, magnesium sulfate), and polyethylene glycols. Lactose is not effective as a laxative agent in all cats.[35] Lactulose is the most effective agent in this group. The organic acids produced from lactulose fermentation stimulate colonic fluid secretion and propulsive motility. Lactulose administered at a dosage of 0.5 mL/kg body weight q8-12h fairly consistently produces soft feces in the cat. Many cats with recurrent or chronic constipation have been well managed with this regimen of lactulose. The dosage may have to be tapered in individual cases if flatulence and diarrhea become excessive. Magnesium salts are not currently recommended in the treatment of feline constipation and idiopathic megacolon. Some veterinarians have reported anecdotal successes with the polyethylene glycols.

Stimulant Laxatives

Stimulant laxatives (bisacodyl, phenolphthalein, castor oil, cascara, senna) are a diverse group of agents that have been classified according to their ability to stimulate propulsive motility. Bisacodyl, for example, stimulates nitric oxide–mediated epithelial cell secretion and myenteric neuronal depolarization.[36] Diarrhea results from the combined effect of increased mucosal secretion and colonic propulsion. Bisacodyl, at a dosage of 5 mg q24h PO, is the most effective stimulant laxative in the cat. It may be given individually or in combination with fiber supplementation for long-term management of constipation. Daily administration of bisacodyl should probably be avoided, however, because of injury to myenteric neurons with chronic usage.[36]

Colonic Prokinetic Agents

Stimulation of colonic smooth muscle contraction might improve colonic motility in cats affected with idiopathic dilated megacolon.[4,5,37] Unfortunately, many currently available gastrointestinal prokinetic agents have not proved useful in the therapy of feline constipation either because of significant side effects (e.g., bethanechol) or because the prokinetic effect is limited to the proximal gastrointestinal tract (e.g., metoclopramide, domperidone, erythromycin). The 5-HT_4 serotonergic agonists (e.g., cisapride, prucalopride, tegaserod, mosapride) appear to have the advantage of stimulating motility from the gastroesophageal sphincter to the descending colon with relatively few side effects. Cisapride, for example, increases gastroesophageal sphincter pressure, promotes gastric emptying, and enhances small intestinal and colonic propulsive motility.[38] Cisapride enhances colonic propulsive motility through activation of colonic neuronal or smooth muscle 5-HT receptors in a number of animal species.[39,40] In vitro studies show that cisapride stimulates feline colonic smooth muscle contraction,[5,40] although it has not yet been conclusively shown that cisapride stimulates feline colonic propulsive motility in vivo. A large body of anecdotal experience suggests that cisapride is effective in stimulating colonic propulsive motility in cats affected with mild to moderate idiopathic constipation; cats with long-standing obstipation and megacolon are unlikely to show much improvement with cisapride therapy. Cisapride was widely used in the management of canine and feline gastric emptying, intestinal transit, and colonic motility disorders throughout most of the 1990s.[38,41,42] Cisapride was withdrawn from the American, Canadian, and certain West European countries in July 2000 following reports of untoward cardiac side effects in human patients. Cisapride causes QT interval prolongation and slowing of cardiac repolarization via blockade of the rapid

component of the delayed rectifier potassium channel (I_{Kr}).[43] This effect may result in a fatal ventricular arrhythmia referred to as torsades de pointes. Similar effects have been characterized in canine cardiac Purkinje fibers,[44] but in vivo effects have not yet been reported in dogs or cats. Withdrawal of cisapride has created a clear need for new gastrointestinal (GI) prokinetic agents, although cisapride continues to be available from compounding pharmacies throughout the United States. Tegaserod and prucalopride have been used in the therapy of several of the GI motility disorders, but have limited availability around the world.[37]

Tegaserod is a potent partial nonbenzamide agonist at 5-HT_4 receptors and a weak agonist at 5-HT_{1D} receptors.[45,46] Tegaserod has definite prokinetic effects in the canine colon, but it has not yet been studied in the feline colon. Intravenous doses of tegaserod (0.03 to 0.3 mg/kg) accelerate colonic transit in dogs during the first hour after intravenous administration.[45] Tegaserod at doses of 3 to 6 mg/kg PO normalizes intestinal transit in opioid-induced bowel dysfunction in dogs,[47] and it may prove useful in other disorders of intestinal ileus or pseudoobstruction. Gastric effects of tegaserod have not been reported in dogs, so this drug may not prove as useful as cisapride in the treatment of delayed gastric emptying disorders. In vitro studies suggest that tegaserod does not prolong the QT interval or delay cardiac repolarization as has been occasionally reported with cisapride. Tegaserod was marketed under the trade name of Zelnorm in the United States in September 2002 for the treatment of constipation-predominant irritable bowel syndrome in women. As with cisapride, it was eventually removed from the American market because of untoward cardiac side effects.

Prucalopride is a potent 5-HT_4 receptor agonist that stimulates giant migrating contractions (GMCs) and defecation in dogs and cats.[48,49] Prucalopride also appears to stimulate gastric emptying in the dog.[50] In lidamidine-induced delayed gastric emptying in dogs, prucalopride (0.01 to 0.16 mg/kg) dose-dependently accelerates gastric emptying of dextrose solutions. Prucalopride has not yet been marketed in the United States or elsewhere.

Misoprostol is a prostaglandin E_1 analogue that reduces the incidence of nonsteroidal antiinflammatory drug-induced gastric injury. Main side effects of misoprostol therapy are abdominal discomfort, cramping, and diarrhea. Studies in dogs suggest that prostaglandins may initiate a giant migrating complex pattern and increase colonic propulsive activity.[51] In vitro studies of misoprostol show that it stimulates feline and canine colonic smooth muscle contraction.[52] Given its limited toxicity, misoprostol may be useful in cats (and dogs) with severe refractory constipation.

Ranitidine and nizatidine, classic histamine H_2 receptor antagonists, may also stimulate canine and feline colonic motility. These drugs stimulate contraction apparently through inhibition of tissue acetylcholinesterase and accumulation of acetylcholine at the motor endplate. It's not yet clear how effective these drugs are in vivo, although both drugs stimulate feline colonic smooth muscle contraction *in vitro*.[53] Cimetidine and famotidine, members of the same classification of drug, do not have this effect.

Surgical

Colectomy should be considered in cats that are refractory to medical therapy. Cats have a generally favorable prognosis for recovery following colectomy, although in some cases mild to moderate diarrhea may persist for weeks to months postoperatively.[54,55] Pelvic osteotomy without colectomy has been recommended for cats with pelvic fracture malunion and hypertrophic megacolon of less than 6 months' duration.[56] Pathologic hypertrophy may be reversible with early pelvic osteotomy in such cases. Some surgeons still prefer colectomy in this instance because of the technical difficulty of some pelvic osteotomies.

Prognosis

Many cats have one or two episodes of constipation without further recurrence, although others may progress to complete colonic failure. Cats with mild to moderate constipation generally respond to conservative medical management (e.g., dietary modification, emollient or hyperosmotic laxatives, colonic prokinetic agents). Early use of colonic prokinetic agents (in addition to one or more laxative agents) is likely to prevent the progression of constipation to obstipation and dilated megacolon in these cats. Some cats may become refractory to these therapies, however, as they progress through moderate or recurrent constipation to obstipation and dilated megacolon. These cats eventually require colectomy. Cats have a generally favorable prognosis for recovery following colectomy, although in some cases mild to moderate diarrhea may persist for 4 to 6 weeks postoperatively.

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CHAPTER 11

Diarrhea

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Definition

Diarrhea is an increase in the frequency, fluidity, or volume of feces[1] that is best characterized by duration (acute versus chronic), pathophysiologic mechanism, and anatomic location. Diarrhea is considered acute if it lasts for less than 14 days, and chronic when it persists for more than 14 days. Acute, self-limiting diarrhea is a relatively common problem in dogs and cats and usually requires minimal diagnostic testing and therapy. In contrast to most animals with acute diarrhea, chronic diarrhea can be particularly challenging to diagnose, because most animals will not respond to empirical therapies, necessitating a well-formulated and cost-effective diagnostic and therapeutic plan. Specific therapeutic modalities are based upon a definitive diagnosis or histologic characterization of intestinal biopsies.

Although diarrhea is the primary sign of intestinal dysfunction, there are a number of secondary clinical signs that may become the principal one for which the animal is presented, and it is noteworthy that diarrhea may or may not accompany these secondary clinical signs. These secondary signs include *abdominal distention*, *abdominal pain*, *borborygmus*, *dehydration*, *flatulence*, *halitosis*, *melena*, *hematochezia*, *polydipsia*, *polyphagia*, *tenesmus*, *vomiting*, and *weight loss*. Animals may present with alterations in appetite ranging from polyphagia to anorexia, and these same alterations in food intake can be recognized as a consequence of disease progression (e.g., inflammatory bowel disease, intestinal lymphangiectasia, and lymphoma). Weight loss is often associated with nutrient malabsorption of diffuse mucosal disease. Vomiting can be associated with a variety of gastrointestinal disorders and is relatively common in animals with inflammatory bowel disease (IBD). Colorectal disorders are often associated with tenesmus, dyschezia, and large bowel diarrhea characterized by hematochezia, increased mucus on feces, marked increase in defecation frequency, and a reduction in fecal volume.

Pathophysiology and Mechanisms

There are four major pathophysiologic mechanisms that can result in diarrhea, although more than one mechanism can contribute to diarrhea simultaneously.

Osmotic Diarrhea

Osmotic diarrhea is caused by unusually large amounts of poorly absorbable osmotically active solutes in the intestinal lumen. Osmotic diarrhea occurs with malabsorptive disorders where nutrients are maldigested or malabsorbed, remain within the intestinal lumen, and osmotically attract water. Exocrine pancreatic insufficiency is an example of an osmotic diarrheal disorder. Retention of nutrients can lead to alterations in intestinal microflora and fermentation of carbohydrates, further increasing numbers of osmotically active particles. The fecal water output in osmotic diarrhea is directly related to fecal output of the solute or solutes that are exerting an osmotic gradient across intestinal mucosa. Electrolyte absorption is unaffected by these osmotically active substances, and fecal water typically contains very little unabsorbed sodium or potassium.[2] This is the basis for the calculation of the "fecal osmotic gap." In this calculation, the difference between luminal osmolality (equal to body fluid osmolality, approximately 290 mOsm/kg, because the colon cannot maintain an osmotic gradient against plasma) and osmolality of luminal contents contributed by fecal electrolytes is estimated. The contribution of fecal electrolytes is calculated as twice the sum of sodium and potassium ions to account for the anions that accompany these cations. A fecal osmotic gap greater than 50 mOsm/kg suggests osmotic diarrhea.[2] One of the major hallmarks of osmotic diarrhea is that diarrhea resolves when the patient stops ingesting the poorly absorbable solute.

Secretory Diarrhea

Secretory diarrhea is caused by abnormal ion transport in intestinal epithelial cells. The most common cause of secretory diarrhea in dogs and cats are abnormal mediators resulting in changes in intracellular cyclic adenosine monophosphate (cAMP), cyclic guanosine monophosphate (cGMP), calcium, and/or protein kinases, which in turn cause a decrease in neutral sodium chloride absorption or an increase in chloride secretion.[3] Such mediators include endogenous enteric hormones or neuropeptides, inflammatory cell products, bacterial enterotoxins, laxatives, fatty acids, and bile acids (see Chapters 1 and 57 for more detail). Secretory diarrhea has two important distinguishing features; first, fecal osmolality can be accounted for by sodium, potassium, and their accompanying anions, and thus the osmotic gap is small; and second, the diarrhea usually persists despite fasting because the diarrhea is caused by abnormalities in ion transport that have nothing to do with food. Enteropathogenic *Escherichia coli* and IBD are examples of secretory diarrheas.

Increased Mucosal Permeability

Increased mucosal permeability causes loss of fluids, electrolytes, proteins, and red blood cells into the intestinal lumen. Erosive or ulcerative enteropathies, inflammatory (IBD), or neoplastic disorders (intestinal lymphoma) are common causes of alterations in mucosal permeability.

Deranged Motility

Experimental studies in dogs show that abnormal ileal and colonic motility patterns may contribute to clinical symptomatology of IBD.[4,5] The two major motor abnormalities in intestinal inflammation are suppression of phasic contractions, including migrating motor complexes, and stimulation of giant migrating contractions (GMCs), the powerful ultrapropulsive contractions that usually propagate uninterruptedly form the point of their origin in the small intestine to the terminal ileum and often into the colon.[4] Stimulation of GMCs in fasting and fed states produces ultrarapid transit of intestinal and pancreaticobiliary secretions and undigested food into the colon to increase its osmotic load with resultant diarrhea.[4] Platelet-activating factor (PAF) may be one of the inflammatory response mediators that stimulates GMCs,[5] and it is synthesized and released from several immunocytes, including polymorphonuclear (PMN) leukocytes, monocytes, macrophages, mast cells, and eosinophils.[5]

Differential Diagnosis

Box 11-1 lists differential diagnoses for acute and chronic diarrhea in dogs and cats, as well as those disorders that are potentially life-threatening. Many cases of chronic diarrhea can manifest initially as acute diarrhea. Localization of the disease process into "small bowel" versus "large bowel" has some limitations, as many diarrheal diseases with primary manifestations of one compartment (large bowel *or* small bowel) may have diffuse gastrointestinal (GI) involvement (large *and* small bowel). This point is underscored by a study in 40 dogs suggesting that routine collection of ileal biopsies is warranted in dogs with colonopathy, and that routinely sampling of duodenum and ileum increases the diagnostic yield compared to biopsy of one anatomic site.[6] Regardless, the initial differentiation into small and large bowel components helps to further clarify the medical investigation (see Figs. 11-1 and 11-2).

Evaluation of the Patient

Signalment

Awareness of the importance of the animal's signalment and breed predilections for GI disease can facilitate development of a differential diagnosis for the particular animal. A 3-year-old Yorkshire Terrier dog with a 2-month history of small intestinal diarrhea, weight loss, and progressive abdominal distention has a signalment and history suggestive of intestinal lymphangiectasia. Likewise, a young Boxer dog with a 3-month history of tenesmus, hematochezia, increased stool frequency, and mucoid stools could be consistent with histiocytic colitis. Tunnel vision should be avoided, however, as it is plausible that a Boxer dog could have diarrhea from any number of underlying causes.

History

History and physical examination often indicates the anatomic localization and severity of the disease process, and it helps prioritize differential diagnoses. History should ensure that systemic causes of diarrhea are not overlooked. A comprehensive history should also identify important predisposing factors (e.g., exposure to parasites, infectious agents, drugs, toxins). It is equally important to fully characterize the nature of diarrhea and appearance of feces (Table 11-1). For dogs with a history of tenesmus, it is pivotal to determine whether signs are secondary to colitis or to a discrete mass or polyp in the colorectal region. The latter is often associated with a change in the appearance of the stool ("ribbon-like," "pencil-thin") in the absence of a marked increase in frequency of bowel movements or increased fecal mucus as seen with colitis. Likewise, absence of clinical signs of diarrhea does not rule out severe underlying intestinal disease; dogs with protein-losing enteropathy (PLE) may have anorexia and weight loss without associated vomiting and diarrhea. Failure to consider the role of diet or dietary supplements in precipitating or alleviating the diarrhea can cause delayed diagnosis or improper dietary recommendations. Box 11-2 outlines specific questions that should be addressed.

Box 11-1 Differential Diagnoses for Acute and Chronic Diarrhea

Differential diagnoses for acute and chronic diarrhea in dogs and cats, with annotation of potentially life-threatening causes of disease.

Dietary
Abrupt dietary change*
Overeating*
Dietary indiscretion*
Dietary intolerance/allergy‡

Inflammatory
Inflammatory bowel disease†
Antibiotic-responsive diarrhea†
Lymphangiectasia†
Hemorrhagic gastroenteritis #,*

Infectious
Parasitic helminths,‡ protozoa‡
Bacterial *Salmonella,*#,* *Campylobacter,** *Clostridium perfringens,*#,* *Clostridium difficile,*#,* *E. coli,*#*
Viral parvovirus,#,* coronavirus,* feline leukemia virus (FeLV),† feline immunodeficiency virus (FIV)†
Fungal histoplasmosis,#,† *Pythium,*#,† cryptococcosis#,†
Rickettsial salmon poisoning#,*

Extraintestinal Disorders
Pancreatitis#,*
Exocrine pancreatic insufficiency†
Liver disease#,‡
Kidney disease#,‡
Hypoadrenocorticism#,‡
Hyperthyroidism†

Functional Ileus/Mechanical Obstruction

Miscellaneous
Toxemia (pyometra, peritonitis)#,*
Septicemia (leptospirosis)#,‡
Apudomas (gastrinomas, VIPomas, carcinoid syndrome)#,‡

Neoplastic
Carcinoma#,‡
Mast cell tumors#,‡
Leiomyosarcomas (gastrointestinal stromal tumors)#,‡
Lymphoma#,‡

Drugs and Toxins
Nonsteroidal antiinflammatory drugs‡
Antibiotics‡
Digoxin‡
Cancer chemotherapeutics‡
Copper chelators‡

Key: #, potentially life-threatening; *, typically associated with acute diarrhea; †, typically associated with chronic diarrhea; ‡, associated with acute or chronic diarrhea.

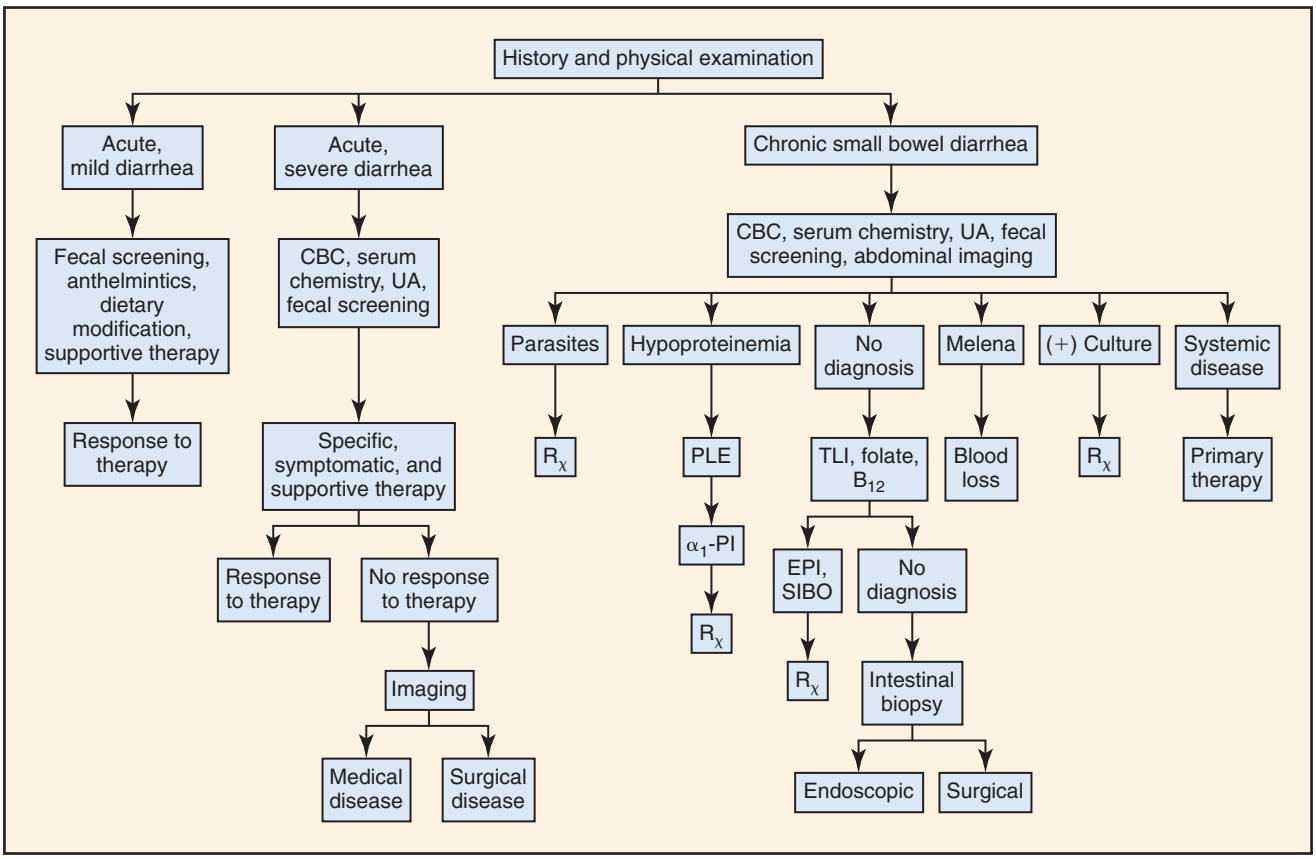

Figure 11-1 Medical workup for dogs and cats with diarrhea primarily of small bowel origin.

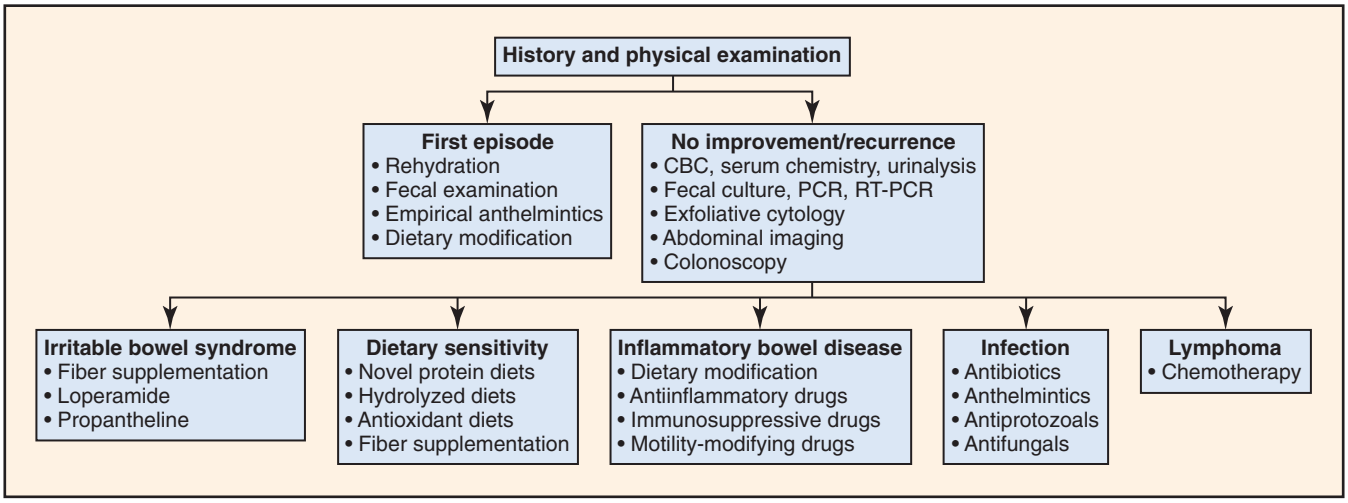

Figure 11-2 Medical workup for dogs and cats with diarrhea primarily of large bowel origin.

Physical Examination

A thorough physical examination helps determine severity and likely origin of the problem. Careful attention should be placed on physical appearance of the animal (emaciation or malnutrition suggestive of malassimilation from IBD, intestinal lymphoma, lymphangiectasia, or pancreatic insufficiency); detection of fever (infectious enteropathy or breakdown of the intestinal mucosal barrier); abdominal effusion and edema (secondary to protein losing enteropathies); and mucous membrane pallor (secondary to intestinal blood loss). Abdominal palpation is performed for detection of mass lesions, thickened bowel loops (neoplasia, intussusception, IBD, fungal enteropathies, mesenteric lymphadenopathy), or pain (bowel inflammation, pancreatitis, peritonitis, ischemia of bowel, and gas-associated bowel distention). In cats the thyroid region should be carefully palpated for thyroid nodules, and the kidneys and liver examined for changes in size and contour. Digital rectal palpation is important for detection of rectal masses or irregular thickening of rectal wall, colorectal strictures, and collection of feces for gross inspection and further evaluation. Digital rectal

Table 11-1 Differentiation of Small Versus Large Bowel Diarrhea*

Differentiation of small versus large bowel diarrhea based upon clinical signs and the physical appearance of feces.

Sign	Small Bowel	Large Bowel
Frequency of defecation	Normal to mildly increased	Markedly increased
Fecal volume	Normal to increased	Decreased
Fecal mucus	Usually absent	Often present
Fecal blood	Melena	Hematochezia
Tenesmus	Absent	Often present
Urgency	Absent	Often present
Vomiting	May be present	May be present
Steatorrhea	May be present	Absent
Dyschezia	Absent	Often present
Weight loss	Common	Uncommon

*Caution should be heeded with the oversimplistic attempts at compartmentalizing the diarrhea into a small bowel versus a large bowel compartment, as many diarrheal diseases can have diffuse involvement histologically.

Box 11-2 Questions that Should be Asked in Patients with Diarrhea

- What is the clinical course or onset of the diarrhea (congenital or acquired; abrupt or gradual in onset; continuous or intermittent)?
- What is the duration of signs?
- What are the physical characteristics of the diarrhea?
- Are there any alleviating or exacerbating factors for the diarrhea such as dietary changes, antibiotic administration, stress, recent travel, or recent kenneling?
- What is the animal's past medical history, and is this diarrhea episode a new problem or a recurrent one? If recurrent, how was the diarrhea managed previously, and what was the outcome?
- What is the animal's anthelmintic and vaccination history?
- Are any other pets in the household similarly affected?
- Is the diarrhea associated with any other systemic (e.g., polyuria/polydipsia) or gastrointestinal signs such as weight loss, vomiting, and anorexia?

palpation of the rectum in cats is usually performed under general anesthesia or deep sedation. Macroscopic examination of a fresh fecal specimen is essential for assessment of bulk, color, consistency, detection of blood and mucus, and detection of foreign material. Small bowel diarrhea is generally free of grossly visible mucus or red blood, but prominent steatorrhea may cause the feces to appear lighter in color. Acholic or pale feces can also be seen in association with extrahepatic bile duct obstruction causing a lack of the bile pigment stercobilin in the feces. Rapid intestinal transit time can be associated with yellow or green stools caused by incomplete metabolization of bilirubin.

Laboratory Evaluation and Tests

An important part of the workup is determining whether the animal has a self-limiting or potentially life-threatening problem. This distinction is pivotal as it determines the level of diagnostic testing and therapy needed and helps determine the likelihood of an animal having a self-limiting diarrhea that could be managed empirically, or an animal having a chronic disease that warrants hospitalization and a more comprehensive workup. This distinction is based on a comprehensive history, thorough physical examination, clinical experience and judgment, and awareness of the differential diagnoses for the diarrhea. Animals showing one or more of the following physical examination findings or signs at presentation warrant a more comprehensive workup and possible hospitalization: fever; abdominal pain; abdominal effusion; organomegaly; moderate to severe dehydration; severe lethargy; melena or hematochezia; mucous membrane pallor; jaundice or congestion; palpable abdominal mass or dilated loop of bowel; frequent vomiting; or other signs of systemic disease such as polyuria/polydipsia.

For animals with acute, mild diarrhea that appear relatively healthy on physical exam and are deemed likely to have a self-limiting gastroenteropathy, a minimum database consisting of centrifugation fecal flotation using zinc sulfate (specific gravity of 1.18 to 1.2) complemented with a fecal enzyme-linked immunosorbent assay (ELISA) or immunofluorescence test for *Giardia* is typically adequate for assessment of parasitic disease. In addition, measurement of hematocrit and total protein are helpful to assess hydration status. Fecal cytology in diarrheic dogs is a low-yield diagnostic test because finding of "safety pin"-shaped endospores consistent with *Clostridium perfringens* are of no diagnostic value. Their detection does not correlate with the presence of *C. perfringens* enterotoxin, the putative virulence factor associated with diarrhea.[7,8] Likewise, detecting "spiral-shaped" bacteria assuming the appearance of "seagulls" is insufficient for a diagnosis of *Campylobacter*-associated diarrhea because spiral-shaped bacteria resembling *Campylobacter* spp. are commonly identified in feces from healthy, nondiarrheic dogs and cats. Isolation of the microaerophilic organism utilizing selective culture media is a far more sensitive diagnostic tool compared with stained fecal smears.[9] In contrast to direct fecal cytology, exfoliative rectal cytology is a useful diagnostic test in dogs and cats with signs of colitis, and is best indicated for diagnosis of specific enteropathogens such as *Histoplasma* spp., *Pythium insidiosum*, or *Prototheca*,[10] or for colonic neoplasms such as lymphoma and carcinoma.

Animals with potentially life-threatening diarrhea or diarrhea that has not responded to conventional therapeutic approaches within 2 to 4 weeks warrant the time and effort required to make a specific diagnosis. The decision of whether to embark on an attempt to make a specific diagnosis usually depends on the nature of the problem, the availability of specific diagnostic facilities, and any client constraints (e.g., financial). For undiagnosed chronic or life-threatening diarrhea, the minimum database should include a complete blood count (CBC), a serum biochemistry profile, a urinalysis, a centrifugation fecal flotation using zinc sulfate, and a direct smear of saline admixed fresh feces for protozoa. A fecal ELISA for parvovirus in puppies should be considered based on signalment, vaccination history, clinical signs, and hematologic findings. The minimum database is performed to determine whether primary GI or metabolic/systemic disorders are associated with diarrhea. Baseline testing should also include specific tests for common disorders known to be likely in a particular animal (e.g., serum thyroxin testing in a 14-year-old cat with a history of chronic weight loss, diarrhea, and polyphagia).

Baseline Laboratory Tests

Complete Blood Count. The complete blood count may reveal an *eosinophilia* secondary to endoparasitism, eosinophilic enteritis, hypoadrenocorticism, or mast cell neoplasia. *Anemia* may result from enteric blood loss or from depressed erythropoiesis caused by systemic disease, chronic inflammation, or malnutrition. A

peripheral *neutrophilia* could reflect stress, inflammation, or infection. Finding a left shift with toxic neutrophils should warrant an aggressive workup for underlying causes (infection, immune disease, etc.). *Lymphopenia* is a relatively common finding in dogs with intestinal lymphangiectasia.

Serum Chemistry. The serum biochemistry panel should be scrutinized for elevations in *urea* and *creatinine* concentration from dehydration or renal disease. The *blood urea nitrogen (BUN)-to-creatinine* ratio can be discordantly elevated from dehydration (prerenal azotemia) or gastrointestinal bleeding. In addition, *panhypoproteinemia* and *hypocholesterolemia* can be recognized in animals with a protein-losing enteropathy from intestinal lymphangiectasia or other infiltrative bowel disorders. Electrolyte changes as a consequence of diarrhea should be carefully scrutinized, and corrected whenever warranted. *Hyperkalemia* and *hyponatremia* are typical electrolyte alterations commonly found in Addisonian dogs; however, these electrolyte changes have been documented in dogs with whipworm infestations and other enteropathies in the absence of Addison disease (pseudo-Addison disease). In addition, dogs with atypical Addison disease can manifest diarrhea in the absence of electrolyte changes. Elevated hepatic enzyme values should be interpreted cautiously in patients with gastrointestinal disease because drainage of bacteria or endotoxin via the portal circulation can precipitate a reactive hepatopathy with elevations of hepatocellular leakage enzymes. Serum thyroxine concentrations are typically included on serum biochemistry panels performed at reference laboratories, and routine measurement of serum T_4 is warranted in any diarrheic cat older than 8 years, independent of concurrent signs such as polyphagia and weight loss.

Feline Leukemia Virus and Feline Immunodeficiency Virus Serologic Screening. Serologic screening for feline leukemia virus (FeLV) and feline immunodeficiency virus (FIV) is warranted in diarrheic cats based upon habitat and housing environment. The enteritis sometimes caused by FeLV and FIV is incompletely understood, although it has long been recognized that FeLV can directly infect intestinal epithelial cells as well as gut-associated lymphoid tissue.[11]

Fecal Enteric Panel. The fecal enteric panel is a low-yield and expensive diagnostic test with misleading results if not performed judiciously in diarrheic dogs and cats. The clinical documentation of enteropathogenic bacteria causing diarrhea in dogs and cats is clouded by the presence of these organisms in apparently healthy animals. A fecal enteric panel consisting of a Gram-stained fecal smear, culture for *Salmonella* and *Campylobacter*, and ELISAs for immunodetection of *Clostridium difficile* toxins A and B and C. *perfringens* enterotoxin is an expensive test (approximately $120 in the author's laboratory) that should be reserved for diarrheic dogs and cats that are systemically ill (fever, severe lethargy, leukocytosis with or without a left shift and toxicity), have an acute onset of hemorrhagic diarrhea, or a recent onset of diarrhea following kenneling or attendance at a show. Lastly, fecal enteric panels should be proactively done when the zoonotic enteropathogens, *Campylobacter* or *Salmonella*, are considerations in diarrheic pets owned by people who are immunocompromised.

Diagnostic Imaging

Survey Abdominal Radiography. Survey abdominal radiographs are a relatively low-yield diagnostic procedure in most dogs and cats with chronic diarrhea, but are indicated in animals for detection of fluid–gas patterns suggestive of mechanical obstruction from foreign bodies, intussusceptions, or masses (see Chapter 26). Although many medical causes of GI disease result in mild to moderate intestinal wall thickening, measurements of wall thickness should not be attempted on survey radiography.

Upper Gastrointestinal Tract Contrast Radiography. Partial or complete mechanical gastrointestinal obstructions are the main indications for upper GI contrast radiography. The modality has been used for determination of gastrointestinal transit; however, disturbances in motility can be difficult to document using liquid barium, and the stress associated with hospitalization can alter gastric and intestinal transit times. Upper GI contrast radiography has also been used to evaluate mucosal abnormalities such as ulcers and filling defects; however, the procedure has limitations and subtle lesions are easily missed (see Chapter 26). The diagnostic yield of upper GI contrast radiography is frequently compromised as a consequence of improper patient preparation (inadequately fasted), too low a volume of barium administered, and insufficient radiographs at suitable time points.

Abdominal Ultrasonography. Abdominal ultrasonography is complementary to survey abdominal radiographs, and has largely replaced contrast radiography for the diagnosis of GI neoplasia, intussusception, and diffuse mural infiltrative disease (see Chapter 26). In addition, ultrasound-guided percutaneous biopsy or aspiration of masses or enlarged mesenteric lymph nodes is an effective diagnostic procedure. Both IBD and small-cell lymphoma of the bowel can have manifestations ranging from normal ultrasonographic appearance to generalized thickening of the intestinal wall with enlarged mesenteric lymph nodes. A loss of intestinal wall layering is more consistent with a diagnosis of lymphoma than IBD. A recent study revealed that cats showing a pattern of thickening of the muscularis propria on ultrasound exam were more likely to have lymphoma compared to cats with IBD and healthy controls.[12] In addition, cats with ultrasonographic evidence of moderate to marked mesenteric lymphadenopathy are more likely to have a diagnosis of intestinal lymphoma.[12]

Specialized Gastrointestinal Function Tests

Serum Trypsin-like Immunoreactivity. Steatorrhea and weight loss in the face of a normal to increased appetite is consistent with a malassimilation disorder such as exocrine pancreatic insufficiency (EPI). A genetic predisposition to development of pancreatic acinar atrophy has been reported in German Shepherd dogs and rough-coated Collies, although many other breeds, including mixed breeds, are affected. Pancreatic acinar atrophy predominantly affects dogs between 1 and 5 years of age, although it also may occur in older dogs. Pancreatic insufficiency is rare in cats, and occurs as a consequence of chronic, intermittent bouts of pancreatitis in this species. In contrast to most dogs with the disease, cats often have loss of both exocrine and endocrine pancreatic function, and are thus typically diabetic as well. The optimal test for the diagnosis of EPI in dogs and cats is a species-specific assay of trypsin-like immunoreactivity (TLI). Assay of fecal proteolytic activity (PA) using an azoprotein- or casein-based method can also be used, but it is not as sensitive as the TLI assay and is more impractical to perform. Microscopic examination of Sudan- and iodine-stained fecal smears for excessive fat droplets and undigested starch muscle is subjective, imprecise, and notoriously unreliable.

Serum Cobalamin and Folate. Measurement of serum vitamin B_{12} (cyanocobalamin) and folate concentrations are used to evaluate the absorptive function of the ileum and jejunum, respectively, and

are abnormally decreased in infiltrative bowel disorders such as IBD or lymphoma affecting these regions of bowel. A deficiency of cyanocobalamin can adversely affect DNA replication in the intestinal crypts, and affect the overall response of the animal to dietary and medical therapy. Cyanocobalamin is easily supplemented via parenteral (subcutaneous) injection on a weekly basis for 6 weeks, with periodic reevaluations of serum cyanocobalamin concentrations recommended thereafter. Measurement of serum cobalamin and folate concentrations are also commonly utilized to diagnose "small intestinal bacterial overgrowth" (SIBO) in dogs, although several studies highlight the relative insensitivity of this assay for this specific purpose.[13,14]

^{51}Cr-EDTA, Polyethylene Glycols, and Differential Sugar Absorption Studies. The integrity of the barrier function of the GI tract has been evaluated by permeability testing in several species, and many different marker molecules, including ^{51}chromium-labeled ethylenediaminetetraacetate[15] (^{51}Cr-EDTA), polyethylene glycols, and mono- and disaccharides have been evaluated.[16] Mannitol and lactulose are nonmetabolizable, hydrophilic, and lipophobic, with negligible affinity for the monosaccharide transport system, and are absorbed passively by nonmediated means. Recovery in urine is almost total and renal clearance is high. The simultaneous use of two allows a differential estimation of transcellular pathways through small-size channels, and paracellular pathways through large-size channels (tight junctions). Furthermore, the simultaneous use of these two sugars and the calculation of the ratio of the sugars makes the test independent of the degree of completion of the urine collection. Finally, it is known that intestinal permeability to mannitol is close to that of rhamnose and permeability to lactulose is similar to that of ^{51}Cr-EDTA.[17] GI permeability and mucosal function testing is used predominantly in the research arena, and not used very often in routine clinical practice.

Fecal α_1-Proteinase Inhibitor. PLE is a syndrome caused by a variety of gastrointestinal diseases causing enteric loss of albumin and globulin. Intestinal inflammation, infiltration, ulceration, blood loss, and primary or secondary lymphangiectasia are well-documented causes of PLE. If left untreated, the final outcome of PLE is panhypoproteinemia with decreased intravascular oncotic pressure and the development of abdominal and pleural effusion, peripheral edema, and death. Protein-losing enteropathy is uncommon in cats, and most cats with PLE are diagnosed with intestinal lymphoma or severe IBD. Serum albumin and total protein should be carefully evaluated in all patients with a history of weight loss, anorexia, vomiting, or diarrhea. Although PLE is typically associated with panhypoproteinemia, the absence of hypoglobulinemia does not preclude a diagnosis of PLE because chronic antigenic stimulation could increase the serum globulin concentration into the "normal" reference range. Additional abnormalities found on the serum biochemistry profile in association with PLE include hypocholesterolemia (secondary to malabsorption) and hypocalcemia. The causes for the hypocalcemia are multifactorial and include hypoalbuminemia (affects total calcium), decreased absorption of vitamin D, and malabsorption of magnesium.

Measurement of fecal α_1-proteinase inhibitor (α_1-PI) can be used to further support a diagnosis of PLE in animals with concurrent liver disease or protein-losing nephropathy (PLN), although this test is limited by logistical constraints in that samples must be shipped frozen, and there is currently only one laboratory that performs the ELISA at Texas A&M University.[18] α_1-PI is the same size as albumin and is lost in the intestinal tract and excreted via the feces where it can be measured as a marker for PLE. Three separate voided fecal specimens are collected into special volume-calibrated cups available from the laboratory. It is important that fecal specimens be naturally voided as digital extraction of the fecal specimen can result in microscopic blood loss and false elevations in fecal α_1-PI. Fecal specimens should be immediately frozen after collection and shipped on ice via overnight mail to the laboratory.

Intestinal Biopsy

Flexible Endoscopy and Biopsy. Endoscopic examination with mucosal biopsy is warranted for definitive diagnosis and to provide prognostic information for patients with chronic diarrhea once dietary, parasitic, systemic or metabolic disorders, and infectious diseases have been excluded (see Chapter 27). There are several inherent disadvantages of flexible endoscopy, including the inability to access the entire length of the gastrointestinal tract (unless enteroscopy is performed), and the inability to acquire deep biopsies involving the muscularis mucosa or submucosa consistently.

Rigid Proctoscopy and Biopsy. Rigid proctoscopy can be performed using a stainless steel or plastic Welch-Allyn sigmoidoscope, which consists of a hollow tube with an eyepiece on the proximal end, an insufflation bulb, and a cold light source with a fiber bundle for the transmission of light to the distal end. Sigmoidoscopy only allows direct examination of the rectum and descending colon; however, the procedure entails less risks, time, and cost than colonoscopy, and is able to diagnose the majority of large bowel disorders because of the diffuse nature of the disease. Flexible colonoscopy is indicated for evaluation of upper colonic disease, including cecal inversion, colonic neoplasia, and occult *Trichuris* infection, and is also warranted for examination and biopsy of the ileum (see Chapter 27).

Exploratory Celiotomy and Biopsy. Exploratory celiotomy allows direct visual inspection, palpation, and collection of multiple full-thickness intestinal mucosal specimens, which can facilitate the differentiation of IBD from intestinal lymphoma. In addition, procurement of biopsy specimens from the liver, mesenteric lymph nodes, and pancreas can be performed.

Treatment and Management of Acute, Self-Limiting Diarrhea

General Principles

Symptomatic therapy of the dog and cat with acute, self-limiting diarrhea typically involves empirical therapy because the causes for many of these diarrheal disorders are often undetermined. Principal goals of symptomatic therapy are restoration and maintenance of fluid and electrolyte balance, dietary modification, administration of broad-spectrum anthelminthics such as fenbendazole, and judicious use of antimicrobials when warranted. The unfounded recommendation of withholding food for 24 to 48 hours to facilitate "bowel rest" is completely unsubstantiated, and there is growing evidence that the benefits of early enteral nutritional support are far superior for promoting intestinal integrity, promoting weight gain, and improving patient outcome.[19]

Medical

Dietary Therapy

Dietary therapy consisting of either a highly digestible, moderately fat-restricted, low-residue intestinal formula or an elimination diet consisting of a novel, select protein source are typically used for animals with acute diarrhea. Fat delays gastric emptying, and

fat-restricted diets appear to be better tolerated in a variety of gastrointestinal diseases. Assimilation of dietary fat is a relatively complex process, and malabsorbed fatty acids are hydroxylated by intestinal and colonic bacteria. Hydroxy–fatty acids stimulate colonic water secretion and exacerbate diarrhea and fluid loss.[20] Fat malassimilation can also be associated with malabsorption of bile acids, resulting in deconjugation of unabsorbed bile acids and increased mucosal permeability and secretion.[21]

Antimicrobials

Use of antimicrobials as empirical therapy in the management of uncomplicated or noninfectious diarrhea is not recommended because of adverse effects of the antibiotics on the normal intestinal microflora (dysbiosis) and their tendency to promote resistant strains of bacteria. Antibiotics are indicated when specific bacterial or protozoan enteropathogens, such as *Campylobacter*, *Clostridium*, or *Giardia* are isolated from the feces. In addition, broad-spectrum bactericidal antibiotics should be considered in conditions associated with severe mucosal damage and a high risk of bacterial translocation with consequent bacteremia or endotoxemia. Lastly, antibiotics such as tylosin or metronidazole can be used to manage dogs with antibiotic-responsive diarrhea, a chronic disorder that is seen more commonly in large-breed dogs, and that is a diagnosis of exclusion.

Oral Protectants

Oral protectants such as kaolin-pectin, bismuth, activated charcoal, and barium are purported to act locally within the gut lumen to adsorb bacteria and toxins and to provide a protective coating on inflamed mucosal surfaces. Bismuth subsalicylate is the most useful of these agents because it has antienterotoxin, antibacterial, antisecretory, and antiinflammatory actions. Caution should be heeded with the use of salicylate-containing compounds in cats because of the prolonged elimination of this compound in cats. Bismuth dosed at 0.5 to 1 mL/kg BID for 2 to 3 days is safe in cats.

Fluids

Acute diarrhea may cause severe dehydration for which intravenous fluid therapy may be required (see Chapter 48).

Treatment and Management of Chronic Diarrhea

Medical

Dietary Therapy

Dietary management for dogs and cats with chronic diarrhea is dependent upon the underlying diagnosis. Elimination and hydrolyzed protein diets have proved to be effective for the management of dogs and cats with IBD involving the small and large bowel. Elimination diets contain single, novel protein sources, whereas hypoallergenic diets contain hydrolyzed protein sources that have been enzymatically hydrolyzed into polypeptides. Although more expensive and less palatable, hydrolyzed diets are particularly beneficial as elimination diets for the diagnosis and management of food hypersensitivity, when a patient appears to be allergic to multiple allergens, when a complicated dietary history makes it difficult to identify a "novel" protein, or when a patient has severe IBD.[22] The supplementation of *fermentable fiber* sources such as psyllium or oat bran may be necessary in patients with IBD involving the large intestine that show partial resolution of their clinical signs. The gelling and binding properties of fatty acids and deconjugated bile acids in fermentable fibers may be beneficial in certain gastrointestinal diseases. The use of fermentable fiber in preference to nonfermentable fiber is generally advocated because most soluble fibers generate butyrate, the principal source of energy for the colonocyte, and other short-chain fatty acids. Short-chain fatty acids may lower the colonic luminal pH, impeding the growth of pathogens.[23] The health benefits derived from dietary supplementation of *prebiotics* have yet to be fully recognized in dogs and cats with chronic diarrhea, although prebiotic administration has been shown to decrease the concentrations of fecal ammonia and amines and increased the numbers of bifidobacteria in dog feces.[24]

Fish oil is reported to be beneficial in ulcerative colitis and Crohn disease patients,[25] but the results are controversial. Only a few studies found significant decreases in rectal leukotriene (LT) B_4 concentrations; the others simply reported clinical improvement. There are no published studies in the veterinary literature to date demonstrating the efficacy of n-3 fatty acid supplementation in managing canine or feline patients with IBD. *Water-soluble vitamins* are often depleted by the fluid losses associated with diarrhea and *fat-soluble vitamin* loss can be significant in animals with steatorrhea. *Magnesium* deficiency has been documented in Yorkshire Terriers with severe IBD and lymphangiectasia,[26] and dogs that are severely hypomagnesemic warrant parenteral supplementation of magnesium sulfate administered at 1 mEq/kg/24h as a constant-rate infusion.[26] Magnesium can also be supplemented orally as magnesium hydroxide (milk of magnesia) at a dosage of 5 to 15 mL per dog q24h. Cats and dogs with severe IBD frequently have subnormal serum *cobalamin* concentrations. Cyanocobalamin should be supplemented parenterally (subcutaneously), and is empirically administered at a dose of 250 μg per cat or toy-breed dog up to 1000 μg per large- or giant-breed dog, at a dosing interval of once weekly for 6 consecutive weeks. Cyanocobalamin concentrations should be rechecked every 6 to 8 weeks, particularly in cats, given the shorter half-life of the vitamin in cats.

The goal of therapy for intestinal lymphangiectasia, a common cause of PLE, is to decrease the enteric loss of plasma protein, resolve associated intestinal or lymphatic inflammation, and control effusion or edema. *Marked dietary fat restriction* is one of the most important aspects in the management of dogs with intestinal lymphangiectasia. Diets that are highly digestible and that contain less than 20% fat calories on a metabolic equivalent basis are recommended.[27] The author recommends feeding of a premium commercial-based diet if possible; however, there are a small number of dogs with severe lymphangiectasia that will need further fat restriction than available in commercial diets, and home-cooked diets are warranted. These home-cooked diets should be made up by a veterinary nutritionist to ensure that the diets are complete and balanced. Dogs with concurrent IBD and lymphangiectasia are more challenging to manage from a dietary perspective because these animals need a novel, select protein source diet that is also markedly fat restricted and virtually no commercial diet fits these criteria. An alternative to consider is the use of hypoallergenic diets containing hydrolyzed protein sources and moderate amounts of dietary fat. Failure to respond favorably to these diets warrants a home-cooked diet that is more fat-restricted and contains a novel, select protein source. Administration of medium-chain triglycerides (MCTs) to enhance the caloric density of the diet is controversial because of unpleasant taste and potential for inducing diarrhea. MCTs are not transported entirely via the portal circulation to the liver and can exacerbate lymphangiectasia.

Antimicrobials

Metronidazole (Flagyl), an inhibitor of cell-mediated immunity,[28] has been frequently used as an adjunctive agent for the management of IBD. The dose of metronidazole is 10 to 15 mg/kg q12h.

Metronidazole tablets have a sharp, unpleasant, metallic taste when scored that can cause severe salivation. Side effects are rare, although metronidazole is associated with a peripheral neuropathy in humans and animals. Less-common side effects include inappetence, nausea, vomiting, seizures, and reversible neutropenia. Reversible genotoxicity in feline peripheral blood mononuclear cells has been observed in cats after only a single dose of metronidazole, but resolved within 6 days of discontinuing the metronidazole.[29]

Tylosin (Tylan) is a macrolide antibiotic that has been reported to be effective and safe in managing canine IBD and antibiotic-responsive diarrhea (ARD).[30] Although the drug's mechanism of action is unknown, it appears to be effective in some dogs refractory to other forms of therapy. The dose range is 20 to 30 mg/kg q12h.

Motility Modifiers

Motility modifiers are *only* indicated as a last resort if the diarrhea is intractable, other causes of diarrhea have been ruled out, the diarrhea is *not* due to an infectious cause, and the patient has failed to respond to appropriate conventional therapy (e.g., diet change, deworming, corticosteroids, antibiotics). The opiate and opioid narcotic analgesics such as loperamide (Imodium; 0.1 to 0.2 mg/kg q8-12h [dogs], q12h [cats] PO) are the most effective motility modifiers for managing diarrhea. Anticholinergic agents are contraindicated because they may cause generalized suppression of all motility and potentiate ileus.

Probiotics

Administration of probiotics to dogs and cats with IBD represents a novel alternative therapeutic modality that warrants further investigation. It has been demonstrated that colitis in both humans and mice is associated with increased levels of cytokines such as tumor necrosis factor (TNF)-α, interleukin (IL)-6, IL-12p70, and IL-23.[31,32] Thus a proper selection of probiotic strains for the treatment of IBD is crucial and should be based on the estimation of their capacity to induce antiinflammatory pattern of cytokines (IL-10^{high}, TGF-β^{high}, IL-12p70^{low}, IL-23^{low}, TNF-α^{low}). Apart from immunomodulatory effects, probiotics have a protective effect on the normal microflora of the human gut by their antimicrobial activities directed toward intestinal pathogens.[33]

Probiotics also have been used to facilitate eradication of intestinal parasites. A recent study documented the ability of the probiotic organism *Enterococcus faecium* SF68 (Forta-Flora, Nestle-Purina, St. Louis, MO) to antagonize *Giardia intestinalis* infection in mice.[34] Oral feeding of *E. faecium* strain SF68 starting 7 days before inoculation with *Giardia* trophozoites significantly increased production of specific anti-*Giardia* intestinal immunoglobulin (Ig) A and blood IgG. This humoral response was mirrored at the cellular level by an increased percentage of CD4(+) T cells in Peyer patches and spleens of SF68-fed mice. Improvement of specific immune responses in probiotic-fed mice was associated with a diminution in the number of active trophozoites in small intestine as well as decreased shedding of fecal *Giardia* antigens (GSA65 protein). A recent study evaluating efficacy of *E. faecium* SF68 in 20 adult dogs with chronic naturally acquired giardiasis failed to affect cyst shedding or antigen content and did not alter innate or adaptive immune responses.[35] Additional studies are warranted in dogs and cats to further assess the immunomodulatory effects of probiotics and to evaluate their safety. The latter issue is particularly important given the recent finding of increased intestinal adhesion of *Campylobacter jejuni* in an in vitro model of canine intestinal mucus following incubation with *E. faecium*.[36] It should be noted that this *E. faecium* strain is different from the *E. faecium* SF68 strain available commercially; moreover, there has been no clinical or anecdotal evidence of *Campylobacter*-associated diarrhea in dogs administered probiotics to date.

Despite the paucity of prospective, randomized, placebo-controlled clinical trials in dogs and cats, tremendous interest has been shown among commercial pet food companies who are marketing probiotics for use in these species. Unfortunately, most of the evidence surrounding the use of probiotics in puppies or adult dogs with stress colitis or ARD is anecdotal, with no prospective, randomized, placebo-controlled studies in these disorders published to date.

Immunomodulatory Therapy

Most dogs and cats with moderate to severe IBD (canine IBD disease activity index >6 to 8) will require adjuvant immunotherapy in combination with dietary management and antimicrobial therapy. It is important to understand that the therapy of IBD must be tailored according to each patient's response.

Oral Corticosteroids

Corticosteroids remain the cornerstone of medical therapy for IBD, despite the lack of published controlled clinical trials documenting their benefit in dogs and cats with IBD. The value of corticosteroids relates to their antiinflammatory and immunosuppressive properties, although they also increase intestinal sodium and water absorption in the small and large bowel, and regulate basal colonic electrolyte transport. The dosage and duration of therapy is based on severity and duration of clinical signs, severity and type of inflammation, clinical response, and tolerance to the drug. The initial dosage of prednisone for therapy of IBD in dogs is 1 to 2 mg/kg q12h, not to exceed a total dose of 50 mg q12h. Cats are typically administered prednisolone, and the drug is started at a dose of 5 mg per cat q12h. The drug is gradually tapered over a 6- to 10-week period once clinical remission is attained. Combination therapy with dietary therapy, azathioprine, or metronidazole is undertaken with the goal of attempting to reduce the dose of prednisone. Parenteral corticosteroid therapy is reserved for the initial management of cats and dogs with intractable vomiting or those with severe malassimilation.

Budesonide

Budesonide, an orally administered corticosteroid structurally related to 16-hydroxyprednisolone, has high topical antiinflammatory activity and low systemic activity because of its high affinity to the steroid receptor and rapid hepatic conversion to metabolites with minimal or no steroid activity. Despite the drug's theoretical benefits, budesonide is associated with significant suppression of the hypothalamic–pituitary–adrenal axis.[37] The drug is dosed at 1 mg once daily for cats and toy-breed dogs, up to 2 mg q12h for large- or giant-breed dogs.

Azathioprine

Azathioprine is an antimetabolite that is converted to 6-mercaptopurine in the liver and then to thioinosinic acid. The latter compound impairs purine biosynthesis and this biochemical reaction inhibits cellular proliferation and reduces natural killer cell cytotoxicity.[38] Onset of these immunologic effects is slow and can require several months for maximal effectiveness. The drug is most useful in dogs as adjunctive therapy in severe or refractory IBD. Azathioprine can also be used for its steroid-sparing effects when adverse effects of prednisone are unacceptably high. The dose for dogs is 50 mg/m^2 or 1 to 2 mg/kg q24h for 2 weeks, followed by

alternate-day administration, whereas cats should receive 0.3 mg/kg q48h. The most significant side effect of azathioprine is bone marrow suppression, particularly in cats. Other side effects include anorexia, pancreatitis, and hepatic dysfunction.

Chlorambucil

The alkylating agent chlorambucil is beneficial for managing refractory cases of IBD and T-cell (small-cell) lymphoma of the gastrointestinal tract, particularly in cats.[39] Hematologic monitoring is warranted every 3 to 4 weeks to assess for neutropenia. In dogs chlorambucil is administered at 1.5 mg/m^2 on alternate days.

Cyclosporine

Cyclosporine is effective in dogs with IBD that are refractory to prednisone immunotherapy.[40] The recommended dose of cyclosporine is 5 mg/kg q24h. Although extremely expensive, particularly for large-breed dogs, the drug overall is relatively well tolerated.

Sulfasalazine

The drug consists of sulfapyridine linked to mesalamine (previously called 5-aminosalicylic acid) by an azo bond that is cleaved by colonic bacteria with subsequent release of the active moiety of the drug, mesalamine. Sulfapyridine is almost completely absorbed in the colon, metabolized in the liver, and excreted in the urine. The mesalamine moiety is locally absorbed and inhibits the formation and degradation of inflammatory mediators, including leukotrienes, prostaglandins, thromboxane, platelet activating factor, histamine, and a number of cytokines.[41] Sulfasalazine is of no value in managing small bowel inflammation because colonic bacterial metabolism is needed to release the active moiety. The usual initial dose in dogs is 20 to 40 mg/kg q8h for 3 weeks, followed by a progressive tapering every 2 to 3 weeks of the dose frequency (q8h to q12h to q24h to q48h). The drug should be used with caution and at a lower dose (10 to 20 mg/kg q24h) in cats because of the salicylate portion of the drug. The most common side effects of sulfasalazine are anorexia, vomiting, cholestatic jaundice, allergic dermatitis, and keratoconjunctivitis sicca (KCS).

Colloids

Administration of colloids such as Dextran 70 or hetastarch are used to increase the plasma oncotic pressure in dogs with intestinal lymphangiectasia or other PLEs when severely hypoalbuminemic. Colloids are typically administered prior to surgery in an effort to minimize complications associated with low plasma colloidal oncotic pressure. Administration of fresh-frozen plasma is an expensive and less efficient means of increasing colloidal oncotic pressure in dogs that are severely hypoalbuminemic. Loop diuretics such as furosemide (1 to 2 mg/kg subcutaneously or PO) can be used to decrease abdominal or pleural effusions, although caution should be heeded in monitoring the patient's hydration status and serum potassium concentrations. Potassium-sparing diuretics such as spironolactone (2 to 4 mg/kg PO or IV) can be used together with furosemide to decrease the likelihood of hypokalemia arising.

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CHAPTER 12

Dyschezia and Tenesmus

Albert E. Jergens

Definition

Dyschezia and tenesmus are clinical signs usually associated with colorectal disease. *Dyschezia* is the term applied to difficult or painful defecation, which is most commonly observed with anorectal disorders. *Tenesmus* is the clinical sign associated with straining to defecate (more common) or urinate (less common). Tenesmus is usually caused by large bowel disease, particularly colitis. Straining is usually evident as an animal maintaining a posture of defecation for an extended period, or as repeated, nonproductive attempts to defecate are observed. Tenesmus is often associated with other clinical signs of colonic disease including large bowel diarrhea (e.g., increased frequency of defecation, the production of scant fecal volume), hematochezia (fresh red blood on the feces), and/or excessive fecal mucus. Tenesmus is a clinical sign and not a disease; consequently, an underlying cause must be identified. In general, tenesmus and dyschezia are more commonly associated with colorectal disorders in dogs than in cats. Dysuria in cats with lower urinary tract disease may be misinterpreted as dyschezia and tenesmus.

Pathophysiology and Mechanisms

Inflammation of the colonic or rectal mucosa is the most common cause of tenesmus and dyschezia in dogs and cats.[1-4] Tenesmus may also occur with colonic, rectal, or anal obstruction, and constipation. Dyschezia is usually caused by diseases involving anal and perianal structures.[3,4] Severity of inflammation causing tenesmus or dyschezia is generally dictated by the magnitude of the host immune response. For example, mucosal inflammation of colonic inflammatory bowel disease (IBD) may be explained by (a) aberrant host responses to the colonic microbiota and (b) disturbances in colonic motility.[5] A generic inflammatory response involving infiltrating immune cells (e.g., B and T lymphocytes, macrophages), secretomotor neurons (e.g., vasoactive intestinal polypeptide, substance P), cytokines (both T-helper type 1 [Th]1 and Th2 derived), and various inflammatory mediators (e.g., leukotrienes, prostanoids, reactive oxygen species, and nitric oxide metabolites) drive the chronic inflammatory process.[5] Inflammation can cause suppression of normal colonic motility patterns, which may contribute to onset and severity of clinical signs. Other factors that may contribute to large bowel signs include previous therapies (especially antibiotics), bacterial fermentation (e.g., short-chain fatty acids [SCFA], lactate) products, altered composition of the colonic microbiota, and perturbed mucus secretion.

Other inflammatory conditions causing tenesmus and dyschezia can include helminths (*Trichuris* spp., *Ancylostoma* spp.), protozoa (*Giardia* spp., *Trichomonas* spp.), fungi (*Histoplasma* spp.), oomycetes (*Pythium* spp.), algae (*Prototheca* spp.), bacteria (*Campylobacter* spp., *Clostridia* spp., enteropathogenic/enterotoxigenic *Escherichia coli*), colorectal tumors, and rectal/anal strictures.[2] Mechanism for mucosal inflammation with these disorders varies and includes local mucosal irritation (e.g., nematode parasites), robust host immune responses (e.g., histoplasmosis, pythiosis), and direct mucosal association (e.g., adherent and invasive *E. coli* [AIEC] as seen with granulomatous colitis).

Constipation is another important cause of tenesmus and dyschezia in animals.[2] Constipation is defined as difficult, reduced, or painful evacuation of feces that occurs secondary to colonic hypomotility or dysmotility disorders, mechanical obstruction, or colorectal diseases. Dry, hardened feces are difficult to pass, and chronically constipated cats have intermittent episodes of tenesmus, hematochezia, or diarrhea due to the mucosal irritant effect of impacted feces. Fiber-responsive colitis is a unique large bowel diarrheal syndrome of dogs in which altered colonic motility causes clinical signs of excessive fecal mucus, hematochezia, and tenesmus.

Urogenital disease may occasionally cause tenesmus in some animals as nonbacterial (e.g., feline lower urinary tract disease [FLUTD], neoplasia, calculi) and bacterial-mediated inflammation involving the urinary bladder, urethra, and genital organs (e.g., prostate) is relatively common in dogs and cats.

Differential Diagnosis

Box 12-1 presents causes for tenesmus and dyschezia in companion animals. Although diseases affecting colon and rectum are the predominant source of clinical signs, it is important to exclude disturbances in other organs (e.g., urogenital disease) that can also cause tenesmus. Cats are notorious for stranguria associated with FLUTD, which can confound accurate assessment of ineffective straining associated with colorectal disease. A thorough patient history and observation of the animal's elimination process are essential for avoiding misdiagnosis.

Evaluation of the Patient

History

Always obtain a history pertaining to both urinary and gastrointestinal tracts in animals with tenesmus. A careful history and complete physical examination are required to determine which organs are affected and to assess potential severity of the dysfunction. Besides tenesmus, lower urinary tract disorders (especially cystitis or urethritis) often result in hematuria and pollakiuria, which are

Box 12-1 Causes for Tenesmus and Dyschezia in Dogs and Cats

Colorectal Disease
Constipation
Colitis-proctitis
Inflammatory bowel disease
Histoplasmosis
Clostridium enterotoxicosis
Protothecosis (rare)
Rectal stricture
Neoplasia or polyps
Foreign material
Fiber-responsive diarrhea

Perianal Disease
Anal sacculitis, impaction, or abscess
Anal sac neoplasia
Perianal fistula
Perianal hernia

Urogenital Disease
Cystitis–urethritis–vaginitis
Urinary bladder–urethra calculi
Prostatitis–prostatomegaly
Neoplasia of urethra, bladder, prostate, vagina

Other Causes
Caudal abdominal mass
Pelvic fracture–neoplasia

readily apparent to most clients. Normal urinary habits are most suggestive of tenesmus caused by colorectal disorders. Tenesmus preceding defecation usually indicates an obstructive lesion, whereas inflammatory disorders are often associated with persistent tenesmus following evacuation. A history of large bowel signs may be evident in patients with colonic disease alone and in animals having more extensive colorectal disease. Systemic signs of disease, such as anorexia, weight loss, vomiting or diarrhea, may be reported especially in animals having concurrent systemic disease or disorders involving other segments of the gastrointestinal tract. Animals are generally alert, active, and well-fleshed with normal appetites on presentation. The following historical concerns are of significance in animals with tenesmus and dyschezia:

- Is the diarrhea (if present) acute or chronic? Acute, self-limiting large bowel diarrhea is common and rarely requires an in-depth diagnostic evaluation.
- Are clinical signs static, progressive, or cyclical? Colorectal neoplasia may cause progressive signs whereas colonic IBD is characterized by a waxing/waning clinical course.
- Is there evidence of dietary, environmental, parasitic, or infectious causes for large bowel signs? Dietary and parasitic causes may constitute up to 50% of clinical cases dependent upon the geographic area.
- What type of diet is the animal being fed? Note recent dietary changes (this might incriminate responsible nutrients), the amount and frequency of feeding, and the administration of medications (e.g., antibiotics, narcotics, motility modifiers, laxatives) that might alter colonic function.
- Do clinical signs resolve when the animal is fed either an intact protein or hydrolysate elimination diet? This might suggest the presence of an adverse food reaction (i.e., dietary sensitivity or intolerance).
- A positive response to glucocorticoid therapy may indicate inflammatory or immune-mediated diseases, such as IBD or perianal fistula.
- Does the animal roam freely? If so, parasitic, toxic, and infectious causes for colorectal diseases may be more likely.
- Does the animal's travel history suggest an increased risk of disease with a regional incidence, such as histoplasmosis (Midwest United States) or intestinal parasites (Southern United States)?

Physical Examination

Physical examination provides important localizing information regarding potential cause(s) for dyschezia and tenesmus. The perineal region is carefully examined for perineal hernia, perianal fistula, abnormalities to the anal sacs (e.g., inflammation, rupture, tumor), or perianal masses. Abdominal palpation might yield a large turgid bladder (indicative of urinary obstruction), a fecal impacted colon (indicative of constipation), or prostatomegaly. Rectal examination is performed to rule out colonic stricture (rare); intraluminal masses (polyps or malignant tumors); abnormalities to the anal sacs, prostate, or urethra; and caudal abdominal cavity disorders (mass, pelvic fracture). Penis and vagina are also closely examined by the clinician for evidence of pain, masses, or calculi. Rectal evaluation permits the inspection of fresh feces for hematochezia or mucus and can provide valuable exfoliative specimens for cytological review. Some animals with exquisite rectal sensitivity because of inflammation, stricture, or mass lesion may require sedation or general anesthesia before rectal evaluation can be safely and adequately performed.

Laboratory Evaluation and Tests

Diagnostic strategies for colorectal disorders vary considerably depending on severity, chronicity of signs, presence of systemic illness, and historical or likely responses to therapy (Fig. 12-1). A laboratory database consisting of a complete blood count, biochemistry profile, and urinalysis should be performed in animals having tenesmus associated with systemic signs (e.g., anorexia, weight loss, dehydration). Other specific diagnostic tests include the following:

- *Fecal parasitic examination* (e.g., direct fecal smears and fecal flotation studies), which should be performed to evaluate for helminth or protozoal infections. Some parasites (e.g., *Trichuris vulpis* and *Giardia* spp.) may require serial fecal flotations. To identify *Giardia* cysts, a zinc sulfate flotation test is recommended. Direct saline fecal smears are used to detect motile trophozoites of *Giardia*, *Tritrichomonas*, *Balantidium*, or *Entamoeba*.
- *Fecal cytologic examination* involves evaluation of stained rectal/colonic mucosal scrapings under high power or oil immersion to identify etiologic agents or inflammatory cells. A flat conjunctival spatula (carefully advanced digitally) procures excellent quality specimens that are placed on a microscope slide, air-dried, and stained with Diff-Quik or Wright stain. Increased numbers of leukocytes indicate a possible inflammatory or infectious etiology. Finding fungal (*Histoplasma*) organisms or clostridial spores may suggest an infectious cause for gastrointestinal signs. Finding clostridial spores should be confirmed by culture and toxin assays.
- *Fecal bacteria cultures* are sometimes useful when infectious diarrhea is suspected. The major bacterial pathogens in dogs and cats include *Campylobacter jejuni*, *Salmonella* spp., pathogenic *E. coli*, and *Clostridia*. Fecal specimens for culture must be fresh, of adequate quantity (e.g., small, pea size amount of stool), and transported rapidly for inoculation into enrichment media. Results should always be interpreted in light of clinical signs and results

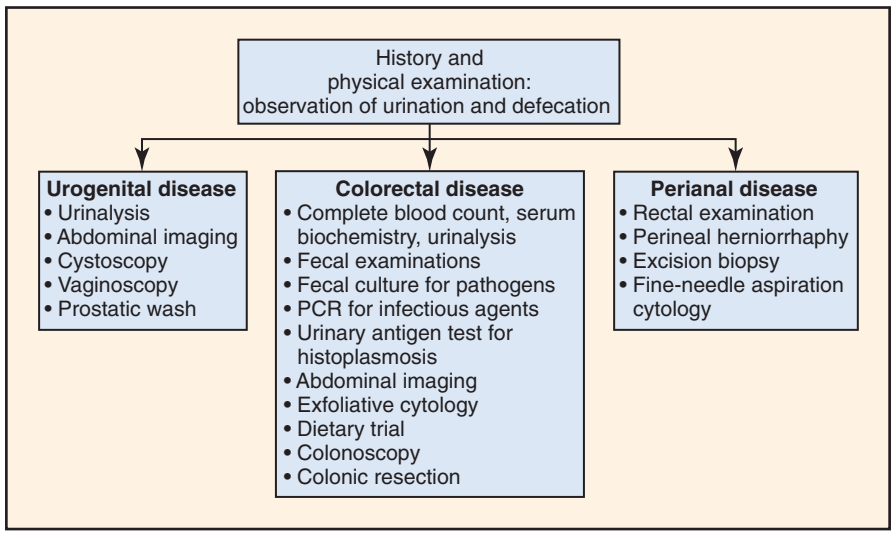

Figure 12-1 Diagnostic strategies for determining causes of tenesmus and dyschezia.

of laboratory tests. Fecal culture of a bacterial species is not necessarily definitive evidence for bacterial infection.

- *Molecular testing* using polymerase chain reaction (PCR) may be indicated for diagnosis of certain infectious agents, such as *Tritrichomonas foetus*, which may cause large bowel diarrhea in cats.[6]
- *Imaging* is infrequently diagnostic in animals with colorectal disease. Survey abdominal radiography may identify radiopaque foreign objects, fecal impaction, or extraluminal obstruction (e.g., pelvic canal stenosis, prostatomegaly, or lymphadenopathy). Pneumocolon may facilitate visualization of rectal masses. Ultrasonography is useful for confirming structural abnormalities to the genitourinary system causing tenesmus.
- *Fine-needle aspiration* of rectal or anal masses is useful for diagnosis of some perianal and rectal tumors. Excision biopsy is usually required for definitive diagnosis.
- *Colonoscopy with mucosal biopsy* often helps provide a definitive diagnosis of colonic mucosal disease.[7,8] Either flexible colonoscopy or rigid proctoscopy may be performed. Rigid proctoscopes are inexpensive and easy to use but only permit endoscopic evaluation of the distal colon and rectum. Flexible endoscopy is generally preferred as it enables evaluation of the entire colon, cecum, and the ileum. Proper patient preparation is critical for successful colonoscopy and facilitates procurement of diagnostically adequate specimens for histopathologic examination. Colonoscopy should only be performed after routine noninvasive diagnostic tests have failed to determine the cause for clinical signs. Simple proctoscopy may be sufficient in animals with isolated anorectal disease.

Treatment and Management

General Principles

Treatment of dyschezia and tenesmus depends predominantly on the cause. If genitourinary disease is the suspected cause of tenesmus, then specific therapy may include antibiotics for bacterial urinary tract and prostatic infection, surgical removal of calculi, drainage of prostatic cysts, and surgery or chemotherapy for genitourinary neoplasia. Tenesmus and dyschezia caused by colorectal or perianal disorders will also require specific medical or surgical intervention (Table 12-1).[1-4,9]

Table 12-1 Therapeutic Interventions for Tenesmus and Dyschezia

Causes for Tenesmus and Dyschezia	Therapeutic Interventions
Parasitic colitis	Anthelmintic or antiprotozoal therapy
IBD colitis	Elimination diet; immunosuppressive drugs; pre- and probiotic therapy
Colonic histoplasmosis	Antifungal drug therapy
Clostridial enterotoxicosis	Antibiotic therapy; fiber supplementation
Constipation	Correct underlying cause; medical therapy with dietary modification, enemas, laxatives, and prokinetic drugs; colectomy for megacolon
Rectal stricture	Balloon dilation of stricture
Neoplasia or polyps	Surgical excision of masses ± chemotherapy
Fiber-responsive diarrhea	Fiber supplementation
Anal sacculitis/impaction	Express contents ± antibiotic therapy
Anal sac neoplasia	Surgical excision ± chemotherapy
Cystitis or urethritis	Antibiotics based on urinary culture
Lower urinary calculi	Lithotripsy, cystotomy, hydropropulsion
Prostatomegaly or prostatitis	Neuter; antibiotics for prostatitis
Lower urinary neoplasia	Surgical excision ± chemotherapy

Medical

Tenesmus associated with acute, large bowel diarrhea is usually self-limiting. Dietary modification (see following discussion) will reduce signs and expedite clinical recovery in most instances. *Anthelmintics* should be administered if parasitic colitis is suspected. Fenbendazole and praziquantel have established efficacy against *Trichuris* spp. infection; treatment should be repeated at 3 weeks and again in 3 months to assure parasite eradication. Any coexisting intestinal infection (e.g., cryptosporidiosis, *Giardia* spp.) with *T. foetus* should be identified and treated if possible. Empirical therapy with fenbendazole is recommended and will improve signs but may not resolve

T. foetus infection. However, most cats (88%) will show spontaneous resolution of diarrhea within 2 years. *Antibiotics* are indicated for bacteria-mediated diarrhea causing tenesmus and when a specific enteropathogenic bacterial strain is identified through diagnostic (e.g., bacterial culture, PCR) testing. Metronidazole or tylosin may be used for treatment of acute or chronic *Clostridium perfringens* infection. Antibiotics also serve as adjunct therapy for anal sac impaction, anal sacculitis, and abscessation of the anal sacs following removal of contents.

Idiopathic IBD with colorectal involvement causing tenesmus is best treated using a combination of dietary and pharmacologic interventions. Drug therapy for IBD remains empirical but generally includes antiinflammatory (e.g., sulfasalazine, prednisone/prednisolone, budesonide), immunosuppressive (e.g., azathioprine, cyclosporine, chlorambucil), and select antimicrobial (e.g., metronidazole, tylosin) drugs. Histiocytic ulcerative colitis caused by adherent invasive *E. coli* (AIEC) is usually responsive to enrofloxacin therapy.[10]

Drug therapy for recurrent *constipation* is multifaceted and includes dietary modification, water enemas, oral laxatives, and colonic prokinetic agents in some combination.[2] Early use of drug therapy for episodes of constipation will prevent progression to obstipation or megacolon which eventually requires surgical intervention. *Malignant colorectal tumors*, including lymphomas, adenocarcinomas, and gastrointestinal stromal tumors, are associated with signs of inflammation (e.g., hematochezia, tenesmus) and obstruction in dogs. Benign colonic tumors, such as polyps, are generally restricted to the distal rectum. Depending upon tumor type, colorectal tumors are treated by surgical excision, chemotherapy, or antiinflammatory therapy in some combination.

Dietary therapy is an important treatment modality for canine and feline colitis caused by chronic immunologically mediated inflammation (e.g., idiopathic IBD) or adverse food reactions (e.g., food allergy, food intolerance). Both intact protein or hydrolysate elimination diets should be fed to reduce dietary sensitivities that occur secondary to impaired intestinal barrier function. Importantly, diets should also be highly digestible, low in fat content, lactose and gluten free, and should be fed for a sufficient time to elicit the desired clinical response. Dietary trials in cats are performed over a 7- to 10-day period; dogs with gastrointestinal signs caused by dietary ingredients are generally trialed for 3 to 4 weeks with an elimination diet to rule out adverse food reactions. Animals diagnosed with IBD will often require lifelong therapy with an elimination diet. Modification of the *n-3–to–n-6 fatty acid ratio* in the diet may further decrease mucosal inflammation and reduce tenesmus in animals.

Adjunct therapy for colitis also includes administration of *soluble fiber* (e.g., Metamucil, 1 to 3 tbsp. per meal), which serves to (a) normalize colonic motility patterns, (b) bind colonic irritants that may stimulate colonic secretions, and (c) produce beneficial SCFAs for colonic health, such as butyrate. Fiber-supplemented diets may be useful as primary therapy in certain forms of large bowel diarrhea in dogs.[11]

Surgical

Surgical therapy for treatment of tenesmus and dyschezia is required in animals with tumors affecting the colon and anorectum.[9] Complete surgical excision is indicated for colonic adenocarcinomas, cecal leiomyosarcomas, and obstructing lymphomas although complete surgical excision may not be possible for rectal carcinomas. Rectal tumors are generally excised by surgical eversion while benign rectal polyps may be removed endoscopically using a snare. Histopathology of the mucosa and submucosa is important for correct diagnosis and for defining the completeness of surgical removal. Cats diagnosed with severe recurrent obstipation or megacolon that is refractory to medical therapy will require subtotal colectomy to resolve clinical signs.[2]

Radiation and Endoscopy

Radiation therapy is uncommonly required for tenesmus seen with colonic disease but may be used to treat some rectal tumors that are inadequately excised. Balloon dilation via flexible endoscopy is the treatment of choice for benign rectal strictures causing obstruction, tenesmus, and dyschezia.[12] Multiple (two to three procedures) endoscopic balloon interventions may be required to adequately dilate the narrowed rectal lumen. Postprocedural glucocorticoid therapy is indicated to help prevent fibrosis and restricturing.

Alternative and Complementary

The alternative of n-3 and n-6 fatty acids in the diet to reduce production of key inflammatory mediators (e.g., leukotriene B_4) important in chronic inflammation was previously discussed (see Chapter 11). Other novel therapies for treatment of IBD have been proposed and include the administration of probiotics and prebiotics that modulate composition of the commensal microbiota to reduce gut inflammation. *Probiotics* are living microorganisms that, upon ingestion in sufficient numbers, impart health benefits beyond those of inherent basic nutrition. Lactobacilli and bifidobacteria have been the most commonly used human probiotics, but multistrain cocktails (e.g., VSL#3), *E. coli* Nissle 1917, and nonbacterial *Saccharomyces boulardii* have also been used for probiotic effect. Probiotic bacteria have measurable host benefits including ability to improve epithelial barrier function, modulate mucosal immune system, and alter intestinal flora.[13]

Prebiotics are nondigestible dietary carbohydrates—lactosucrose, fructooligosaccharides (FOS), psyllium, bran—that stimulate growth and metabolism of endogenous enteric protective bacteria upon consumption.[14] Beneficial effects of prebiotics are also associated with production of SCFA caused by fermentation by colonic bacteria. *Synbiotic therapy* (i.e., a combination of probiotics and prebiotics) is an emerging therapeutic modality. Increasing evidence supports a therapeutic role for probiotics, prebiotics, and synbiotics in gastrointestinal diseases of humans, including infectious diarrhea, *Helicobacter pylori* infection, irritable bowel syndrome, lactase deficiency, and IBD. Unfortunately, controlled clinical trials with these products in dogs and cats have not been performed, and future studies are needed to explore therapeutic efficacies and mechanisms of action of these mixtures in therapy of colonic inflammation causing tenesmus.

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CHAPTER 13

Dysphagia and Gagging

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Definition

The term *dysphagia* derives from the Greek roots *dys*, meaning "difficulty" or "disorder," and *phagia*, meaning "in eating." Broadly defined, *dysphagia* would apply to a large number of oropharyngeal disorders for which there is difficulty in eating. Thus the term could be used to describe problems associated with prehension of food or water, bolus formation, rostral-to-caudal contraction of pharyngeal constrictor musculature, dropping of food and/or water from the commissures of the mouth, and swallowing. Over time, *dysphagia* has become more strictly defined as difficulty in swallowing. *Gagging* or the *gag* reflex is an involuntary retching reflex stimulated by mechanical irritation of the posterior palate or pharynx. Dysphagia may provoke gagging, but gagging does not necessarily imply dysphagia. *Regurgitation* is a clinical sign more consistent with esophageal disease and should be differentiated from dysphagia, gagging, and vomiting (see Chapter 21). Regurgitation differs from vomiting in that it is characterized by passive retrograde evacuation of undigested food from the esophagus. *Vomiting* is characterized by coordinated activities of the gastrointestinal, musculoskeletal, and nervous systems culminating in the active evacuation of digested or partially digested food from the gastrointestinal tract (see Chapter 23).[1] Vomiting usually signifies disease caudal to the gastroesophageal sphincter. Signs referable to aspiration pneumonia, for example, *coughing* and *dyspnea*, may be the major presenting complaint in some animals. A good history will usually differentiate these signs from others (e.g., dysphagia, gagging) associated with oropharyngeal disorders.

Pathophysiology and Mechanisms

The oropharyngeal phase of swallowing is subdivided into three stages.[2-6] The first or *oral* stage begins with prehension of food with teeth and tongue and formation of the bolus at the base of the tongue. In the second or *pharyngeal* stage, rostral to caudal pharyngeal contractions propel the bolus from the base of the tongue to the cricopharyngeal or cranial esophageal sphincter opening. Mechanical stimulation of the caudal pharynx activates an afferent neural pathway that has its synapse in the brainstem, and which activates an efferent neural pathway back to the cricopharyngeus leading to inhibition and relaxation. The cricopharyngeus relaxes during the third or *cricopharyngeal* stage, and the bolus passes into the cranial esophageal body (Fig. 13-1). The cricopharyngeus subsequently contracts, pharyngeal muscles relax, and the oropharyngeal phase is repeated with successive swallows.

Abnormalities in any of the oropharyngeal stages can produce oropharyngeal dysphagia.[6] Oropharyngeal dysphagias are either morphologic or functional in origin. Morphologic disorders that interfere with oropharyngeal phase of swallowing include strictures, foreign bodies, and neoplastic, traumatic, and inflammatory processes of the oral cavity and pharynx. Most functional disorders consist of failure, spasticity, or incoordination of muscular contractions and are due to neuromuscular diseases.

Differential Diagnosis

Oropharyngeal Dysphagia

Three types of oropharyngeal dysphagia have been characterized in companion animal species: (a) *oral* stage dysphagias with prehension deficits mainly as a consequence of loss of tongue function; (b) *pharyngeal* stage dysphagias with transport deficits mainly as a consequence of loss of cranial and caudal pharyngeal constrictor function; and (c) *cricopharyngeal* stage dysphagias with cricopharyngeal opening or closure (achalasia or chalasia) deficits, or incoordination between pharyngeal contraction and cricopharyngeal sphincter relaxation.[6,7] Neuromuscular disease is the underlying pathogenesis of oropharyngeal dysphagia, but precise etiologies are rarely identified. Some cases have been associated with brainstem disease, peripheral neuropathy, myasthenia gravis, polymyositis, muscular dystrophy, and hypothyroidism. A unique form of oropharyngeal dysphagia bearing some resemblance to muscular dystrophy has been described in the Bouviers des Flandres breed (Table 13-1) [8,9]

Cricopharyngeal Achalasia

Cricopharyngeal achalasia is a neuromuscular disorder of young dogs characterized by hypertension of the cranial esophageal sphincter and inadequate relaxation of the sphincter with swallowing. Dysfunction of the inhibitory neuron mediating sphincteric relaxation has been postulated, but etiology, pathogenesis, and breed predisposition of this disorder are unknown.

Evaluation of the Patient

History

Dysphagia and gagging are the most important clinical signs with oropharyngeal disorders. Pet owners may also describe difficulties in drinking water or forming a solid bolus, excessive mandibular or head motion, persistent forceful ineffective swallowing efforts, dropping of food from the mouth, nasal discharge because of misdirection

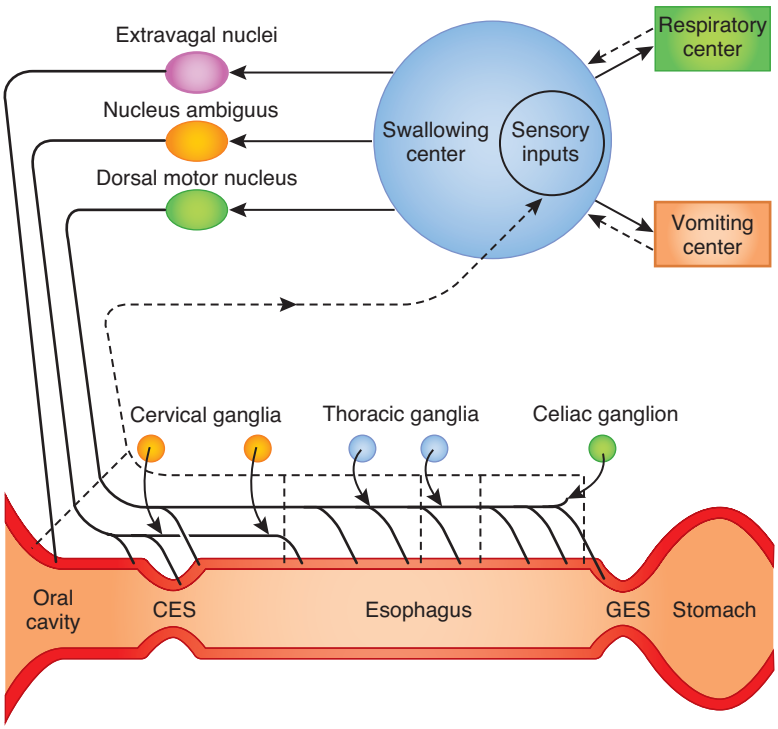

Figure 13-1 Neural regulation of swallowing in the dog and cat. (Reprinted with permission from Washabau RJ, Holt DE. Pathophysiology of gastrointestinal disease. In: Slatter D, ed. *Textbook of small animal surgery*, 3rd ed. Philadelphia, Saunders, 2003.)

Table 13-1 Known Breed Predispositions for Diseases of the Oropharynx Causing Dysphagia and Gagging

Condition	Breed
Oral neoplasia	Golden retriever, Weimaraner, Boxer, Cocker Spaniel
Oropharyngeal dysphagia	Bouvier des Flandres, Golden Retriever, Labrador Retriever
Oral eosinophilic granuloma	Siberian Husky

of food into the nasopharynx, excessive salivation, foaming from the mouth, coughing, failure to thrive, and reluctance to eat.[6,10] Regurgitation, a common sign of esophageal disease, is less frequently reported with oropharyngeal dysphagias.

Physical Examination

Physical examination findings are dependent upon the pathogenesis and severity of dysphagia. Many morphologic abnormalities (e.g., neoplasia, stricture, inflammation, foreign body) are fairly obvious on examination of the pharynx. Animals with oropharyngeal dysphagias, on the other hand, may have few morphologic abnormalities. Focal or generalized muscle atrophy and diminished or absent gag reflex may be the only abnormal findings in animals with neuromuscular disease.

Diagnostic Tests

Figure 13-2 depicts an approach to diagnosis of dysphagia and gagging associated with oropharyngeal disease. Diagnosis of a morphologic abnormality is usually straightforward and, except for tissue biopsy or culture, usually does not require any additional diagnostic testing. Survey radiography, ultrasound, computerized tomography, and magnetic resonance imaging (MRI) may be performed to assess for severity of local traumatic injury, or to assess for distant metastasis.[11] Diagnosis of oropharyngeal dysphagias is more difficult and may require use of videofluoroscopy[6,7] and/or electrophysiology.[2] If these techniques are not readily available in the private practice setting, cases should be referred to a specialty center.

Clinical Examination

Diagnosis of oropharyngeal dysphagia is usually made on the basis of clinical signs and by exclusion of other oropharyngeal pathology. Once an oropharyngeal dysphagia is suspected, it should be further classified into an oral, pharyngeal, or cricopharyngeal stage disorders.

Diagnosis

Videofluoroscopy is the diagnostic test of choice because it is impossible to further classify these disorders on the basis of physical examination or survey radiography. Videofluoroscopy findings of *oral* stage dysphagias are typified by weak tongue-thrust action, retention of contrast medium in the oropharynx, and loss of contrast medium from the mouth.[6,7] Aspiration pneumonia is not a typical finding in oral stage dysphagias. Videofluoroscopic findings consistent with a *pharyngeal* stage dysphagia include (a) incomplete pharyngeal contraction with adequate cricopharyngeal relaxation, (b) slow induction and slow progression of peristaltic-like contractions from the rostral to the caudal pharynx, and (c) laryngotracheal aspiration. Aspiration pneumonia is a typical finding in pharyngeal stage dysphagias. In *cricopharyngeal* stage dysphagia, the cricopharyngeus fails to relax (achalasia) or relaxes at an inappropriate time (incoordination) following pharyngeal contraction.

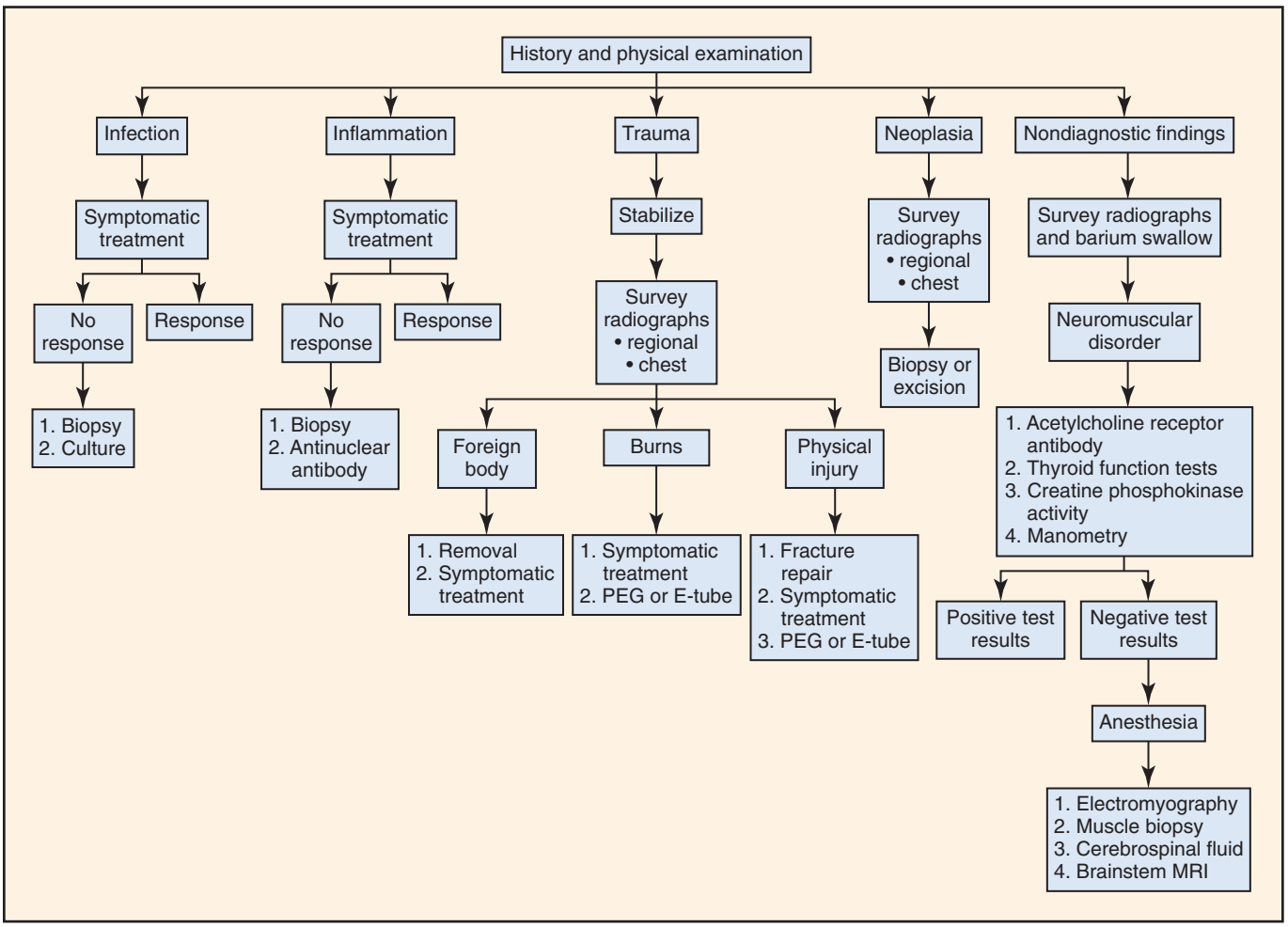

Figure 13-2 General diagnostic and therapeutic approach to dysphagia and gagging.

Electromyography may be useful in distinguishing oropharyngeal dysphagia from cricopharyngeal achalasia. Fibrillation and positive sharp waves observed in oropharyngeal musculature suggest that the disorder involves the structures of the oral cavity and pharynx instead of the cricopharyngeus.

Other diagnostic tests that may be warranted after an oropharyngeal dysphagia has been diagnosed are serology for nicotinic acetylcholine receptor antibody, antinuclear antibody, thyroid function test (e.g., thyroid-stimulating hormone [TSH] assay, TSH stimulation, serum thyroid hormones), serum creatine phosphokinase activity, muscle biopsy, and brainstem magnetic resonance imaging (see Fig. 13-2). Other oropharyngeal and esophageal pathologies are the major differential diagnoses for the oropharyngeal dysphagias.

Treatment and Management

General Principles

Except for cricopharyngeal achalasia, which is treated surgically by cricopharyngeal myotomy, oropharyngeal dysphagias are all treated medically. Cricopharyngeal myotomy appears to be of no benefit in oral and pharyngeal stage dysphagias; indeed, oropharyngeal dysphagias may be worsened by cricopharyngeal myotomy.

Medical

Medical therapy for oropharyngeal dysphagias is mostly supportive and consists of nutritional support (e.g., gastrostomy tube feeding) on a temporary or permanent basis. Elevated feedings and different food consistencies may be attempted, but these efforts are often of little clinical benefit. In early cases of myasthenia gravis, acetylcholinesterase inhibitors (e.g., pyridostigmine 0.5 to 3.0 mg/kg PO, BID-TID) may yield substantial clinical improvement.[12,13] Glucocorticoid therapy (prednisone 1.0 to 2.0 mg/kg PO, BID) will also improve clinical signs in many myasthenic and polymyositis patients, although many cases of canine myasthenia gravis appear to resolve spontaneously without immunosuppressive therapy.[14] Thyroid hormone replacement therapy (levothyroxine 22 µg/kg PO, BID) should be attempted in animals with documented hypothyroidism (see Fig. 13-2; Box 13-1).

Surgical

It is difficult to generalize based on the small number of cases that have been reported, but cricopharyngeal disorders are probably best treated with cricopharyngeal myotomy.[15] Most animals experience immediate relief following surgery.[16] Effective medical management has not been described for this disorder.

Box 13-1 Therapeutics for Oropharyngeal Disease

Broad Spectrum Antibiotics
- Aminoglycosides (gentamicin, amikacin), ampicillin, cephalosporins (cefoxitin, cephalexin, cephalothin), clindamycin, enrofloxacin, metronidazole

Chemical Diffusion Barriers
- Sucralfate 0.5 to 1.0 PO TID—should be given as oral suspension; much less effective when given as intact tablet

Gastric Acid Secretory Inhibitors
- Cimetidine 5 to 10 mg/kg PO or IV TID-QID
- Ranitidine 1 to 2 mg/kg PO or IV BID-TID
- Famotidine 0.1 to 0.5 mg/kg PO or IV BID
- Nizatidine 2.5 to 5 mg/kg PO QD
- Omeprazole 1-2 mg/kg PO q24h
- Pantoprazole 1 mg/kg IV
- Esomeprazole 1 mg/kg IV

Smooth Muscle Prokinetic Agents
- Metoclopramide 0.2 to 0.4 mg/kg PO, TID-QID
- Erythromycin 0.5 to 1.0 mg/kg PO, IV, BID-TID
- Bethanechol 5 to 15 mg/dog PO TID, 1.25 to 5 mg/cat PO TID

Glucocorticoids
- Prednisone 0.5 to 1.0 mg/kg SC or IM BID for esophageal strictures
- Prednisone 1.0 to 2.0 mg/kg PO BID for systemic lupus erythematosus and bullous pemphigoid

Thyroid Replacement Therapy
- Levothyroxine 22 µg/kg PO BID

Acetylcholinesterase Inhibitors
- Pyridostigmine 0.5 to 3.0 mg/kg PO BID-TID

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CHAPTER 14

Fecal Incontinence

Nick Cave

Definition

Fecal incontinence is defined as the inability to retain feces in the colon and rectum leading to uncontrolled leakage of fecal material at times other than during conscious defecation. The recorded prevalence of fecal incontinence is 43 of 260,000 admissions to the University of Missouri and University of California Veterinary Medical Teaching Hospitals.[1] This is probably an underestimation of the true incidence of the disease. There is no sex predilection, but the majority of affected animals are 11 years of age or older. Although fecal incontinence in itself is not a significant cause of morbidity in cats and dogs, it can be a clinical sign associated with serious disease. It can be disastrous for a household pet irrespective of the underlying cause because it commonly leads to euthanasia.

Pathophysiology and Mechanisms

Similar to micturition, production and elimination of feces has a storage phase, a phase of awareness of the need to defecate, and the act of defecation. During each phase, there is coordination of four main anatomic structures: descending colon, rectum, internal anal sphincter (IAS), and external anal sphincter (EAS).

Storage Phase

During formation and storage of feces, distal colonic longitudinal contractions are inhibited by sympathetic activity. The main sympathetic supply to the distal colon and anorectum originates at L2-L5, synapses in mesenteric ganglia, and exits within the hypogastric nerve. Sympathetic stimuli via hypogastric and lumbar colonic nerves inhibit defecation in part by inhibiting colonic contractions. The site of inhibition appears to be in the caudal mesenteric and pelvic plexuses through synapses on parasympathetic motor neurons within vagal and pelvic nerves, respectively. The pelvic plexus lies lateral to the middle portion of the rectum.[2]

Fibers from lumbar colonic and hypogastric nerves also innervate the IAS leading to contraction.[3] Thus the internal anal sphincter is important in maintaining the resting pressure of the anal canal.[4,5] The region of increased tone extends from approximately the pelvic brim to the anus. Coordination of colonic contraction and sphincter relaxation occurs in the enteric nervous system, notably the pelvic plexus. Injury to the autonomic nerve fibers in the pelvic plexus may lead to fecal incontinence after resection of part of the distal colon or rectum. However, resection of the IAS does not necessarily completely interfere with fecal continence.[4]

Contraction of EAS under somatic control of the pudendal nerve (caudal rectal branch) can further raise pressure in the anal canal. In dogs it is likely that EAS and levator ani play an important role in maintenance of continence.

Awareness of the Need to Defecate

As feces form in the descending colon, occasional peristaltic waves push material distally into the rectum. In dogs, feces arriving from the colon are halted at the rectocolonic junction by sphincteric pressure, thus stool stops short of the rectocolonic junction instead of passing directly to the rectum.[6] Rectal tone is maintained mostly through sympathetic innervation.[7] Expansion of the rectal walls stimulates stretch receptors that send afferent signals through the pelvic nerve to ascending spinal cord tracts that ultimately lead to the frontal cortex. This leads to the awareness of the urge to defecate. Afferent fibers in the pudendal nerve convey the sensation to reinforce urge when fecal material extends to the level of the anus. A reflex arc is present whereby even slight distention of the rectum of humans or dogs results in relaxation of the IAS. This is the *rectosphincteric inhibition reflex*.[8] This arc is suppressed by upper motor neurons (UMNs) until the conscious decision is made to initiate defecation. Thus a disturbance of descending UMNs decreases inhibition. Contraction of the IAS is unlikely to be important in maintaining continence when pressure in the rectum becomes high, but may help guard against incontinence of small amounts of liquid stool. Additionally, reflex relaxation of the IAS in response to rectal distention allows for conscious "sampling" of the rectal contents and helps distinguish flatus from feces.

If the urge is not acted upon, material in the rectum is often returned to the colon where more water is absorbed. This is an act of conscious suppression that is reliant upon intact neural pathways from rectum to frontal cortex.

Defecation Phase

At the appropriate time, the impulse for defecation originates in the cerebral cortex and descends via motor tracts through the brainstem to the lower motor neurons of sacral, pelvic, and pudendal nerves leading to relaxation of the IAS. During normal defecation, there is relaxation of the rectum prior to colonic contraction, then migrating contractions of the colon pass aborally to the rectum. The IAS muscles continue to relax while large amplitude contractions of the colon migrate to the rectum.[4,9]

Migrating colonic contractions under control of the pelvic and sacral nerves advance fecal material into the rectum. The rectum

shortens as material is forced into the anal canal and peristaltic waves propel feces out of the rectum. Relaxation of the IAS is achieved by inhibitory reflexes carried predominantly by pelvic and sacral nerves to the mesenteric plexuses.[10] This inhibitory reflex is absent in animals with a congenital absence of distal colonic ganglionic neurons (Hirschsprung disease) causing failure to relax and functional colonic obstruction.[11] Vagal nerve function may compensate for denervation of the pelvic nerve leading to recovery of defecation reflexes after several weeks [12] Finally, somatic inhibition of skeletal muscle of the EAS via the pudendal nerve permits defecation into the animal's environment.

Overall coordination of defecation involves parasympathetic nervous system (via the vagus and pelvic nerves), sympathetic nervous system (via the hypogastric nerve), and somatic nervous system (via the pudendal nerve). Fecal incontinence can occur because of failure of storage (reservoir incontinence), failure of UMN control (UMN incontinence), or failure of IAS and EAS contraction (sphincter incontinence). Box 14-1 and Figure 14-1 outline causes of fecal incontinence.

Box 14-1 Causes of Fecal Incontinence

- Anorectal disease
  - Lacerations
  - Neoplasia
  - Perianal fistula
  - Surgical trauma
  - Anal sac removal
  - Perineal hernia repair
  - Perianal fistula excision
- Colorectal disease
  - Inflammatory disease–proctitis, colitis
  - Neoplasia
  - Constipation
  - Diarrhea
- Myopathies and neuromuscular junctionopathies
  - Trauma
  - Myopathy
  - Myasthenia gravis
- Peripheral neuropathies
  - Trauma
  - Drug-induced (e.g., vincristine)
  - Polyneuropathy
  - Dysautonomia
  - Chronic tenesmus
  - Diabetes mellitus
- Spinal cord disease
  - Congenital vertebral malformations (e.g., Manx syndrome)
  - Trauma
  - Neoplasia
  - Vascular compromise
- Intervertebral disk herniation
- Arachnoid cyst
- Instability
- Lumbosacral stenosis
  - Hemorrhage
  - Diskospondylitis
  - Infectious myelitis (e.g., *Neospora caninum*, distemper)
  - Degenerative myelopathy
- Prostatic disease
- Adverse behavior
- Cognitive dysfunction

Reservoir Incontinence

A reservoir mechanism is essential for continence, because the maximum period of sustained voluntary contraction of striated anal sphincter muscles is brief. Reservoir incontinence results from a failure of the large bowel to accommodate to the colorectal content. Animals with reservoir incontinence are usually aware of feces in the rectum and are able to sense imminent defecation. Reservoir incontinence is most often characterized by frequent, conscious defecation, but not by inadvertent anal dribbling. Adequacy of large bowel reservoir function is affected by colorectal irritability, capacity, compliance, and motility, and volume of feces. Causes of reservoir incontinence include acute or chronic proctitis, rectoanal neoplasia, and diffuse colitis.

Sphincter Incontinence

Failure of tonic anorectal and anal sphincter tone can occur due to trauma to the pudendal nerve, as part of cauda equina syndrome, or as part of more generalized degenerative or inflammatory neuropathies such as degenerative myelopathy of German Shepherds. Neurogenic sphincter incontinence is most commonly associated with lower motor neuron dysfunction, as seen with lumbosacral disease. Animals with lumbosacral disease often have decreased anal tone, decreased anal and rectal sensation, and loss of the rectosphincteric reflex. In a study of 69 surgically treated cases of degenerative lumbosacral stenosis in dogs, four (6%) had fecal incontinence prior to surgery, and of those only one improved without surgical correction.[13] Following dorsal decompressive laminectomy, a further four developed fecal incontinence. Although rare in cats, lumbosacral disease is occasionally seen and has been associated with fecal incontinence.[14] Perianal surgical procedures can result in damage to the EAS or its innervations leading to incontinence.[15-17]

Aging has a gradual and progressive effect on anal function. Effects of aging in human colon and anal sphincter include thinning of the external anal sphincter, weakening of muscular contraction, and increased latency of pudendal nerve firing.[18] This may be relevant to geriatric dogs and cats.

Upper Motor Neuron Incontinence

Loss of fecal continence secondary to spinal cord disease is usually associated with a severe compressive lesion. Some dogs may present with only mild proprioceptive deficits and normal spinal reflexes.[15,19] Lesions of the UMNs associated with fecal incontinence have been located in thoracic, cervical, and rarely central portions of the central nervous system (CNS). Lesions can be diffuse, but are most commonly a result of focal disease of which arachnoid cysts are the most frequently reported.[15,20] In many cases, fecal incontinence is reported to develop prior to development of gait defects in the pelvic limbs. Most described lesions were located in the dorsal or dorsolateral aspects of the spinal cord where ascending sensory tracts are located, thus disrupting ascending signals from rectal stretch receptors leading to defecation as soon as fecal material is advanced into the rectum.

Differential Diagnosis

Fecal incontinence can occur with both neurologic and nonneurologic disorders (see Box 14-1). It is important to differentiate true incontinence from behavioral problems. House soiling is a common cause for presentation and is more common than true fecal incontinence.[21,22] In a study of behavioral problems in old dogs, 10 dogs were presented with house soiling as the primary complaint, but only one was truly because of incontinence.[22] Once

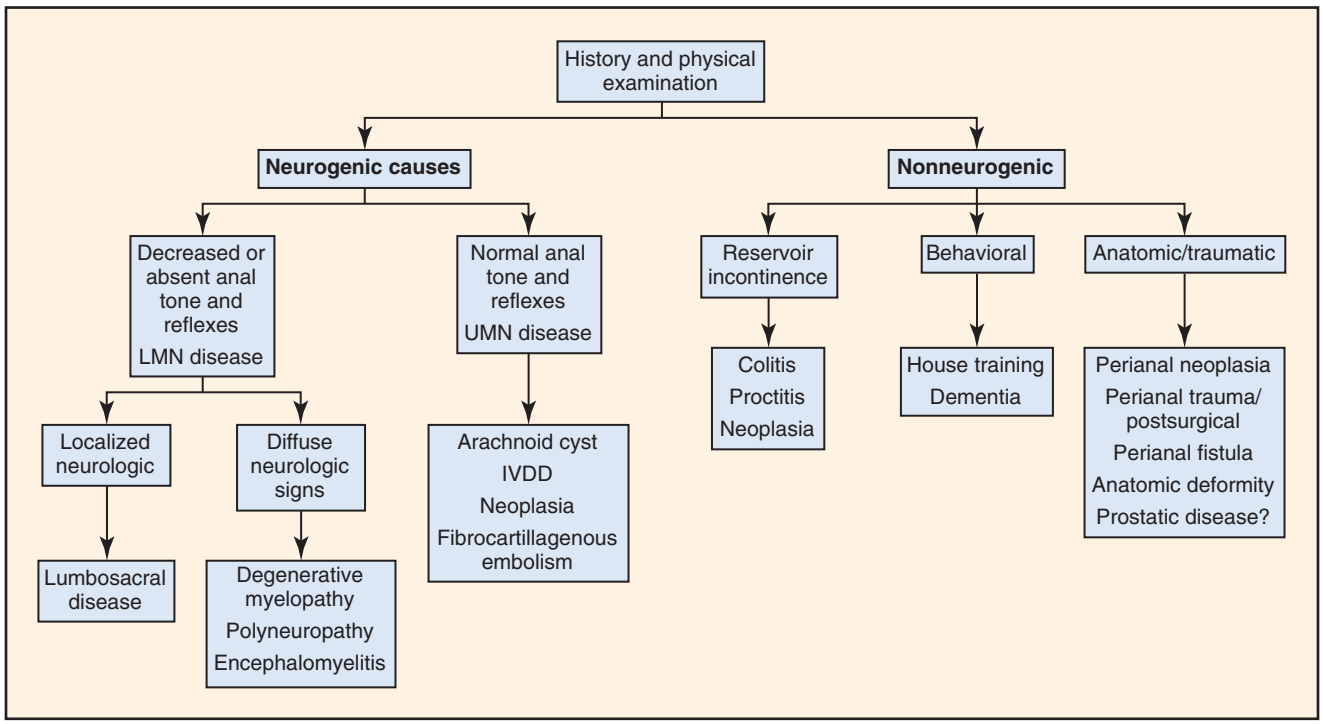

Figure 14-1 Algorithm for the investigation of fecal incontinence.

it is established that incontinence is present, nonneurologic and neurogenic causes should be differentiated. Common examples of conditions associated with neurogenic sphincter incontinence include diseases involving cauda equina (e.g., intervertebral disk disease, neoplasia, congenital malformations such as Manx deformity in cats).[13,15,19,20,23,24] Lesions of the UMN are commonly caused by arachnoid cyst formation. Sporadic cases have been described from more diffuse neurologic disease, such as dysautonomia, and diffuse inflammatory disease, such as meningoencephalitis of unknown origin, distemper encephalitis, and disseminated malignant histiocytosis.[25,26]

Conditions associated with nonneurogenic sphincter incontinence include perianal fistula, perianal neoplasia, prostatic disease, traumatic injury to the sphincter, and iatrogenic damage during perianal surgery such as anal sac removal or surgery for anal furunculosis.[16,27] Transient sphincter failure has been reported following traumatic lavage of the anal sac.

Evaluation of the Patient

History

Onset can be sudden leading to acute presentation, or gradual over weeks to months with slow progression of abnormal defecation prior to presentation. In some cases, animals have had abnormal patterns of defecation for years prior to evaluation.[15] Questions specific to the presenting problem should attempt to elucidate the following:

- The act of defecation—The owner's description of the animal's act of defecation should be carefully scrutinized. Does the animal consciously defecate (i.e., adopt a posture appropriate to defecation) and, if it does posture to defecate, whether the time and place it has chosen is appropriate? Failure to make any attempt at conscious defecation suggests a severe anorectal sensory derangement. These animals usually have a history of unconscious anal dribbling often occurring at times of increased abdominal or rectal pressures such as during coughing or physical exertion. Alternatively, is the defecation associated with tenesmus, urgency, or even dyschezia? In a house-trained animal, conscious defecation at inappropriate times or places, without the associated distress and urgency of reservoir incontinence, is more suggestive of a behavioral problem or a confused state. In a young animal, inappropriate defecation may be simply caused by a failure of house training. Dogs with UMN lesions associated with fecal incontinence may retain the ability to defecate normally at appropriate times, yet remain unaware of inappropriate defecation at other times, such as while walking, sitting, or sleeping.[19]
- Frequency of incontinence—This might range from very occasional episodes associated with colitis or adverse behavior to almost continuous and associated with functional failure of the anal sphincters.
- Fecal quality—Ascertain for diarrhea, constipation, hematochezia, and fecal mucus.

More general questioning should elucidate:

- Micturition—Is there any abnormality such as urinary incontinence or dysuria? If fecal incontinence is caused by neurologic disease, there may be simultaneous urinary incontinence.
- Gait and neurologic abnormalities—Is there a history of lameness, which might be associated with difficulty walking outside or posturing? Is there any other evidence of neurologic disease such as peripheral neuropathies, spinal ataxia, or brain disease such as senile cognitive dysfunction?
- Previous history of pelvic trauma or difficulty whelping.
- Drug or toxin exposure that might cause peripheral neuropathy.
- Environmental changes that could exacerbate adverse behavior or cognitive dysfunction.

Physical Examination

Thorough physical examination is indicated in all animals presenting with fecal incontinence. Particular attention should be paid to visual inspection of the anal area looking for dermatologic disease (e.g., fistula formation), resting anal tone, and tail carriage. Anal reflexes are usually assessed at this time (see "Neurologic Examination" below). This must be followed by careful digital examination of the anorectum to palpate for the presence, quality, and appearance of feces; the density or texture of the rectal mucosa; the presence of anorectal masses; and extraintestinal structures such as the prostate and urethra.[27] At this time anal tone is assessed, although qualitative assessments of anal tone are poorly correlated with more objective measures of anal sphincter function. This is partly because a denervated external anal sphincter does not readily atrophy, and partly because UMN lesions will often result in normal anal tone.[15] Abdominal palpation assesses colorectal content, bladder tone, and ease of bladder expression. The skin of the hind limbs should be carefully examined for areas of self-trauma, which may be suggestive of paresthesias, and the dorsal lumbosacral skin and musculature should be palpated for evidence of hyperesthesias. Hind-limb paresthesia and hyperesthesia are both suggestive of cauda equina syndrome.

Testing for the presence of lumbosacral (LS) pain should be performed by tail elevation and manipulation to produce lordosis and extension of the hip. Pain consistent with lumbosacral or lumbar spinal disease will occur in the absence of pain on abduction or rotation of the hip joints.[28] Coexistence of degenerative coxofemoral and lumbosacral diseases increase the difficulty in making a clinical diagnosis of LS disease.

Neurologic Examination

All animals with fecal incontinence should be subjected to neurologic examination. In neurogenic causes of incontinence, it is important to determine if incontinence is caused by an UMN or lower motor neuron (LMN) lesion. Neurologic examination demands observation of gait, cranial nerves, postural reactions, myotactic reflexes, and reflexes specific to defecation. Anal reflex is evaluated by pricking or pinching the perianal skin and looking for contraction of the anal sphincter. Rectal-inflation reflex is induced by inflating with 15 to 30 mL of air a Foley catheter that has been placed in the caudal extremity of the rectum. This induces anal contraction in both dogs and humans. Pudendal–anal reflex is evaluated by applying digital pressure to the penis while observing for anal contraction. All three reflexes assess sacral spinal segments, motor neurons in the pudendal nerves, and the external anal sphincter. Anal and pudendal-anal reflexes test perineal nerve afferents, whereas it is likely that the "rectal–inflation reflex" tests pelvic or S3 and C1 nerve afferents. These reflexes are usually preserved in animals with suprasacral spinal transverse myelopathies, whereas conscious perception of perineal and anorectal sensation (induced by the inflated Foley catheter) is not. Thus the history of fecal incontinence with normal perineal and anal reflexes is consistent with an UMN lesion cranial to the L3 spinal cord segments.[15] Lumbosacral disease may be associated with depressed cranial tibial, ischiatic, and withdrawal reflexes, and normal to exaggerated patellar reflexes.[28]

Laboratory Evaluation and Tests

Proctoscopy with biopsy is indicated if reservoir incontinence is suspected. Radiography may reveal diseases of the vertebral column responsible for incontinence. Myelography, epidurography, discography, and computed tomography (CT) scanning are of value in the diagnosis of deforming lesions affecting the spinal cord, including cauda equina. Electrodiagnostic evaluation of the incontinent animal greatly facilitates diagnosis. Electromyographic examination of muscles of continence may reveal denervation or myopathy. Clinical assessment of the pudendal–anal reflex can be made more objective by electrophysiologic evaluation of the reflex. The cerebrospinal fluid (CSF) examination may include a CSF distemper titer to assist diagnosis of canine distemper.

Treatment and Management

General Principles

Therapy of fecal incontinence is more likely to be successful following identification and treatment of the underlying cause. For instance, resolution of incontinence may follow successful treatment of diarrhea. Alternatively, behavior modification will be required to eliminate behavioral house soiling.[21] Successful surgical decompression of spinal lesions such as intervertebral disk herniations, and arachnoid cysts can restore fecal continence, even when the incontinence has been present for months.[13,15] Restoration of IAS tone after denervation may be a result of intrinsic myogenic properties of the sphincter.[3] However, complete recover of function is uncommon, and prognosis for LMN incontinence is generally guarded to poor.

Some patients may be managed by a dedicated pet owner with the use of daily warm water enemas. Alternatively, defecation may be induced by inflation of a rectal Foley catheter. This technique will not produce conscious defecation in animals with anorectal anesthesia but may produce involuntary rectal evacuation.[29] In animals with chronic posterior paralysis as a result of spinal cord damage, a minor stimulus to the hind limbs or perineum (e.g., light toe pinch or warm wash cloth) may stimulate appropriate elimination. Despite loss of rectal or anal function, unconscious passage of feces may still be precipitated by stimuli of colonic contractility. Exercise and eating are both prominent stimulants of colonic activity. Finally, application of diapers (nappies) may, if tolerated, enable persistence of an incontinent animal in the household.

Medical

The use of low-residue diets such as cottage cheese and rice reduces fecal volume by up to 85% if preceded by a poorly digestible diet. They also reduce frequency of defecation. Commercial premium diets often have a high digestibility, and several diets formulated for "intestinal disease" are reasonable empirical choices. Dietary fiber can increase fecal water content, increase fecal bulk, and thereby exacerbate fecal incontinence. However, nonfermentable fiber can also increase fecal firmness and increase segmental colonic contractions. In humans it may improve incontinence, especially when fecal quality is poor.[30] Addition of a mixed fermentable fiber such as psyllium (Metamucil) can be used on a trial basis. Dose is empirical and should be based on fiber content of the existing diet, but could range from 2% to 8% on a dry matter basis (1 rounded teaspoon of Metamucil contains 5 g of fiber). A reasonable approach is to initially introduce a highly digestible commercial dry diet that contains a source of fermentable fiber of between 2% and 8% on a dry-matter basis. If the animal is already consuming such a diet, or if there is little response, then the judicious addition of supplementary fiber can be attempted. This should be performed on a trial basis, as simple increase of fecal bulk that occurs with dietary fiber may be counterproductive.

Drug treatment is frequently instigated in hope of slowing colonic transit. Opioids such as loperamide increase segmental contractions and inhibit longitudinal colonic contractions and may be useful in the management of fecal incontinence when fecal water content is high. However, even in humans efficacy of loperamide

for managing fecal incontinence is inconclusive, and its efficacy has not been proved in dogs or cats.[31] Loperamide may be given for prolonged periods with little development of tolerance to their effects. A suggested dosage for loperamide is 0.1 to 0.2 mg/kg PO, given every 8 hours initially and to effect thereafter. Another pharmacologic approach is to attempt to increase anal tone. Phenylephrine gel (30%) causes contraction of the IAS, but has not been shown to be effective in humans.[32] Perhaps more promising are the recent studies in humans reporting the efficacy of injections into the anal submucosa of a gel of stabilized nonanimal hyaluronic acid with dextranomer gel (Zuidex), normally used for increasing urethral tone in urinary incontinence.[33] Although only half of patients appear to respond (defined as a 50% reduction in frequency of defecation), those that do respond experience 12 months of improvement after a single treatment of four 1-mL submucosal injections.

Surgical

Surgical techniques have been developed to improve or restore fecal continence in dogs. Such techniques are reserved for when identification and management of an underlying cause is either not possible or has not restored continence, and when medical therapy has failed. Sling techniques designed to increase pressure on the terminal rectum to reduce leakage have been published, including the use of a silicone elastomer sling.[34] A return to continence was reported in five of six dogs in one study, and only mild fibrosis was associated with the implant. In other techniques, reconstruction of a muscular sphincter using regional skeletal muscle flaps have shown promise in dogs rendered experimentally incontinent.[35,36] However, such techniques rely on either exogenous electrical stimulation or persistence of normal pudendal nerve function. Artificial sphincters using inflatable cuffs have also been used experimentally but there are no published reports of their clinical use.[37]

Conclusion

Fecal incontinence in dogs and cats can be devastating because of difficulties in management, and euthanasia is a high risk. Initial history should allow differentiation among patients with prostatic, neurologic, and neuromuscular disease. Any patient presenting with fecal incontinence should have a thorough neurologic assessment to determine if the cause is a result of LMN or UMN disease. If the neurologic assessment shows normal anal tone, reflex, and sensation, an UMN lesion may be present in which case a spinal magnetic resonance imaging is required to determine specific lesion location. If the lesion is focal in nature, it may be amenable to surgery. Surgical intervention may reverse signs of UMN fecal incontinence even when clinical signs have been present for many months to years. Thus diagnosis of UMN fecal incontinence has a better prognostic outlook with surgical intervention than does LMN fecal incontinence. Long-term management may need to be multifaceted and include dietary manipulation, behavioral management, and, potentially, drugs. Injection of stabilized nonanimal hyaluronic acid with dextranomer gel into rectal submucosa warrants investigation.

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CHAPTER 15

Gastrointestinal Gas: Eructation, Borborygmus, and Flatulence

Nick Cave

Definition

Eructation is defined as the expulsion of gastrointestinal gas from the oral cavity; whereas *flatulence* is defined as the expulsion of gas from the anorectal canal. *Borborygmus* is the term used to describe the rumbling noise of gas as it is propagated through the gastrointestinal tract. All three can be normal manifestations of gastrointestinal tract function, but may be presented as problems because of frequency, intensity, or odor. Flatulence is common in pet dogs, for example, and nearly 40% of pet owners would alter the diet if that strategy prevented flatulence.[1]

Pathophysiology and Mechanisms

Gastrointestinal gas is derived from four sources: (a) aerophagia, (b) luminal chemical reactions, (c) bacterial fermentation, and (d) diffusion from circulation into the lumen. The majority of intestinal gas is composed of nitrogen, oxygen, hydrogen, methane, and carbon dioxide, all of which are odorless. Most intestinal nitrogen and oxygen is derived from ingested air. The predominant gases in flatus are CO_2, H_2, and N_2, with lesser quantities of CH_4 and H_2S.[2] Odiferous compounds identified in canine flatus include carboxylic acids, phenols, ammonia, hydrogen sulfide, indole, skatole, mercaptans, volatile amines, ketones, alcohols, and short-chain fatty acids, which together comprise less than 1% of intestinal gas.[3]

Aerophagia and Eructation

Some air is inevitably swallowed during normal feeding, although individual dogs and cats differ in volumes of swallowed air. Variables affecting the volume of air swallowed have not been defined but likely involve the size of the food bolus, rate of ingestion, physical characteristics of food, and head and neck posture during eating. In the stomach, gas bubbles coalesce and accumulate in the dorsal fundus and cardia, which activates stretch receptors in the wall of the gastric cardia.[4] Afferent vagal fibres arising from the cardia of the stomach induce transient relaxations of the gastroesophageal sphincter (GES).[5] These are relatively prolonged relaxations of the GES that have a pattern distinctly different from swallow-induced gastroesophageal sphincter relaxation. This reflex, induced by gastric gas, has been termed the *belch* or *eructation reflex*. As gas is refluxed through the relaxed GES postprandially, reflux of gastric contents and acid may occur simultaneously.[6]

Disease processes that disrupt stretch receptors, sensory vagal afferents, or vagal inhibition of the GES may impede sphincteric response to gastric gaseous distention. Development of gastric dilation–volvulus syndrome in dogs is believed to depend upon such defects. Indeed, gastric volvulus has been reported in dogs with a prior history of eructation, borborygmus, and flatuluence.[7] When chronic gastric bloating is a prominent sign, excessive aerophagia and defective eructation should be considered as underlying mechanisms. Aerophagia during eating may account for large amounts of intestinal gas, although dogs described as "greedy eaters" by their owners are not reported to have an increased incidence of flatulence.[1]

Aerophagia and gastric gaseous distention can also occur secondary to respiratory tract disease. Dyspnea resulting from brachycephalic airway disease can culminate in excessive aerophagia and gastric distention.[8]

Intestinal Gas Transit and Borborygmus

Gas that is present in the small and large intestine can originate from aerophagia or be endogenously formed. Intestinal CO_2 is mostly formed from the reaction between bicarbonate (HCO_3^-) and gastric acid producing water and CO_2 in the upper small intestine. For each mole of H^+ neutralized by pancreatic HCO_3^-, 1 mole of CO_2 is produced. In the 3 hours following a meal a dog may produce 6 mEq H^+, which will result in production of 134 mL CO_2.[9] Most of the CO_2 diffuses into circulation but some remains within the luminal contents. The remaining gases are produced from microbial fermentation, predominantly in the distal small intestine and colon.

Gas is moved along the intestine independently of solids and liquids, and gas transit is more effective in the erect than supine position illustrating active propulsion of gas.[10] Rate of gas passage is influenced by dietary fat, but not by dietary moisture content.[11] Intestinal gas can be rapidly propelled aborally in normal dogs such that infusion of air at 2 mL/min does not produce obvious abdominal discomfort.[12] In humans, up to 30 mL/min can be infused jejunally without discomfort.[11] Gas is actively propelled by a sustained contraction proximal to the gas but it is still not known if intestinal

gas induces classical peristaltic waves responsible for movement of liquid and solid ingesta.[13] Consumption of solid food, but not water, increases volume and rate of transit of gas through the gastrointestinal tract.[11] Duodenal lipid has the most profound inhibitory effect on gas transit times; fiber slows intestinal gas transit, as well as increases volume of gas produced from fermentation.[14]

Physical exercise is known to reduce the retention of gastrointestinal gas.[15] Although not directly studied in dogs, flatulence is reported less frequently by owners of dogs that exercise frequently than by owners of sedentary dogs.[1]

Borborygmus can result from excessive intestinal gas or altered gastrointestinal motility. Patients with irritable bowel syndrome develop intestinal gas retention and pain in response to gas loads that are otherwise well tolerated by normal individuals.[16] In those patients, proximal intestinal gas rather than large intestinal gas is responsible for clinical symptoms.[16]

Flatulence

Ingested atmospheric gases form the largest component of flatulence, but odiferous compounds resulting from microbial fermentation of luminal content are the most notable to pet owners. Flatulence that occurs within 2 hours of feeding is more likely related to rapid transport of aerophagic gases following feeding.[3,17] Fermentative by-products accumulate at other times and are not necessarily related to feeding. Malodor is strongly correlated with presence of hydrogen sulphide, although production of hydrogen sulphide is highly variable amongst animals fed the same diet.[3] Sulphur gases are produced by sulphate-reducing bacteria such as the genera *Desulfotomaculum*, *Desulfobacter*, *Desulfomonas*, and *Desulfobulbus*, and differences in sulphur gas production between animals likely represents differences in these microflora.[18] Sources of sulphur for fermentation include endogenously derived amino acids in mucin, sulphate in cruciferous vegetables and nuts, and poorly digestible sulphated polysaccharides such as the gelling agent carrageenan.

In addition to inhibiting gas transit, fermentable fibers are a significant substrate for luminal production of intestinal gases. In normal humans fiber intake increases the number of daily flatus emissions.[11,19] Thus normal humans high-fiber diets increase gas production by colonic flora and inhibit gas transit leading to gas retention, notable borborygmus, abdominal pain, and flatulence.[11] Ingestion of a "fiber-free" diet for 48 hours significantly reduces the total volume of flatus. Highly purified, highly fermentable fibers will increase flatus volumes more so than nonfermentable fiber, as well as altering the composition of flatus. For example, xylan and pectin diets induce much higher volumes of flatus, including hydrogen, carbon dioxide, and methane content than cellulose or corn bran diets.[20] Intestinal and/or microbial adaptation to changes in fiber content may take several days and flatus volumes may not stabilize until 2 to 5 days postfeeding.[20] Significant differences in intestinal microflora exist between individual dogs and cats, and some of that difference may even be related to breed.[21]

Methane production varies greatly between individuals, and is dependent upon diet, fiber content, and specific methanogenic bacteria.[22] Physiologic concentrations of methane slow ileal transit by augmenting ileal circular muscle contractions.[12] Consequently, inflammatory bowel disease (IBD) patients in whom methane is produced almost universally suffer from constipation and ileal discomfort.[12] Induction of nonpropulsive segmental contractions by methane may trigger dysmotility and discomfort in dogs and cats. Consequently, it is prudent to consider this side effect when supplementing fiber in the diet.

Box 15-1 Causes of Excessive Eructation, Borborygmus, and Flatulence

- Aerophagia with normal gastrointestinal motility
  - Behavioral (obsessive compulsive disorder)
  - Prandial aerophagia
  - Dyspnea
  - Postanesthetic complications
- Motility disorders
  - Megaesophagus
  - Irritable bowel syndrome
  - Foreign body
  - Neoplasia
  - Intussusception
  - Peritonitis
  - Adhesions
  - Postgastric dilation-volvulus syndrome
  - Electrolyte disturbances–K^+, Ca^{2+}
  - Autonomic neuropathy
  - Postoperative ileus
- Dietary causes
  - Indiscretion
  - Metabolic adverse reaction to food (e.g., lactose intolerance)
  - Food hypersensitivity
  - Excessive fermentation (e.g., excessive fermentable fiber, carrageenans, sulfates)
- Inflammatory intestinal disease
  - Idiopathic inflammatory bowel diseases
  - Intestinal parasitism
  - Postviral enteritis (e.g., parvoviral enteritis)
- Microbial
  - Antibiotic therapy
  - Small intestinal bacterial overgrowth?
- Metabolic disorders (Addison disease, uremia, diabetes mellitus, hypothyroidism)

Differential Diagnosis

Box 15-1 outlines known and suggested causes of excessive eructation, borborygmus, and flatulence in dogs and cats. Dietary indiscretion is likely the most important cause of acute onset of signs. In other clinical cases, gaseous signs may be harbingers of more serious intestinal disease. With concurrent abdominal pain and abdominal distention, intestinal dysmotility (e.g., irritable bowel syndrome) should be suspected.

Evaluation of the Patient

For animals presenting with signs of eructation, borborygmus, or flatulence, the initial evaluation of the patient is primarily concerned with distinguishing between patients with transient, self-limiting, or benign conditions and those more serious underlying conditions (Fig. 15-1).

History

It is important to determine the temporal association between eructation, borborygmus, or flatulence, and potential inciting events. Such events include eating, dietary change, dietary indiscretion, exercise, stress, repetitive behavior, and drug therapy. The nature of the flatulence can give some information as to the potential cause. Odorless flatus is more likely to be associated with aerophagia, whereas offensive odors are more likely to be a result of colonic

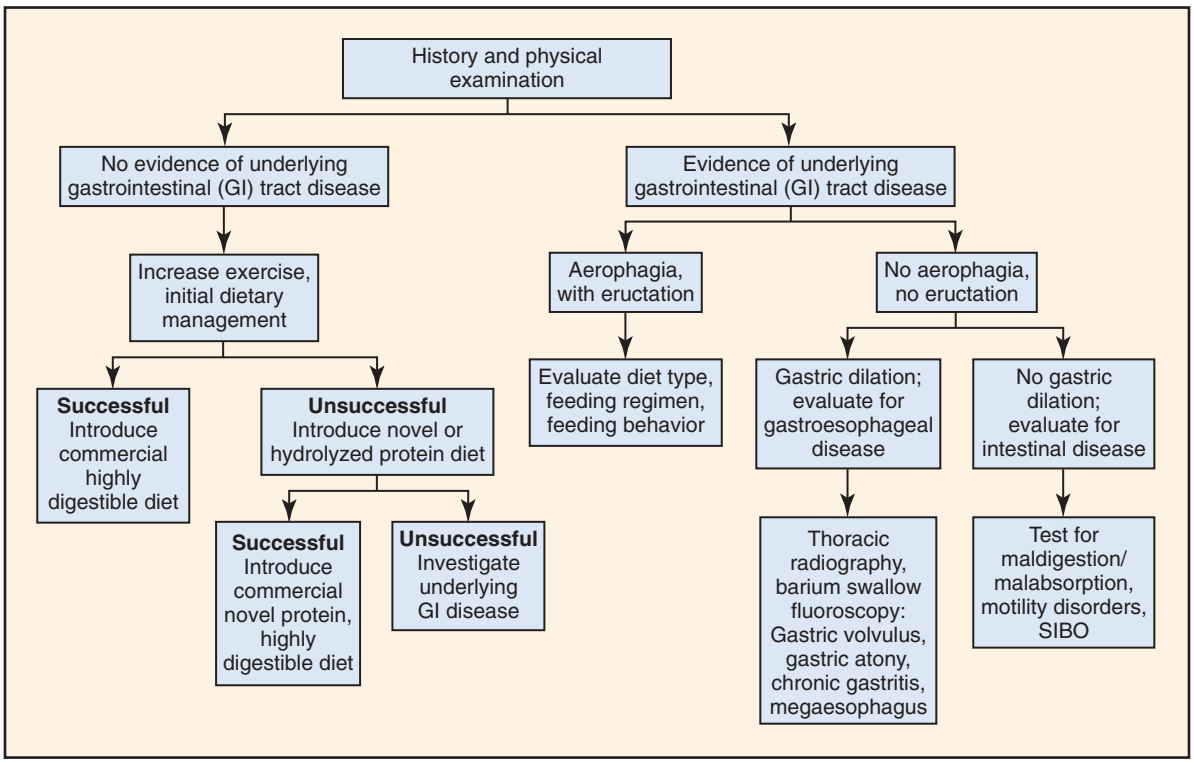

Figure 15-1 Algorithm for eructation, borborygmus, and flatulence.

bacterial fermentation following intestinal maldigestion or malabsorption.

An extensive dietary history is essential. In addition to dietary change, attention should be paid to the dietary composition as well. Diets with a high concentration of fermentable fiber or hydrolysis-resistant starch are more likely to be associated with excessive gas production. Moist, meat-based diets that contain little or no plant material may still contain considerable concentrations of gelling agents such as guar gum and carrageenan that can lead to gas production and malodorous flatulence. Dairy products can cause excess gas production in animals with lactase deficiency. Frequency of feeding and amount and timing of exercise may be important variables in some animals.

Other historical findings of importance include the presence of concurrent signs such as abdominal pain, abdominal distention, vomiting, regurgitation, hypersalivation, diarrhea, melena, and weight loss that might suggest more serious gastrointestinal disease. Abdominal pain may be manifested as a hunched posture with or without stiff gait, unsettled behavior, or the adoption of a praying position. Intermittent abdominal pain is common in dogs with irritable bowel syndrome, and may result from bowel distention by excessive intestinal gas, motility disorders which disrupt passage of gas through the bowel, or increased visceral sensitivity to bowel distention.

Prior medical history should be sought for gastric dilation–volvulus syndrome, and prior or current drug therapy, especially oral antibiotics. Extraintestinal causes of gastrointestinal gas accumulation include behavioral aerophagia, hypothyroidism, cough, and dyspnea.

Physical Examination

The presence of borborygmus, gastric tympany, intestinal gaseous distention, and the elicitation of flatulence during palpation are the most common physical examination findings in affected animals. Other physical examination findings are usually unremarkable unless concomitant gastrointestinal disease is present.

Laboratory Evaluation and Tests

Severe eructation in the absence of other localizing signs is usually consistent with excessive aerophagia or gastroesophageal dysmotility. Thoracic and abdominal radiographs may be required to evaluate the degree and distribution of gas accumulation, as well as the positioning of the gastrointestinal tract. Thoracic radiography is indicated to help rule out megaesophagus, gastric dilation-volvulus, hiatal hernia, and intestinal foreign bodies. Further evaluation of gastroesophageal dysmotility may require continuous imaging such as barium-swallow fluoroscopy (see Chapter 26). When supported by concurrent supportive clinical signs, thyroid function testing is indicated.

Borborygmus and flatulence warrant further investigation if there is suspicion for underlying gastrointestinal disease, or if the signs are nonresponsive to symptomatic management. Investigation into the presence and causes of maldigestion and malabsorption is strongly indicated when malodorous flatulence accompanies diarrhea or weight loss. Tests for maldigestion and malabsorption might include serum trypsinogen–like immunoreactivity, postprandial breath hydrogen measurement, serum B_{12} and folate, culture of duodenal fluid, fecal parasitic and microbial analysis, and intestinal biopsy (see Chapter 25).

Treatment and Management

General Principles

In the absence of a primary diagnosis, the symptomatic management of borborygmus and flatulence should begin with a change to a highly digestible, low-fat diet. As with any dietary variable, there is

no absolute value that constitutes "high" or "low," and they remain relative terms. Importantly, an attempt should be made to introduce a diet that has a *greater* digestibility and a *lower* fat content than the current or implicated diet. Empirical choices would be novel protein diets with less than 20% of calories as fat. Hydrolyzed protein diets have a high-protein digestibility, and most contain highly digestible carbohydrate sources as well. However fat content of some "intestinal diets" may be greater than ideal. Diets with fermentable fiber sources (gums, carrageenan, pectins, resistant starches, etc.) in greater concentrations than the current diet should be avoided. Crude fiber contents of less than 3% should suffice.

As an alternative approach, the owner can prepare a homemade diet comprised of highly digestible protein and carbohydrate sources appropriately balanced with vitamins and minerals. Suitable home-prepared diets for managing acute gastroenteritis or dietary indiscretion in dogs and cats include cottage cheese (1% milk fat) and boiled white rice, or chicken and rice. Cottage cheese and boiled white rice (1:1) provides 33% protein, 6% fat, and 61% carbohydrate as a percentage of calories. It contains 1 kcal/g as fed. Consequently, it is an ideal macronutrient profile, with an easy energy density to calculate in feedings. For short-term purposes, nutrient-balancing of the diet is unnecessary, and these diets can be safely fed to a well-nourished animal for at least 7 days without concern.

The possibility of food hypersensitivity reactions should be considered in any patient with chronic flatulence or borborygmus, and novel or hydrolyzed protein diets should be considered. A short-term trial of a highly digestible, low-fat diet should be considered prior to a trial with a novel protein diet. If the initial dietary change is unsuccessful, a home-prepared or commercial novel or hydrolyzed protein diet could be considered.

Flatulence is reported less frequently by owners of dogs that exercise frequently than by owners of more sedentary dogs.[1] It is not known, however, if the timing of exercise relative to meals is important, nor what amount of exercise is required. It would seem prudent to recommend an increase in daily exercise for dogs, and to encourage physical activity in cats for whom flatulence is problematic.

A study of flatulence in dogs revealed a decrease in frequency of flatus in dogs fed twice compared with once per day.[17] In another study, owners of dogs fed more than once per day did not report flatulence in their dogs more frequently than owners fed once daily.[1] Thus increasing the frequency of feeding may, in some dogs or cats, decrease flatulence, but at best the effect is mild.

Symptomatic therapy for eructation is focused on reducing aerophagia. Avoiding situations that provoke anxiety may be helpful. Feeding multiple small meals may reduce the gastric distention secondary to aerophagia.

In the rare event that dietary manipulation and regular exercise are not successful in eliminating signs, the patient should be evaluated for the presence of organic or functional gastrointestinal disease such as described for small intestinal diarrhea (see Chapter 11). Alternatively, symptomatic pharmacologic management can be tried.

Medical

When an underlying condition such as chronic gastritis or exocrine pancreatic insufficiency is present, medical therapy should be directed toward the underlying condition.

Simethicone is a nonabsorbable, surface-active, antifoaming agent that has been suggested for management of borborygmus, gaseous colic, and flatulence in human beings (25 to 200 mg per dose, q6h), although there is no consistent evidence to support its efficacy in humans and none in dogs or cats.[23]

A supplement incorporating 320 mg activated charcoal, 2.5 mg of an extract from the plant *Yucca schidigera*, and 17 mg of zinc (as zinc acetate dihydride) reduced the hydrogen sulphide content of flatus in dogs by 86%.[24] Of the three components, activated charcoal had the greatest single effect, which is consistent with some studies of its efficacy in humans at reducing odorous flatulence.[25]

In cases where objectionable flatulence is not responsive to dietary manipulation, empirical antibiotic therapy has been used with success in some cases.[26] Reasonable empirical choices are those predicted to be effective against colonic microflora such as metronidazole and tylosin. The nonabsorbable neomycin is another reasonable choice. It is the author's opinion that the empirical use of antibiotics for the sole problem of flatulence is difficult to justify.

Surgical

In large-breed dogs at risk for gastric dilation-volvulus syndrome, recurrent or chronic bloating warrants consideration of prophylactic gastropexy. In some dogs, borborygmus and eructation can indicate the presence of a chronic volvulus, for which gastropexy can resolve the majority of clinical signs.[1]

Surgical therapy for underlying causes of aerophagia may involve relief of chronic upper airway obstruction such as surgical correction of stenotic nares, everted laryngeal saccules, and elongated soft palate.

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CHAPTER 16

Hemorrhage (Gastrointestinal)

Michael D. Willard

Definition

Gastrointestinal (GI) hemorrhage can be occult or it can be heralded by significant blood loss via the oral cavity or anorectum. *Hematemesis* refers to conditions associated with the vomiting of blood (Fig. 16-1). *Hematochezia* refers to frank red or reddish-brown blood pigments in the feces, while *melena* refers to black, tarry feces (Fig. 16-2). Melena requires significant blood loss in a relatively short period of time, and the blood must remain in the stomach and/or small intestine long enough to be at least partially digested before passage in the feces. Many patients have melena and hematemesis concurrently, but some patients may only have one of these signs. Other patients may be dying of severe GI hemorrhage, but may not have obvious melena.

Pathophysiology and Mechanisms

Blood may enter the gastrointestinal tract because of disruption in blood vessel or mucosal integrity (e.g., ulcers and erosions), coagulopathy, or ingestion of blood that sometimes occurs with hemoptysis or external sources (e.g., food).

Pathophysiology of hematochezia is relatively straightforward: either there is a bleeding mucosal lesion (i.e., polyp, tumor, inflammation, trauma, congestion, parasites) or there is coagulopathy. Bleeding associated with hematochezia typically occurs in the most distal segments of the GI tract (i.e., colonic), which is why blood appears as undigested pigment in feces. Dogs affected with severe intestinal hypermotility (e.g., parvoviral enteritis) occasionally will have hematochezia associated with upper GI tract bleeding because the blood does not reside in the small intestine long enough to undergo digestion. Mucosal congestion (e.g., ileocolic intussusception) is rarely sufficient to cause hematochezia.

Hematemesis and melena can have similar causes, all principally upper GI in location. Gastric ulceration or erosion is one of the more commonly sought causes of upper GI hemorrhage.[1] Gastric ulceration or erosion has many causes, including poor gastric mucosal blood flow, interference with normal prostaglandin metabolism, excessive gastric acidity, and direct damage to the mucosa (e.g., chemicals, foreign objects).[2]

Direct damage to gastric mucosa may be caused by drugs (e.g., aspirin and other nonsteroidal antiinflammatory drugs [NSAIDs]), various ingested toxic substances (chemicals, plants), tumors, and even mucosal trauma associated with repeated, vigorous vomiting. Cats are infrequently affected with gastric ulceration or erosion, but have the same possible causes as dogs.[3] *Helicobacter* spp. do not appear to be a major cause of gastric ulceration or erosion in dogs or cats as they do in humans, even though numerous organisms can be found in ulcerative tissue.[4] Despite long-standing beliefs, renal failure does not appear to be a common or important cause of gastric ulceration/erosion.[5]

Intestinal ulceration/erosion is much less common than gastric ulceration/erosion. Disruption of intestinal mucosa is primarily caused by infiltrative disease (e.g., neoplastic or inflammatory) or inability to neutralize gastric acidity (e.g., paraneoplastic effects of mast cell tumors and gastrinomas). It can also be associated with many of the NSAIDs (e.g., flunixin).[6] Hookworms can be surprisingly severe, even in older patients in endemic or unsanitary environments; monthly preventatives do not necessarily eliminate ancylostomiasis.

Differential Diagnosis

Anemia

Anemia can cause obvious clinical signs or may be discovered serendipitously during routine blood testing. Anemia has three major causes: hemolysis, hemorrhage, and bone marrow disease. Anemia occurring in conjunction with hypoalbuminemia is suggestive of blood loss, particularly from the GI tract. Anemia resulting from GI hemorrhage may be regenerative or nonregenerative, depending upon chronicity of the condition, but classically is more often associated with hypoalbuminemia (not necessarily hypoproteinemia or panhypoproteinemia). Chronic GI hemorrhage presents typically as a poorly regenerative, iron deficiency–type anemia (microcytic and hypochromic) with moderate to severe hypoalbuminemia.[7] However, GI blood loss must be substantial and of sufficient chronicity to produce these specific changes; most animals with GI hemorrhage do not have this type of anemia. Hemorrhage sufficient to cause anemia often occurs in the absence of hematemesis, hematochezia, and melena.

Hematemesis

The most common causes of gastric ulceration or erosion in dogs are drug-induced (e.g., NSAIDs, dexamethasone, and other glucocorticoids[8]), stress (e.g., hypovolemic shock, systemic inflammatory response syndrome, excessive physical exertion), cancer disruption of the gastric mucosa, adrenal insufficiency, and hepatic failure.[1,2,9]

Dual or multiple risk factors (e.g., NSAIDs plus dexamethasone or NSAIDs plus poor mucosal perfusion) increase the likelihood of

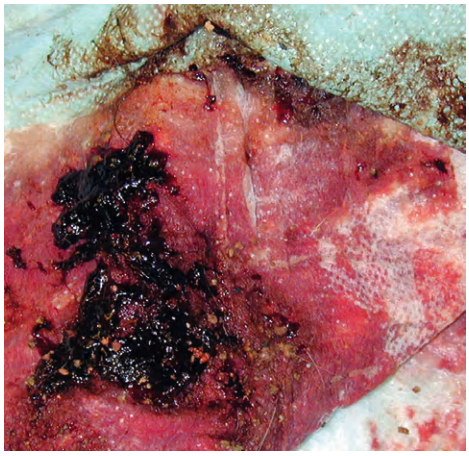

Figure 16-1 Hematemesis in a cat with perforating duodenal ulcer. Red, black, and brown pigments are all consistent with gastrointestinal hemorrhage.

Figure 16-2 Black, tarry feces (i.e., melena) from a thrombocytopenic dog. As the material is smeared across the paper, the obvious red color shows that it is actually blood.

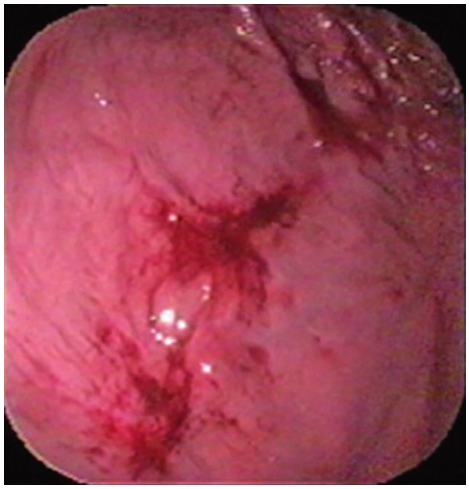

Figure 16-3 Endoscopic image of a dog's stomach. This dog had gastric bleeding as a result of erosions caused by submaximal stress (sled dog racing). The dog was asymptomatic and was racing without any signs of fatigue or illness.

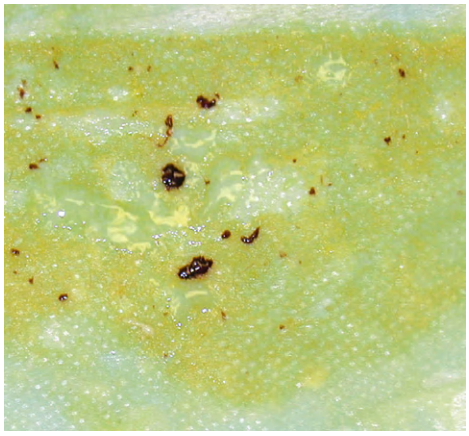

Figure 16-4 Vomitus from a dog with pancreatitis. Most of the material is bilious, but there are several spots of blood present. (Compare with Fig. 16-1.)

gastric ulceration or erosion.[1,10] Cyclooxygenase (COX)-2 selective inhibitors (e.g., carprofen, etodolac, deracoxib, meloxicam) have been developed to minimize the ulcerogenic effect of NSAIDs in the GI tract. Although these newer NSAIDs lessen the risk of gastric ulceration or erosion, they do not completely eliminate it. Many dogs have developed gastric ulceration or erosion following use of these putatively safer NSAIDs.[11,12] Some NSAIDs are especially well known for their ulcerogenic potential in dogs, including naproxen and flunixin meglumine.[6] It should be noted that gastric ulceration or erosion is not excluded by an absence of hematemesis or anemia. Dogs with substantial gastric bleeding because of stress-related gastric ulceration or erosion can appear clinically normal and function at a high level (Fig. 16-3).[2] Furthermore, there appears to be little relationship between bleeding and perforation as they do not necessarily arise from the same pathogenesis.

Cats are infrequently diagnosed with gastric ulceration and erosion. Lymphoma and other tumors appear to be the most important causes of gastric ulceration in this species, but there are very few published studies in cats to confirm or deny this opinion.[3]

It should be confirmed that "hematemesis" is not just reddish tinged gastric fluid caused by food digestion in the stomach. True hematemesis may range from minimal to copious amounts of blood. If there are simply a few spots or "flecks" of blood (Fig. 16-4), gastric mucosal trauma as a consequence of vigorous vomiting is a major differential (Fig. 16-5). If copious, there are numerous possible causes, and a methodical approach is best (Fig. 16-6). If history, physical examination, and routine blood tests do not give clues as to the cause of hematemesis, the basic approach should be to first eliminate coagulopathy, search for evidence of upper GI mucosal disease, and, finally, respiratory tract disease with ingestion of blood following hemoptysis.

Hematochezia

In a patient with hematochezia (Fig. 16-7),[13] one should consider consistency of the feces and whether rectal bleeding occurs independently of defecation. Rectal bleeding in the absence of defecation is strongly suggestive of anal sac disease. If the feces are otherwise normal, focal rectal disease (e.g., polyps, tumors, and fungal infections like pythiosis) is especially likely. Finding blood consistently confined to one side or area of the feces also suggests a rectal lesion. If stools are soft and clearly abnormal, then generalized colitis of any cause (e.g., inflammatory bowel disease [IBD], fungi,

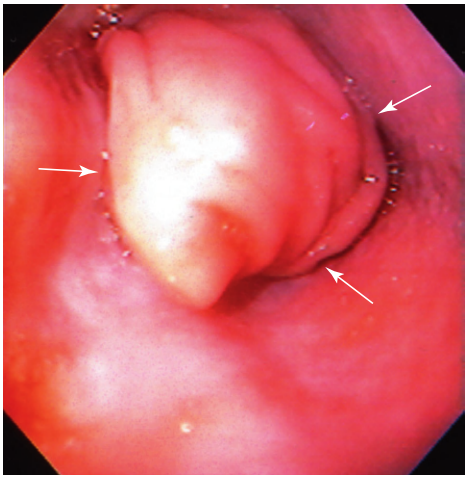

Figure 16-5 Gastric protrusion into the esophagus during vomiting. Vigorous vomiting can cause minor gastric mucosal injury, leading to hematemesis as shown in Figure 16-4.

bacteria, whipworms, and hookworms) are important differentials. Intussusceptions are an uncommon, but important cause of hematochezia. Acute ileocolic intussusceptions are often associated with scant bloody feces, but chronic ileocolic intussusceptions often cause diarrhea without bleeding. Cecocolic intussusceptions are rare causes of hematochezia that often represent a diagnostic challenge. Vascular malformations in the colonic mucosa are another rare cause of hematochezia.

Melena

Melena can be problematic because it is often misdiagnosed.[13] Dark green feces can appear melenic, and oral administration of bismuth compounds (e.g., Pepto-Bismol) consistently produces dark black feces. If melena is confirmed, the next determination is whether melena is part of an acute presentation such as hemorrhagic or parvoviral gastroenteritis. Causes of melena are the same as those that cause hematemesis, with some additional differential diagnoses (e.g., intestinal tumors, hookworms) that are sufficiently aborad that they cannot cause hematemesis.

Evaluation of the Patient

History

Presence of blood pigments in vomitus or feces is readily perceived by most pet owners with the exception of a "coffee-grounds" appearance of hematemesis which many do not recognize as digested blood. Anorexia may be the only other primary sign of gastric disease in some animals. Ataxia or weakness may be seen as a sign of anemia secondary to GI hemorrhage. Ascites or edema secondary to hypoalbuminemia are rarely reported or observed.

Documentation of NSAID usage (including the newer COX-2 drugs) is important and may be surprisingly difficult to elicit from the history. History should determine if dexamethasone or other glucocorticoids have been used. Anorexia or vomiting following shock or excessive exertion may be consistent with "stress" ulceration.

Hematochezia must be accurately described regarding its distribution on or in the feces as well as the consistency of the feces (normal, constipation, or diarrhea). Melena must be distinguished from the "dark" feces of other causes.

Physical Examination

GI hemorrhage is seldom reliably diagnosed at physical examination. Pale mucus membranes or weak thready pulses may provide clues to significant gastrointestinal blood loss. Gastric ulceration, perforation, and peritonitis should be suspected in patients manifesting abdominal pain, hyperthermia, hypothermia, or scleral injection. Cutaneous mast cell tumors can induce gastric ulceration, and they can perfectly mimic lipomas on physical examination.

Laboratory Evaluation and Tests

Most animals with GI hemorrhage are not obviously anemic on *complete blood counts* (CBC). Finding a microcytic, hypochromic anemia would be typical for iron deficiency seen with chronic, severe GI blood loss.[7] Increased RDW (red blood cell distribution width) is more sensitive than decreased MCV (mean corpuscular volume), but scanning blood smears for microcytes is the best way to screen for iron-deficiency anemia. Most anemias caused by GI blood loss are not microcytic, hypochromic. These anemias may be regenerative or nonregenerative, and concurrent hypoalbuminemia is typical. Hemoconcentration may be seen instead of anemia in some GI hemorrhagic disorders. Hemoconcentration in dogs with normal serum protein concentrations and acute hematemesis or hematochezia is very suggestive of hemorrhagic gastroenteritis syndrome.

Leukocytosis and neutrophilia may be observed in animals with perforated gastric ulcer, peritonitis, bacterial and fungal enteritis, nonspecific IBD, neoplasia, pancreatitis, and gastrointestinal foreign body. Leukopenia and neutropenia are more typical findings in young puppies affected with parvoviral enteritis. Eosinophilia is occasionally observed in animals with intestinal parasitism, food allergy, mastocytosis, and hypoadrenocorticism. Buffy coat smears may be useful in identifying circulating mast cells in animals affected with systemic mastocytosis. Adrenocorticotropic hormone (ACTH) stimulation should be considered as part of the further medical investigation of eosinophilia if there is no evidence for parasitism, allergy, or mastocytosis. Thrombocytopenia should be verified by a second platelet count. Gastrointestinal hemorrhage secondary to thrombocytopenia results most often from tick-borne rickettsial infection (Rocky Mountain spotted fever [RMSF], ehrlichiosis), immune thrombocytopenia, and systemic lupus erythematosus. Further medical investigation of thrombocytopenia should consist of RMSF and *Ehrlichia* serologies, antiplatelet antibody, antinuclear antibody, and bone marrow aspirate.

Serum chemistry is crucial to look for evidence of hepatic disease (e.g., increased alanine aminotransferase [ALT], hyperbilirubinemia, hypocholesterolemia, hypoalbuminemia, hypoglycemia, hyperammonemia, increased serum bile acid concentrations), hypoadrenocorticism (e.g., hyponatremia, hyperkalemia, lack of stress response in severely ill patient), and paraneoplastic syndromes (e.g., hypercalcemia associated with lymphosarcoma).

Fecal examinations are necessary to document hookworm and whipworm infestations. Mature dogs can have prepatent hookworm infections severe enough to kill them if they receive a massive exposure from a heavily contaminated environment.

Abdominal ultrasound is valuable in assessing stomach, intestine, colon, liver, and other abdominal organs. Ultrasound is a specific but insensitive test for GI ulceration, hepatic disease, and abdominal neoplasia.[14] Severe hepatic disease and GI ulcers may not be found in routine ultrasound studies. This is especially true of gastric lesions because of gastric gas, ingesta, and motility, which make mucosal detection more difficult. Nonetheless, ultrasound is recommended as it is far more sensitive than radiography. If ultrasound provides

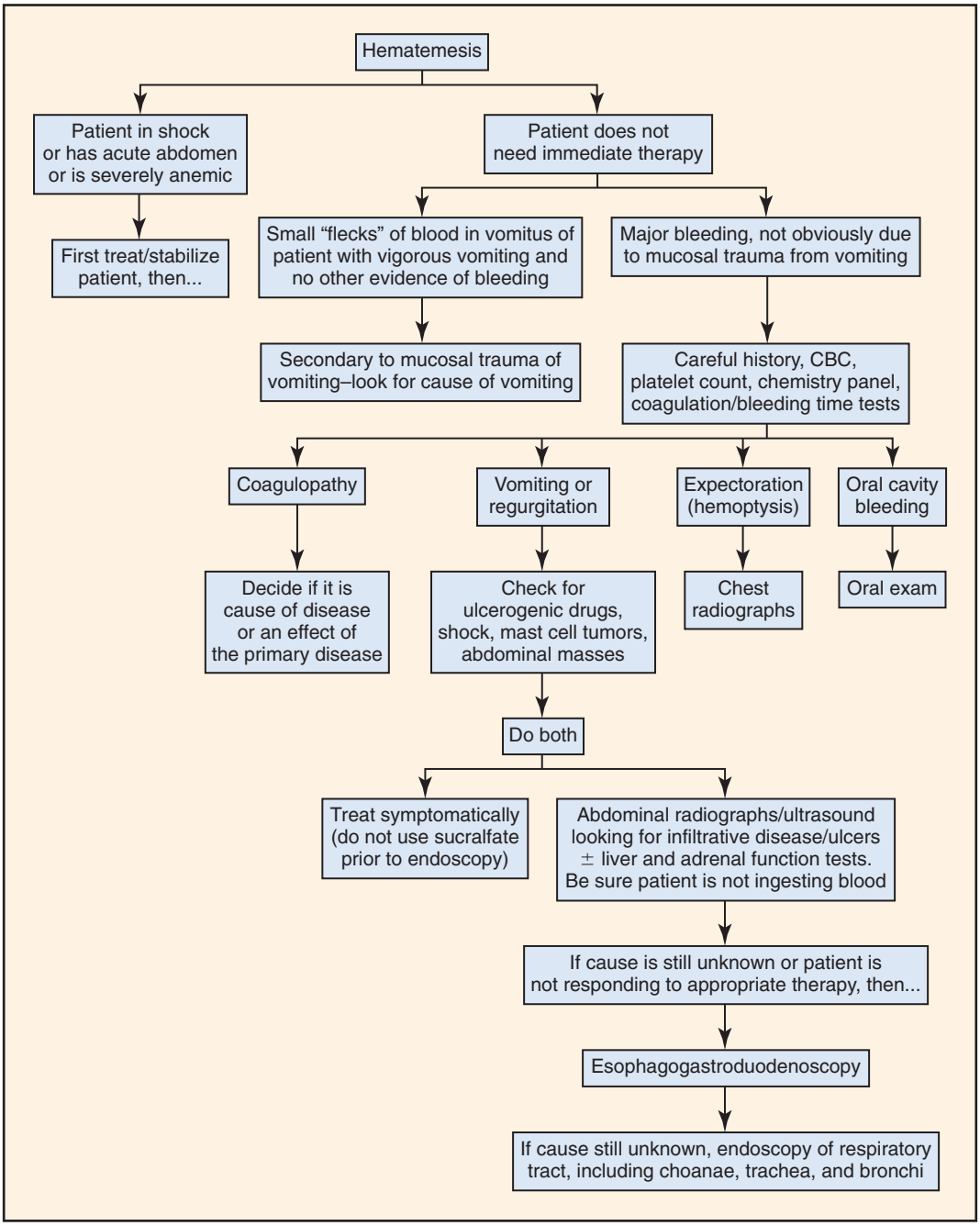

Figure 16-6 General diagnostic and therapeutic approach to hematemesis. CBC, Complete blood count. (Adapted from Nelson and Couto, *Small animal internal medicine*, ed 4, St Louis, 2009, Mosby.)

evidence of a disease with a high mortality rate (e.g., abdominal lymphoma), the pet owners may not wish to proceed with additional testing.

Additional diagnostic tests may be necessary depending upon the outcome of the initial medical investigation. If a definitive diagnosis is not immediately forthcoming, an assessment of coagulation (e.g., prothrombin time, partial thromboplastin time, buccal mucosal bleeding time, von Willebrand factor VIII antigen, fibrin degradation products) should be performed before more invasive and expensive tests are conducted. One or more of these tests will be abnormal with congenital or acquired liver disease, coagulation factor deficiency, disseminated intravascular coagulation, thrombocytopenia, thrombocytopathia, anticoagulant rodenticide toxicity, and hyperviscosity syndrome.

Treatment and Management

General Principles

Emphasis should be placed on finding the cause of GI hemorrhage rather than to simply start nonspecific therapy. Medical therapy is often ineffective if the underlying cause of gastric ulceration is not eliminated. Conversely, gastric ulcers will often spontaneously resolve once the cause is removed. If the cause is untreatable (e.g., nonresectable, scirrhous gastric carcinoma), administration of

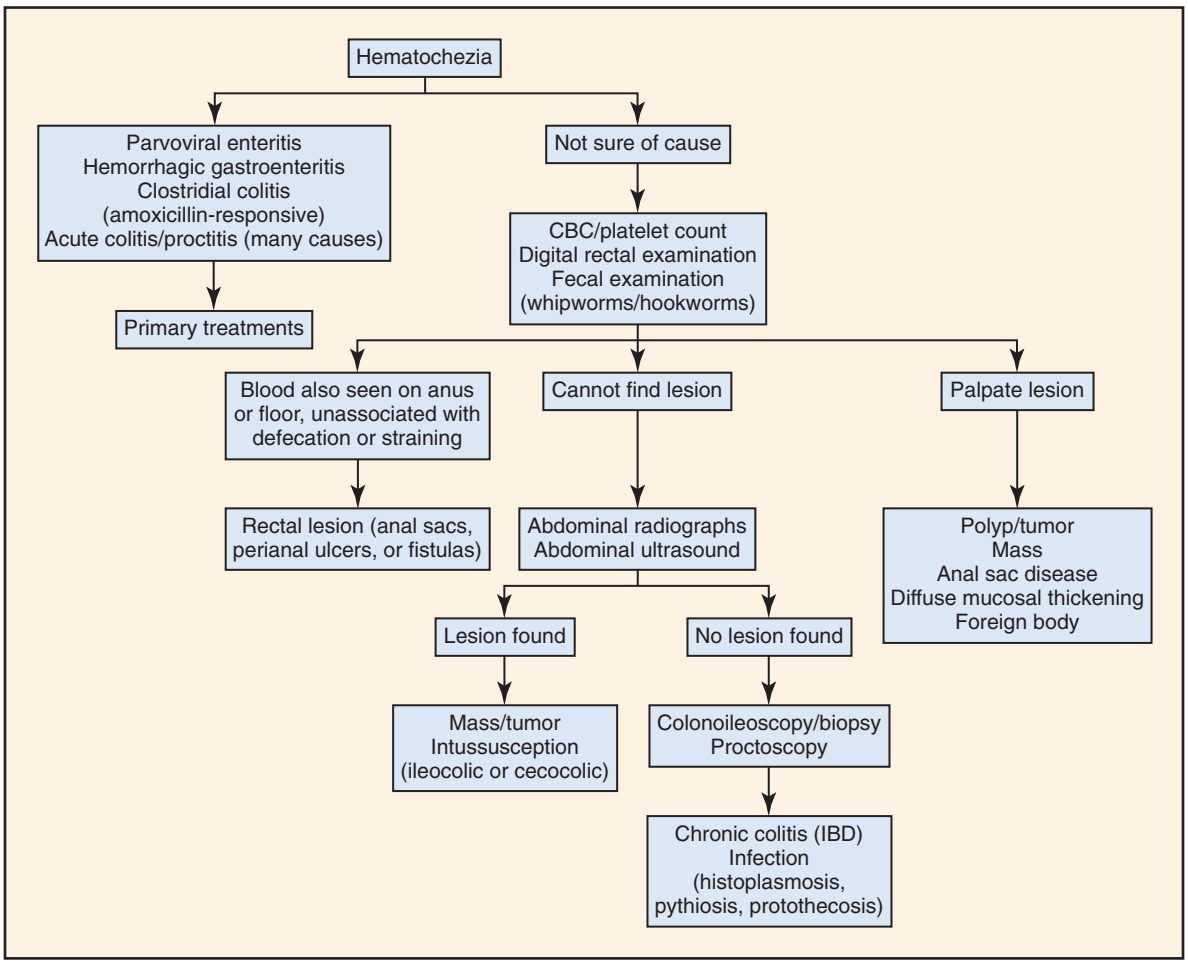

Figure 16-7 Diagnostic approach to hematochezia. CBC, Complete blood count; IBD, inflammatory bowel disease.

symptomatic and supportive therapies may be little more than palliative.

Medical

The *histamine-2 (H_2)-receptor antagonists* competitively inhibit binding of histamine to gastric parietal cell histamine H_2-receptors. They do not completely eliminate gastric acid secretion but substantially decrease it such that gastric ulcer can resolve. Cimetidine has the most side effects while famotidine has the fewest side effects and is the most potent H_2-receptor antagonist. Nizatidine and ranitidine are intermediate in strength, and both have gastric prokinetic effects. H_2-receptor antagonists are generally ineffective in preventing gastric ulcer caused by NSAIDs and steroids,[15,16] but may be helpful in preventing lesions caused by vigorous physical exercise (e.g., racing sled dogs).

The *proton-pump inhibitors (PPIs)* noncompetitively block the H^+-K^+ adenosine triphosphatase (ATPase) and more effectively suppress gastric acid secretion than H_2-receptor antagonists. They typically take 2 to 5 days to achieve maximal efficacy when administered orally but have significant acid suppression activity as soon as they are begun. Omeprazole, lansoprazole, pantoprazole, esomeprazole, rabeprazole, and dexlansoprazole are PPIs that are clinically available, although there is limited experience in dogs and cats with all but omeprazole. Omeprazole may cause diarrhea in some patients. The PPIs prevented gastric lesions caused by aspirin in some studies,[15] but not others.[17] PPIs lessen the incidence and severity of gastric ulcer caused by submaximal exertion in racing sled dogs.

Sucralfate is the sulfated form of sucrose combined with aluminum hydroxide. In the presence of acid, it binds to eroded surfaces offering mechanical protection, stimulating prostaglandin synthesis, and binding to epidermal growth factor. Sucralfate can bind to various other drugs potentially delaying or decreasing their absorption. It can be used in combination with H_2-receptor antagonists, but there is no evidence that this combination is more effective than single-agent therapy. Sucralfate is given orally (which can be problematic in vomiting animals), and it can attach to erosions and ulcers. (Because of its binding properties, sucralfate may prevent the endoscopist from directly viewing ulcerative lesions.) It is not necessarily effective in the prevention of gastric ulcer.[17]

Misoprostol is a prostaglandin E_1 analogue designed to prevent NSAID-induced gastric ulcer in people. It may not be as effective in dogs as has been reported in humans, but it does decrease the frequency of gastric ulcer[18] and helps some patients that do not tolerate NSAIDs well. It is not very effective in preventing steroid-induced gastric hemorrhage or that associated with spinal surgery.[16,17,19] Misoprostol can be used to treat existing ulcers, but it can cause diarrhea, abdominal cramping, and abortion due to its prostaglandin activity. It also tends to be more expensive than the H_2-receptor antagonists or sucralfate.

Surgical

If the underlying pathogenesis is identified and eliminated, most ulcers can be resolved medically, and most patients have evidence of improvement within 5 to 7 days of therapy. Focal lesions that cannot be resolved with medical management or those that pose a substantial risk of exsanguination should be surgically resected.

It is often advantageous to perform gastroduodenoscopy to determine the location and number of bleeding lesions prior to performing surgery. It can be difficult to locate bleeding mucosal lesions when examining gastric mucosa through a gastrotomy incision, and surgery may be unproductive if lesions are unresectable (e.g., widespread gastric erosions). Even when lesions are noted endoscopically prior to surgery, intraoperative endoscopy may be necessary to find all of them. Pyloric ulcers can be especially difficult to locate endoscopically, because of difficulty in carefully examining this area.

Endoscopic electrocautery or injection of clotting agents may be used in select cases. These techniques should not be performed unless the endoscopist has been trained in their use as they have the potential to hurt the patient as well as the equipment. In general, these techniques are done to stop bleeding to allow stabilization prior to surgery.

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CHAPTER 17

Hepatoencephalopathy

Jill Maddison

Definition

Hepatic encephalopathy (HE) refers to a complex of neurologic abnormalities that occur in man and animals as a result of marked hepatic insufficiency.

Pathophysiology and Mechanisms

In the dog and cat HE most commonly results from a single congenital portosystemic shunt (PSS) that bypasses portal circulation and allows mesenteric blood to enter directly the caudal vena cava. Acquired portosystemic shunting also occurs in dogs as a consequence of portal hypertension (e.g., cirrhosis, arteriovenous fistula, hepatoportal fibrosis). HE has also been well documented in cats.

Anatomy

There are various shunt types. Intrahepatic shunts occur most commonly in large breeds (e.g., Doberman Pinschers, Labrador Retrievers, Golden Retrievers, Old English Sheepdogs, Irish Wolfhounds). In contrast, extrahepatic shunts predominate in smaller breeds (e.g., Yorkshire Terriers, Maltese Terriers, Miniature Schnauzers). Extrahepatic shunts predominate in cats although intrahepatic shunts have also been reported.

Pathophysiology

The basis for the neurologic dysfunction that occurs in HE is incompletely understood. The encephalopathy occurring in acute or chronic hepatic failure is usually reversible with amelioration of the underlying hepatic disease. This potential for structural and functional reversal of the neurological abnormalities in HE is consistent with a metabolic encephalopathy.

HE is a complex pathophysiologic state that is probably multifactorial in origin.[1] It is generally accepted that gut-derived substances of bacterial and protein metabolism are important in the pathogenesis. Evidence for this includes the observation that reduction of gut bacterial flora or dietary protein often result in improvement of neurologic function without altering underlying hepatic disease.

Although ammonia has long been implicated as being the most likely neurotoxin involved in HE, actual mechanisms are not well understood despite decades of research. Evidence is accumulating that brain glutamatergic system and astrocytic (glial) function is significantly deranged in HE as a result of their role in detoxifying ammonia.[2,3] Other theories proposed in the past (e.g., alteration in monoamine or catecholamine neurotransmitters because of perturbed aromatic amino acid metabolism, alteration in amino acid neurotransmitters, increased brain γ-aminobutyric acid [GABA], increased cerebral levels of an endogenous benzodiazepine-like substance) have little support today.

There are several observations that provide support for a central role for ammonia in the pathogenesis of HE.[4] Encephalopathy can be precipitated in cirrhotic patients by ingestion of ammonia-generating substances (e.g., protein, urea, ammonium salts). Congenital hyperammonemia caused by urea cycle disorders causes HE and coma in children and dogs. In addition, therapy decreasing intestinal production and absorption of ammonia (e.g., low-protein diet, lactulose administration, reduction of gut bacteria by antibiotics) usually results in improvement of clinical signs. Also of interest is the observation that metabolic derangements that increase movement of ammonia across cell membranes or increase ammonia production can precipitate HE in susceptible patients. Such derangements include alkalosis (which facilitates brain uptake of ammonia by increasing the concentration of ammonia base) and profound hypokalemia (which potentiates alkalosis and increases renal ammonia production).

Further evidence of the role of ammonia includes studies where administration of sodium benzoate to human patients with chronic HE-induced clinical and electroencephalogram (EEG) improvements paralleled reductions in blood ammonia. Sodium benzoate decreases blood ammonia concentrations by promoting its excretion in the form of hippurate. Other treatments that enhance ammonia excretion (e.g., L-dopa, which increases renal blood flow and hence renal ammonia excretion) have also been reported to ameliorate HE in human patients.

However, although blood ammonia concentrations are increased in most patients with HE, correlation between blood ammonia and degree of HE is poor, and some patients are encephalopathic without hyperammonemia. In addition, some medications may influence severity of HE without altering blood ammonia concentrations. Conversely, treatment of human patients with a monoamine oxidase inhibitor decreased blood ammonia concentrations, but failed to improve the encephalopathy.

That glutamate plays a central role in HE is suggested by the finding that there are many alterations of brain glutamate in various models of HE, and virtually all aspects of the glutamate system are

altered (e.g., synthesis, metabolism intercellular trafficking, function and expression of glutamate transporters and receptors).[2] Many of these functions occur in astrocytes (glial cells), cells that are consistently altered histopathologically in HE.

Differential Diagnosis

Clinical signs of HE may often be confused with those of primary gastrointestinal or neurologic disease. However, finding both gastrointestinal and neurologic dysfunction in a young dog or cat should alert clinicians to the possibility of HE. Lead toxicity also causes gastrointestinal and neurologic signs in young animals; however, neurologic dysfunction associated with lead poisoning in dogs is generally more hyperkinetic resulting in seizures and hysteria. In contrast, dogs and cats with HE typically present depressed, apathetic, and disorientated.

Other disorders that may have some clinical signs similar to HE and should be considered where appropriate include urinary tract infection (cystic calculi), intestinal parasitism, primary gastrointestinal disease, hypoglycemias, toxoplasmosis, hydrocephalus, acute ethylene glycol toxicity, rabies, central nervous system (CNS) neoplasia, canine distemper, storage disease, thiamine deficiency, and drug intoxication.

Evaluation of the Patient

History

Clinical signs are usually noticed in dogs and cats younger than 1 year of age, but patients can present at any age. Typical clinical signs in the dog include episodic lethargy and depression with periods of disorientation, aimless wandering, compulsive pacing, head pressing against walls, amaurotic blindness, and/or coma. Occasionally, seizures may be the presenting complaint in dogs. Neurologic signs can be related to a meal in approximately 25% of cases.

Episodes of anorexia and gastrointestinal signs such as vomiting are common in dogs. Other key features of clinical history may include dramatic but temporary resolution of clinical signs with antimicrobial therapy plus prolonged recovery from sedation or anesthesia. Polyuria and polydipsia occur in approximately one-third of dogs with HE. The mechanism has not been elucidated but may be related to central or primary (psychogenic) neuronal stimulation of the thirst center as a manifestation of HE, alterations in portal vein osmoreceptors, or a renal concentrating defect.

Clinical presentation of cats with HE is similar to dogs but has some unique aspects. Hypersalivation is the most frequently reported clinical abnormality in cats with HE but is rarely reported in dogs. Seizures also appear to occur more frequently in cats than dogs with HE. Seizures occurred in approximately 50% of feline cases reported in the literature. In contrast, seizures are not a particularly common feature of canine HE. Inappropriate aggression is also relatively frequently in cats compared to dogs. In contrast, compulsive behavior (head pressing, circling, aimless wandering) is observed more frequently in dogs than cats. Neurologic signs such as disorientation, ataxia, and stupor are frequently observed in both species. Figure 17-1 outlines the diagnostic approach to patients with signs of encephalopathy. Gastrointestinal abnormalities such as vomiting, diarrhea, and anorexia are reported less frequently in cats than dogs. Polyuria and polydipsia are also less frequently reported in cats than dogs. Risk factors that may precipitate HE in susceptible patients include alkalosis, hypokalemia (which may result from profuse vomiting or diarrhea or from excessive diuretic therapy with furosemide or other loop diuretics), anesthetics and sedatives (attributed to both increased cerebral sensitivity to the drugs and to impaired drug elimination; benzodiazepines are relatively safe), gastrointestinal hemorrhage (a common precipitating cause of HE is gastroduodenal ulceration which is common in patients with hepatic disease), transfusion of stored blood (it may contain high concentrations of ammonia), constipation (it increases colonic absorption of neurotoxic products of bacterial protein digestion), and methionine administration.

Physical Examination

Dogs with congenital PSS are usually small or unthrifty, but this is less common in cats. The liver in patients with congenital PSS is usually small and may not be palpable even in thin patients. In patients with acquired HE (acute or chronic) physical examination may reveal a small liver or hepatomegaly and/or jaundice. In all types of HE, physical signs related to hypoalbuminemia may develop (e.g., ascites, pleural effusion, subcutaneous edema). The kidneys may be enlarged. In contrast to dogs, cats with congenital PSS are often well grown and in good body condition.

Laboratory Evaluation and Tests

Nonspecific clinicopathologic changes frequently observed in dogs and cats with HE include hypoalbuminemia and mild to moderate elevations in serum alanine aminotransferase (ALT) and alkaline phosphatase (ALP). However, ALT and ALP may be occasionally in the reference range, especially in cats. Subnormal plasma urea concentrations are often detected. Increased hepatic enzymes and hypoalbuminemia occur less consistently in cats with HE compared to dogs. A small proportion of dogs are hypoglycemic, which may contribute to clinical signs of weakness and seizures.

The majority of affected animals will have fasting hyperammonemia, and all will exhibit intolerance to orally or rectally administered ammonium chloride. Fasting and/or postprandial serum bile acids are invariably increased in dogs but may be normal in cats. An interesting hematologic finding in many dogs with congenital PSS is microcytosis not usually associated with anemia. This hematologic abnormality also has been reported in up to 54% of cats.

Approximately 50% of dogs will have ammonium biurate crystalluria. Occasionally ammonium biurate calculi form and cause signs of urinary tract disease including hematuria and recurrent urethral obstruction. Ammonium biurate crystalluria appears to be less frequent in cats.

Plain abdominal radiographs of dogs with HE show a small liver and often renomegaly. This has been reported less frequently in cats. The increase in the size of the renal shadow in dogs is often marked (i.e., up to greater than four times the length of the second lumbar vertebra). The etiology of this enlargement has not been determined. It may be related to altered splanchnic blood flow or to increased metabolic activity of the kidney in the presence of hyperammonemia. Finding a small liver and enlarged kidneys on plain radiographs of a young dog is highly suggestive of a portacaval shunt. Portacaval shunts are usually confirmed by hepatic ultrasonography, visualization at surgery, operative mesenteric venography, cranial mesenteric angiography, transabdominal splenoportography, celiac arteriography, and/or quantitative hepatic scintigraphy.

No specific gross pathologic findings are characteristic of HE (apart from identification of portacaval shunts). Microscopic findings in the CNS include mild vacuolation of glial cells

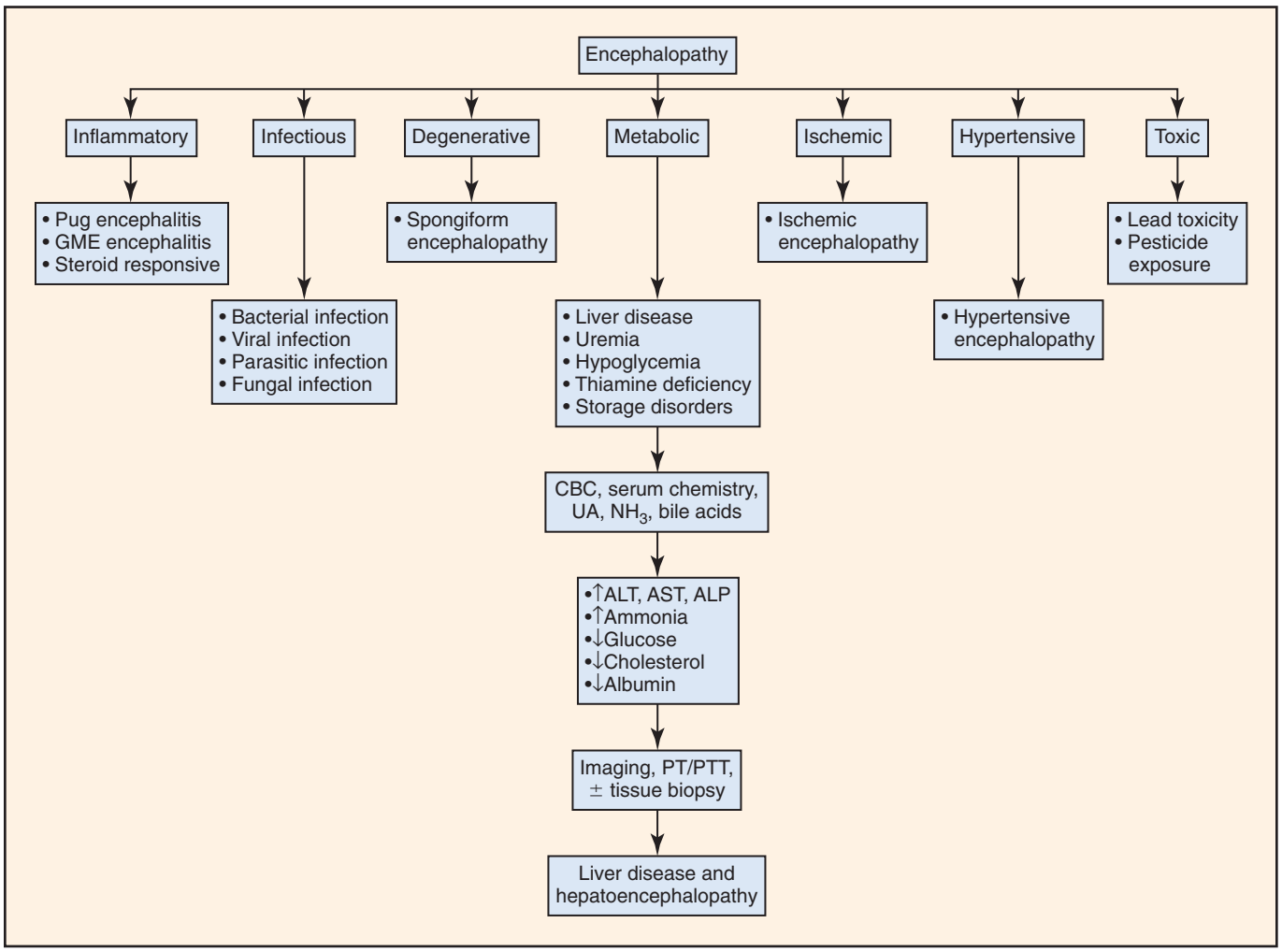

Figure 17-1 Diagnostic approach to patients with signs of hepatoencephalopathy. ALP, Alkaline phosphatase; ALT, alanine aminotransferase; AST, aspartate aminotransferase; CBC, complete blood count; GME, granulomatous meningoencephalomyelitis; PT, prothrombin time; PTT, partial thromboplastin time; UA, urinalysis.

and cerebral edema in severely affected cases (usually acute). In acquired HE, pathologic findings depend on the primary hepatic condition.

Treatment and Management

General Principles

Ideally treatment of any disorder is based on understanding pathogenesis of the clinical signs and abnormalities. Surgical correction of congenital PSS is an example of rational treatment that directly addresses the specific anatomical abnormality causing HE.

However, not all animals with HE have a surgically correctable problem. For example, acute hepatic failure, acquired PSS secondary to chronic hepatic disease, and multiple congenital shunts are not amenable to surgical correction. Surgical correction of single congenital PSS is not always possible because of lack of access to appropriate surgical expertise or economic factors. In addition, patients may need medical management prior to undergoing surgical correction to optimize their condition for surgery. In all of these instances, medical management may be instituted. However, medical management of HE is at best empirical because the pathogenesis of HE is uncertain.

Medical

Medical management may be attempted if surgical correction is not feasible. However, such treatment is palliative and commonly results in temporary alleviation of clinical signs. Medical treatment will not ameliorate portacaval shunting (either congenital or acquired), hence the liver will continue to be deprived of portal blood. As a result there may be continued hepatic atrophy and progressive failure of hepatic function, particularly protein synthesis. In acute hepatic failure, recovery of hepatic function is possible if the patient survives. However, acute hepatic failure carries a poor prognosis, and the treatment of choice in human medicine is hepatic transplantation.

The most successful medical treatment for HE is based on reducing gut bacterial protein metabolism. This is achieved by limiting or altering dietary protein intake and suppressing urease-producing gut bacteria. In addition, limiting absorption of ammonia from the colon may be beneficial.

Diet

The aim is to feed the highest level of protein that the animal will tolerate. Severe protein restriction in a patient with hepatic disease will exacerbate a negative nitrogen balance and lead to further breakdown of lean muscle protein, which aggravates hyperammonemia and may precipitate HE. Also because many affected dogs are large breeds (e.g., Labrador Retriever), excessively restricting dietary protein may lead to developmental orthopedic problems. In such cases rather than recommending typical prescription diets designed for dogs with hepatic disease, it may be preferable to use less-protein-restricted diets (e.g., products designed for dermatologic or gastrointestinal problems), some of which just meet nutritional requirements for growing dogs without being as excessive as most growth diets are. The other advantage of these diets is that the main protein source is often highly processed soy, which has been shown to be beneficial in dogs with HE. Some diets also contain appropriate amounts of calcium and appropriate ratio of calcium to phosphorus.

All patients with hepatic disease should be given enough protein to maintain a positive nitrogen balance, which is unfortunately difficult to quantify in clinical patients. In general, patients with hepatic disease should at least be fed 4 to 5 g protein/100 kcal. Only in cases where HE cannot be acceptably managed with medical therapy alone should protein levels be decreased further and then to no lower than 3 g protein/100 kcal for a short period of time. It is advisable to restrict protein only as needed to ameliorate HE signs and to use antibiotic therapy and lactulose to permit the maximum dietary protein intake possible without precipitating HE.

The source of dietary protein should be considered and have a high biologic value and digestibility. Amino acids from poor quality sources are deaminated at a higher rate yielding more ammonia. Poor quality proteins also undergo greater amounts of intestinal bacterial breakdown. The high content of heme and other nonprotein nitrogenous compounds in red meat makes it highly ammoniagenic; it should be avoided. Studies in human medicine suggest that dairy proteins are better tolerated than meat proteins in chronic HE and are associated with lower blood ammonia concentrations. Consequently, cottage cheese is suitable for dogs and cats as it has a high biologic value and is easily digested.

Recent attention in human medicine has focused on benefits of vegetable proteins compared with animal proteins. Vegetable protein diets appear to improve nitrogen balance, which is particularly important in patients with muscle wasting and cachexia who are at risk of worsening HE if dietary protein is increased. Fiber in the vegetables is beneficial in controlling glucose intolerance and decreasing production of neurotoxic substances in the gut. Commercial or homemade diets based on vegetable proteins may prove beneficial in management of chronic HE in dogs and cats if difficulties with palatability can be overcome.

Drugs

Antimicrobial Agents. Bacterial protein metabolism can also be reduced by use of antibiotics that lessen intestinal bacterial concentrations. Neomycin (10-20 mg/kg PO q6 to 12h) has been used for many years in human and veterinary medicine. Occasional problems associated with ototoxicity, bacterial resistance, and malabsorption have been reported in humans. As a result, neomycin is usually used in humans to treat acute exacerbations of HE rather than for chronic therapy, and this recommendation is reasonable for veterinary patients as well.

Metronidazole has also been used successfully in both human and veterinary medicine to reduce gut flora. Acute CNS dysfunction has been reported in dogs associated with relatively high doses of metronidazole; therefore, a conservative dose not exceeding 30 mg/kg/day is used in patients with HE. Metronidazole treatment should also primarily be used if possible to treat acute exacerbations of encephalopathy rather than as chronic therapy. Other antimicrobial agents that have been used to ameliorate acute signs of HE include ampicillin and vancomycin.

Lactulose. Lactulose (1-4-β-galactosidofructose) is a synthetic disaccharide that is neither hydrolyzed nor absorbed by the small intestine. Although its mode of action is uncertain, it is beneficial in patients with HE caused by PSS and for reducing ammonia absorption from the gut. Daily protein intake can often be increased while lactulose treatment continues without mental deterioration.

The therapeutic effect of lactulose cannot be attributed only to its cathartic effect because sorbitol, which also induces an osmotic diarrhea but without altering stool pH, has little effect on clinical signs of HE in humans. Other possible modes of action of lactulose include (a) an effect of lowered colonic pH on bacterial flora, (b) decreased ammonia absorption from the colon as a result of reduced relative concentration of ammonia (NH_3) (to which the colonic mucosa is more permeable than NH_{4+}), and (c) increased bacterial assimilation of ammonia or decreased ammonia generation by bacteria.

The therapeutic goal is to administer sufficient lactulose to cause passage of two to three soft stools per day. The precise dose rate has not been determined for dogs, but is approximately 2.5 to 25 mL given two or three times daily. Cats usually require 2.5 to 5.0 mL two or three times daily. Lactulose may also be administered as an enema in acute hepatic coma.

Recent studies in humans have suggested that another disaccharide, lactitol (β-galactosidosorbitol), is as effective as lactulose in controlling HE and is associated with fewer adverse effects (e.g., flatulence). The use of lactitol has not been reported in veterinary medicine but it may be considered as an alternative if lactulose-induced flatulence is unacceptable to the owner.

Surgical

Both intra- and extrahepatic PSS can potentially be successfully ligated by experienced surgeons. Single extrahepatic shunts are amenable to surgical correction but the difficulty with surgical correction of intrahepatic shunts lies with their relative inaccessibility.

Complete attenuation of the shunt is often impossible because of unacceptable increases in portal vein pressure. However, long-term amelioration of clinical signs is usually achieved in 85% of canine cases. Good to excellent clinical results can be expected in the majority of dogs regardless of whether the shunt is completely or partially occluded. In contrast, in a study of surgical management of feline portosystemic shunts, all four cats whose shunts were only partially ligated relapsed clinically several months after surgery. Clinical outcome has been reported to be significantly worse in dogs older than 2 years at the time of surgery.

An uncommon postsurgical sequelae in both dogs and cats is the development of intractable seizures and neurologic deficits (e.g., blindness). There are reports of successful management of this problem including use of propofol infusion.[5] However, in many cases management is unsuccessful; mortality is high and irreversible brain damage common in survivors. The pathogenesis of the seizures has not been determined.

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CHAPTER 18

Icterus

Robert G. Sherding

Definition

The term *icterus* is used interchangeably with *jaundice* to refer to yellow discoloration of skin, mucous membranes, and sclerae caused by an accumulation of bilirubin pigment in plasma (hyperbilirubinemia) and tissues. Icterus generally becomes visible when serum bilirubin concentration exceeds 2 to 3 mg/dL (35 to 50 µmol/L), or greater than five- to 10-fold above reference range. Unlike other nonspecific clinical signs of hepatobiliary disease (e.g., inappetence, lethargy, weight loss, vomiting, diarrhea, and dehydration), icterus correlates with hyperbilirubinemia and is therefore a highly specific clinical sign consistent with decreased excretion of bilirubin in association with hepatobiliary disease or increased formation in association with severe hemolysis. Despite excellent specificity, icterus and hyperbilirubinemia are relatively insensitive indicators, found only in moderate to severe hepatic insufficiency and overall in less than 50% of dogs and cats with hepatic disease.[1]

Pathophysiology and Mechanisms

Bilirubin is an end product of hemoglobin metabolism. Icterus occurs when bilirubin formation exceeds hepatobiliary excretion. Three pathophysiologic mechanisms of hyperbilirubinemia and icterus are termed (a) *prehepatic*, which results from accelerated red blood cell destruction (hemolysis) and increased bilirubin production; (b) *hepatic*, which is caused by intrinsic hepatocellular disease and reduced hepatocyte uptake, conjugation, and secretion of bilirubin; and (c) *posthepatic*, which is caused by extrahepatic cholestasis and disruption of bile flow through the extrahepatic biliary system (Fig. 18-1).[1,2] This mechanistic classification helps to explain how different categories of disease can cause hyperbilirubinemia and icterus, although all three mechanisms may be operative in any individual.

Normal Bilirubin Metabolism

Bilirubin is a yellow pigment derived mainly from the degradation of red blood cell hemoglobin (see Fig. 18-1A). Under normal conditions approximately 80% of bilirubin comes from erythrocyte hemoglobin, while the remaining 20% is derived from the breakdown of other heme-containing proteins, such as myoglobin, P450 cytochromes, peroxidase, and catalase.[2] In macrophages of the mononuclear phagocytic system of the spleen, liver, and bone marrow, heme from senescent erythrocytes is cleaved by microsomal heme oxygenase to yield iron and biliverdin, a green pigment, which is then reduced to bilirubin, a yellow pigment, by biliverdin reductase. Daily production of bilirubin in adult mammals is approximately 3 to 5 mg/kg.[3] Unconjugated bilirubin, also called free bilirubin or indirect-reacting bilirubin, is insoluble in plasma. As it is released into the circulation it is tightly bound to albumin for transport to the liver, which completes the *prehepatic phase* of bilirubin metabolism.[2]

In the *hepatic phase*, bilirubin metabolism depends upon hepatocyte uptake, conjugation, and secretion, followed by posthepatic excretion in bile (see Fig. 18-1A).[2] Unconjugated bilirubin is removed from circulation by the liver (uptake), which involves dissociation from albumin at the sinusoid-hepatocyte interface and transport across the cell membrane by a carrier protein. Uptake capacity of hepatocytes greatly exceeds excretory capacity.[4] Once inside the hepatocyte, bilirubin is bound to ligandin, a cytosolic transporter protein that regulates the rate of bilirubin uptake.[2] Within the hepatocyte glucuronyl transferase catalyzes conjugation of bilirubin with glucuronic acid to form water-soluble bilirubin diglucuronide.[5] Conjugated bilirubin, also called water-soluble or direct-reacting bilirubin, is then secreted into the bile canaliculi which is both an energy-dependent process and rate-limiting step in the transfer of bilirubin from plasma to bile.[2] In the *posthepatic phase*, conjugated bilirubin is then transported with bile through the extrahepatic bile duct system, stored in the gallbladder, and excreted into the intestines through the common bile duct. In dogs, intestines and kidneys can also conjugate and excrete a small amount of bilirubin.[6]

Conjugated bilirubin that enters the intestinal tract with bile is poorly absorbed and passes largely into the large intestine where colonic bacteria convert it to colorless derivatives called urobilinogens.[2] A small portion of bilirubin within the intestine is deconjugated by enteric bacteria, reabsorbed by enterocytes, and returned to the liver by the enterohepatic portal venous circulation. The majority of intestinal urobilinogen is oxidized and passed in the feces as stercobilin, a pigment that imparts the normal brown color to feces. Normally, a small amount of intestinal urobilinogen (10% to 20%) is reabsorbed into the enterohepatic circulation and handled once again by the liver, except for approximately 1% to 5% of absorbed urobilinogen that is excreted into urine by the kidneys.[7]

Prehepatic Icterus

Icterus is characterized as *prehepatic* when the primary abnormality is overproduction of bilirubin resulting from hemolysis (see Fig. 18-1B). Accelerated erythrocyte destruction increases formation of

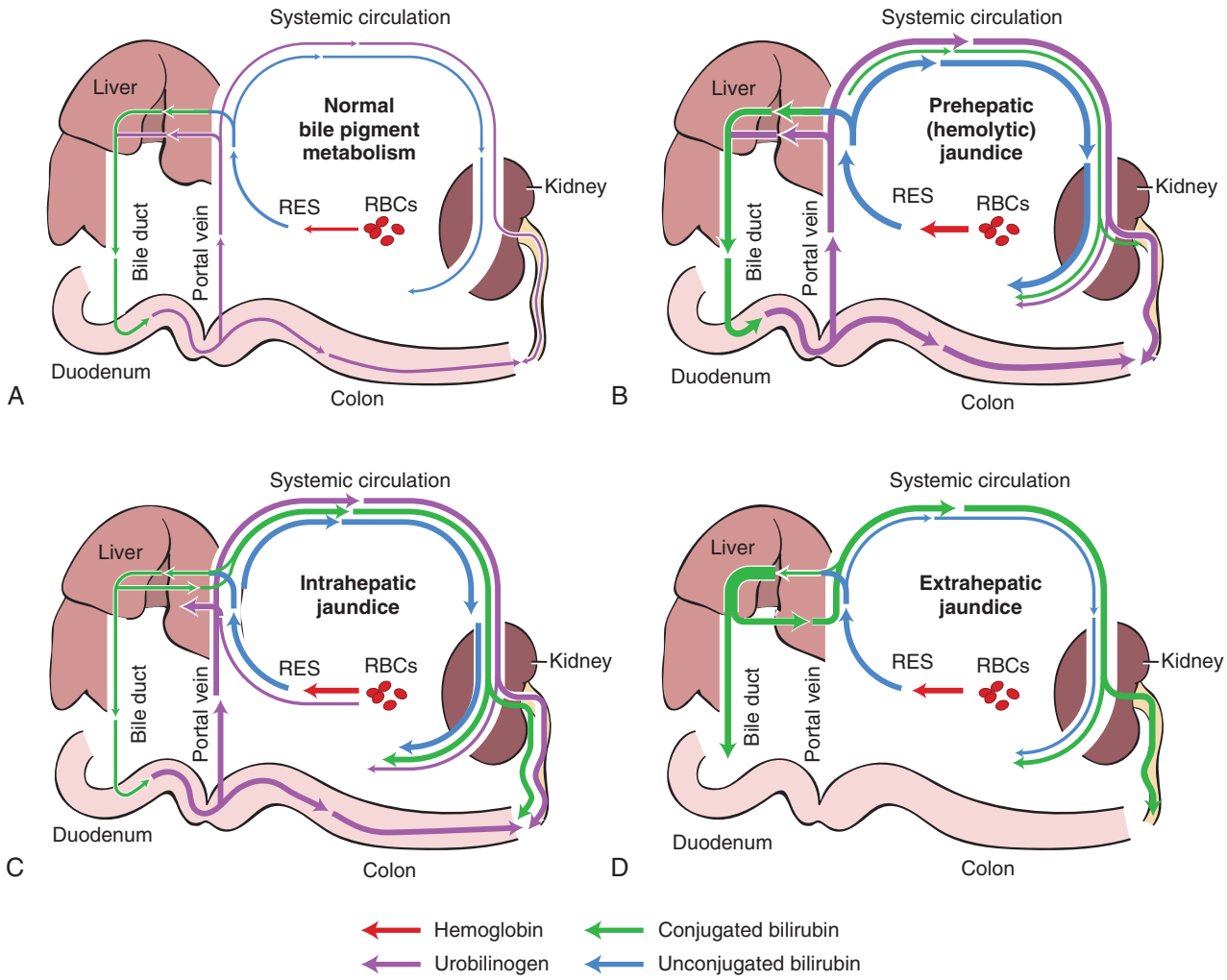

Figure 18-1 Diagrams comparing the formation, excretion, and enterohepatic circulation of bilirubin and other bile pigments in **(A)** the normal animal; **B,** *prehepatic* icterus associated with hemolysis and overproduction of bilirubin; **C,** *intrahepatic* icterus associated with hepatocellular disease and intrahepatic cholestasis; and **D,** *posthepatic* icterus associated with extrahepatic bile duct obstruction. RBCs, Red blood cells; RES, reticuloendothelial or mononuclear phagocytic system. (Courtesy of Dr. Susan Johnson, The Ohio State University.)

bilirubin from heme. If this bilirubinemia overwhelms the liver's functional capacity for uptake, conjugation, and secretion, bilirubin is refluxed from the liver into the circulation resulting in hyperbilirubinemia and icterus.[2] The hemolytic event must be acute and severe to overwhelm the large reserve capacity of the normal liver. Severe hemolytic events can be complicated by anemic hypoxia of the liver, which can secondarily compromise hepatic function and contribute to intrahepatic cholestasis. Icterus and bilirubinemia associated with severe hemolysis are typically a mixture of unconjugated and conjugated bilirubin fractions resulting from combination of overproduction of bilirubin and intrahepatic cholestasis.[8] Increased excretion of conjugated bilirubin into the intestinal tract increases urobilinogen formation, which results in increased urobilinogen in urine and increased stercobilins in feces, which imparts a dark orange–brown color to the feces.[1]

Hepatic Icterus

Icterus is characterized as *hepatic* when the primary abnormality is intrahepatic cholestasis associated with hepatocellular injury, necrosis, or dysfunction (see Fig. 18-1C). Moderate to severe hepatic disease can impair various steps in handling of bilirubin particularly at the level of the canaliculi and intrahepatic bile ductules. Intrahepatic cholestasis and icterus develop most readily with hepatic parenchymal lesions that affect the periportal region of the liver lobule because bile flows from the centrilobular region toward the intrahepatic bile ductules in the portal triad.[3,9] Intrahepatic cholestasis causes reflux of conjugated bilirubin into the circulation. Unconjugated bilirubin also refluxes into circulation because increased bilirubin accumulation within hepatocytes interferes with the conjugation process. In cholestatic hepatic disease, concurrent retention of bile acids may further damage hepatocytes. Hyperbilirubinemia that occurs in most diseases of the liver is a mixture of conjugated and unconjugated bilirubin in varying proportions.[8] Some of the circulating conjugated bilirubin is excreted by kidneys and is detected in urine along with urobilinogen.

Posthepatic Icterus

Icterus is characterized as *posthepatic* when the primary abnormality is impaired excretion of bilirubin caused by extrahepatic biliary disease that interrupts or obstructs the flow of bile (see Fig. 18-1D). Extrahepatic cholestasis primarily causes reflux of conjugated bilirubin into the circulation, but bile retention also interferes with

conjugation and injures hepatocytes which can cause secondary unconjugated bilirubinemia. Thus posthepatic icterus is characterized by mixed hyperbilirubinemia with the conjugated fraction predominating. Some of the circulating conjugated bilirubin is excreted by the kidney and detected in urine; however, urobilinogen is absent in urine because obstructive extrahepatic biliary disease prevents delivery of precursor bilirubin into the intestine. In complete bile duct obstruction, failure of bile to enter the intestinal tract can result in pale gray–colored acholic feces.[1,10]

Differential Diagnosis

In dogs and cats, hyperbilirubinemia and icterus can be associated with many diseases that cause either hemolysis or intra- or extrahepatic cholestasis (Box 18-1). Figure 18-2 outlines an algorithmic approach for differential diagnosis of icterus. The first step is to consider prehepatic (hemolytic) icterus, which is usually indicated by the presence of moderate to severe anemia (hematocrit <20%) and evidence of red blood cell (RBC) regeneration (polychromasia, anisocytosis, and reticulocytosis) in the absence of blood loss.[11] The cause of hemolysis may be suggested by other hematologic findings such as autoagglutination, spherocytosis, Heinz bodies, RBC parasites, or RBC fragments (schistocytes). In icteric patients without clinical and hematologic evidence of severe hemolysis, diagnostic evaluation should focus next on identifying a primary hepatobiliary disease that can cause either intra- or extrahepatic cholestasis. Ultrasonography is especially useful for evaluating the liver, gallbladder, and bile ducts. Posthepatic icterus is unlikely if ultrasonography fails to reveal evidence of obstruction (bile duct distention), rupture (bile peritonitis), or other disease (e.g., cholelithiasis, gallbladder mucocele) in the extrahepatic biliary tract. Ultrasonography also helps to identify pancreatic or duodenal masses that could be obstructing the common bile duct. Once prehepatic hemolysis and posthepatic disruption of bile flow are excluded, diagnostic evaluation should focus on intrinsic hepatic parenchymal diseases that can cause icterus. Hepatic biopsy is required in many such cases.

Box 18-1 Differential Diagnosis of Icterus and Hyperbilirubinemia

Prehepatic (Hemolytic) Icterus
- Immune-mediated hemolytic anemia
- RBC infections
  - *Babesia* spp., hemotropic *Mycoplasma* spp., *Cytauxzoon felis*
- RBC oxidative injury by toxins and drugs (Heinz body anemia)
  - Acetaminophen, onion, garlic, zinc, vitamin K, benzocaine and other local anesthetics (cats), propylene glycol, naphthalene (mothballs)
- Envenomation (spiders, snakes, bees)
- Hypophosphatemia (insulin therapy, refeeding syndrome)
- Hereditary RBC defects
  - Pyruvate kinase deficiency, phosphofructokinase deficiency, stomatocytosis
- Microangiopathic RBC fragmentation
  - DIC, vasculitis, hemangiosarcoma, splenic torsion, heat stroke, heartworm postcaval syndrome
- Incompatible blood transfusion
- Neonatal isoerythrolysis

Hepatic (Hepatocellular) Icterus
- Adverse drug reactions (many)
- Hepatotoxins (many)
- Infectious hepatitis (many causes)
- Noninfectious chronic hepatitis
- Cirrhosis
- Breed-specific copper hepatopathies
- Cholangitis/cholangiohepatitis
- Feline hepatic lipidosis
- Hepatic neoplasia (primary, metastatic)
- Cholestasis of sepsis

Posthepatic (Obstructive) Icterus
- Cholelithiasis, choledocholithiasis
- Bile duct inflammation, stricture, or cyst
- Biliary fluke infestation (*Platynosomum concinnum*, *Amphimerus pseudofelineus*)
- Biliary neoplasia
- Gallbladder disease (cholecystitis, mucocele)
- Pancreatic disease (carcinoma, abscess, pancreatitis)
- Duodenal disease (neoplasia, foreign body, duodenitis)
- Bile duct or gallbladder rupture (bile peritonitis)

DIC, Disseminated intravascular coagulation; RBC, red blood cell.

Evaluation of the Patient

Icterus is sometimes noticed by an observant pet owner and quite readily detected on physical examination. Following a complete history and physical examination, initial diagnostic evaluation of the icteric patient should include a complete blood count (CBC), serum chemistry, urinalysis, and diagnostic imaging of the abdomen, especially ultrasonography. This minimum database usually enables classification of icterus as prehepatic, hepatic, or posthepatic in origin (see Fig. 18-2). Hepatic cytology and biopsy are often indicated for further evaluation of hepatic parenchymal disease. In most icteric patients coagulation status should also be evaluated. Abdominocentesis and fluid analysis are indicated in patients with abdominal effusion, especially if gallbladder or bile duct rupture is suspected. Laparoscopic or surgical intervention is usually the most effective way to confirm, characterize, and decompress posthepatic biliary obstruction.

History

Icterus is an important clinical sign of hemolysis and hepatobiliary disease in dogs and cats. Some owners may report changes in the color of urine or feces. Severe bilirubinuria can cause orange or green discoloration of urine (pigmenturia), whereas intravascular hemolysis can cause dark red or brown urine (hemoglobinuria).[1] Feces may appear dark orange–brown or green with increased excretion of bile pigments into the intestinal tract. Prolonged absence of bile pigments in the intestines in complete bile duct obstruction can result in pale gray–colored acholic feces.[10]

Other clinical manifestations of hepatobiliary disease can include inappetence, lethargy, weight loss, vomiting, diarrhea, polyuria-polydipsia, hepatic encephalopathy, abnormal bleeding tendencies, and abdominal distention related to hepatomegaly or ascites.[1,12] Genetic and breed predispositions for specific diseases (e.g., copper hepatopathy) should be also considered (see Chapters 61 and 62). Owners should be questioned about potential for exposure to infectious agents, hepatotoxins (e.g., xylitol, aflatoxin-contaminated dog food, amanita mushrooms, Microcystis blue-green algae, sago, or cycad palm), or medications that might cause hepatotoxicity (e.g., nonsteroidal antiinflammatory drugs, phenobarbital, and many others) (see Chapter 61).

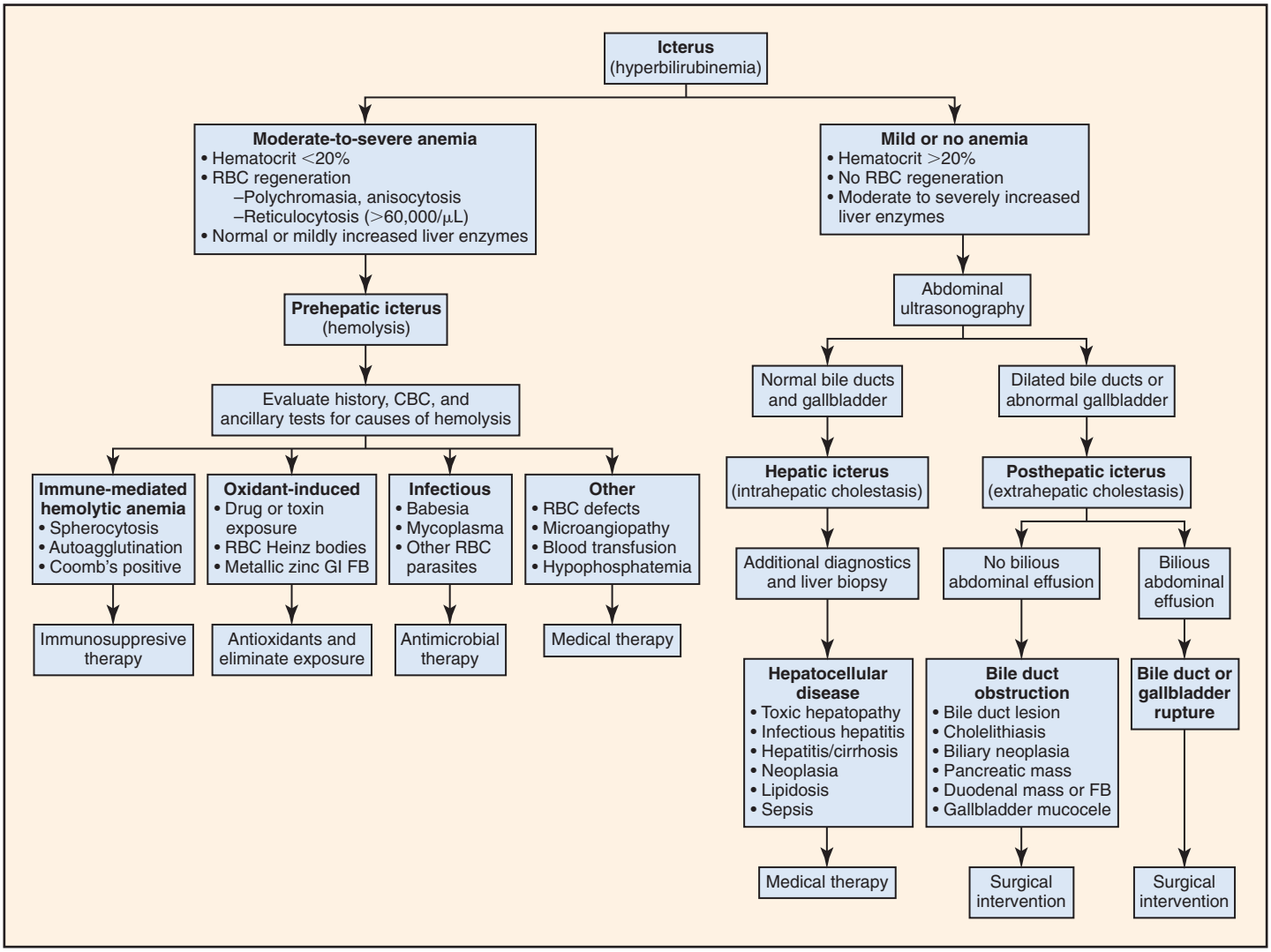

Figure 18-2 Algorithmic approach for the differential diagnosis of icterus in the dog and cat. CBC, Complete blood count; FB, foreign body; GI, gastrointestinal; RBC, red blood cell.

Patients with hemolytic icterus typically have a history of exercise intolerance, lethargy, weakness, and pallor of mucous membranes.[11] When hemolysis is suspected, history should ascertain potential for recent exposure to blood transfusions, oxidant substances, vector-borne hemotropic RBC parasites, venomous snakes and insects, zinc ingested with metallic objects, or zinc oxide sun protectants (see Box 18-1).[11] Breed predispositions to hereditary RBC defects should be taken into account. Signs that could indicate an underlying cause of microangiopathic hemolytic anemia should also be considered. Insulin therapy in ketoacidotic diabetic patients or intensive hyperalimentation can precipitate hypophosphatemic hemolysis when serum phosphorus is less than 1.5 mg/dL.[11]

Physical Examination

The clinical sign of icterus is recognized as yellow discoloration of the skin, oral mucous membranes, and sclerae caused by an accumulation of bilirubin in the tissues. Icterus generally becomes visible when serum bilirubin concentration exceeds 2 to 3 mg/dL. By comparison icteric plasma and bilirubinuria are seen at serum bilirubin concentrations of 1 to 2 mg/dL.[4] Intensity and distribution of tissue bilirubin is determined by (a) total serum bilirubin concentration; (b) proportion of conjugated versus unconjugated bilirubin; (c) background tissue color, which is affected by perfusion, hematocrit, and melanin pigment; and (d) tissue composition.[9] Ambient lighting can also affect the examiner's ability to detect icterus. Water-soluble conjugated bilirubin accumulates preferentially in tissues such as skin and sclerae.[9]

Additional physical findings in hepatobiliary disease can include hepatomegaly, hepatic masses, cranial abdominal pain, or abdominal effusion (ascites or biliary rupture).[12] In prehepatic icterus, the physical examination findings are attributable to severe hemolytic anemia and include mucous membrane pallor, depressed mentation, weakness or collapse, tachypnea, tachycardia, anemic murmur, and splenomegaly.[11]

Laboratory Evaluation and Tests

The CBC usually identifies prehepatic hemolytic icterus. Serum chemistry confirms hyperbilirubinemia and assesses other parameters that can be affected by hepatobiliary disease, including liver enzyme activities, albumin, cholesterol, blood urea nitrogen, and glucose. The urinalysis detects bilirubinuria and urobilinogen. Additional diagnostic tests, such as serum pancreatic-specific lipase, tests for specific infectious diseases, bile culture, and abdominal fluid analysis, are sometimes indicated.

Hematology

Once hyperbilirubinemia is confirmed, the next step is to determine if there is hemolysis. To induce icterus, hemolysis must be severe enough to cause moderate to severe anemia. A hematocrit less than 20% and evidence of RBC regeneration (polychromasia, anisocytosis, and reticulocytosis) in the absence of blood loss are indications to further evaluate for causes of hemolysis.[11] Red discoloration of plasma or serum (hemoglobinemia) can be seen in patients with intravascular hemolysis.

Cause of hemolysis is often suggested by history, physical examination, and other hematologic findings, but ancillary testing may be needed. The presence of autoagglutination, spherocytosis, or a positive direct Coombs test suggests immune-mediated hemolysis.[11] Finding numerous Heinz bodies indicates RBC injury from oxidant drugs or toxins (see Box 18-1). Red blood cell parasites, such as *Babesia* spp., hemotropic *Mycoplasma* spp., or *Cytauxzoon felis*, can sometimes be identified on stained blood smears, but specific immunodiagnostic or polymerase chain reaction (PCR) diagnoses are often required.[11] The presence of numerous RBC fragments (schistocytes) should prompt coagulation testing for disseminated intravascular coagulopathy (DIC) and further evaluation for other causes of microangiopathic hemolytic anemia. Additional evaluations in unexplained hemolytic anemia should include measurement of serum phosphorus for hypophosphatemic hemolysis and abdominal radiography to identify metallic gastrointestinal objects that might contain zinc. Genetic tests are available for some of the rare breed-specific hereditary RBC defects that can cause hemolytic icterus.[11]

Serum Bilirubin

Serum bilirubin concentration must usually exceed 2 to 3 mg/dL (35 to 50 µmol/L) before skin and mucous membranes become noticeably icteric. Although important as a laboratory finding, magnitude of the hyperbilirubinemia does not necessarily have prognostic significance nor does it help to distinguish between prehepatic, hepatic, and posthepatic causes of icterus.[1,8,13] Dry reagent and spectrophotometric methods are used to measure bilirubin. Serum bilirubin concentrations measured spectrophotometrically can be falsely elevated by up to 1 to 2 mg/dL in specimens that are severely lipemic or hemolyzed.[4] Fortunately, newer serum chemistry analyzers are less subject to this interference. Bilirubin is stable for 7 days in specimens refrigerated away from light at 4°C (39.2°F), but exposure to bright light can decrease bilirubin by 50% per hour.

Fractionation of total serum bilirubin into unconjugated (indirect-reacting) and conjugated (direct-reacting) forms in the van den Bergh reaction has little diagnostic value in dogs and cats and is no longer recommended.[1,8,13] Hematocrit and hematologic findings are more reliable for differentiating hemolytic and hepatobiliary icterus.[1] Ratios of bilirubin fractions in all three categories of icterus are unpredictable and do not readily discriminate between hemolytic, hepatic, and obstructive icterus.[1,8,13,14] Studies in dogs show that increased RBC turnover and decreased bilirubin clearance occur together in both hemolytic and hepatobiliary diseases.[8,14] Acute hemolysis is usually accompanied by secondary intrahepatic cholestasis, presumably resulting from hypoxia and oxidative stress.[8,13] This results in a mixed elevation in both unconjugated and conjugated bilirubin in hemolytic icterus. Dogs and cats with primary cholestatic hepatobiliary disease also develop mixed hyperbilirubinemia. Conjugated bilirubin that accumulates in canaliculi and hepatocytes is refluxed back into circulation while at the same time impaired conjugation increases circulating unconjugated bilirubin. This is coupled to increased erythrocyte turnover and a two- to fivefold increase in bilirubin production because of shortened erythrocyte survival time in the circulation. This may be related to instability of erythrocyte membranes in animals with hepatobiliary disease, and in some cases hypersplenism related to portal hypertension.[8,14]

Accumulation of biliprotein complexes in plasma can have variable reactivity on fractionation test procedures. In prolonged cholestasis and icterus, up to 90% of conjugated bilirubin can form irreversible covalent bonds to albumin as biliproteins.[15] The proportion of this tightly bound biliprotein is dependent on the duration and severity of cholestasis. Biliproteins are not filtered by the kidney and do not contribute to bilirubinuria. Disappearance of biliproteins from the circulation depends on the half-life of albumin (10 to 14 days), which can cause persistence of hyperbilirubinemia and icterus long after resolution of the underlying hepatobiliary disease.[15]

Urine Bilirubin and Urobilinogen

Conjugated bilirubin can be excreted by kidneys and detected qualitatively in urine using reagent strips (urine "dipsticks") or tablets (Ictotest; Ames).[1,16] Water-soluble conjugated bilirubin is more reactive than free bilirubin with these reagents. Bilirubinuria usually represents residual conjugated bilirubin that has been filtered by the kidneys but not reabsorbed by renal tubules. Bilirubin is unstable in urine at room temperature or with exposure to light, so urine should be evaluated within 30 minutes of collection or refrigerated at 2°C to 8°C (35.6°F to 46.4°F) in dark conditions.[16] The relative concentration of bilirubin in the urine increases with increasing urine specific gravity, yielding a more positive dipstick reaction than in dilute urine samples. A small amount of bilirubin is normally found in concentrated urine from healthy dogs, especially males, because dogs have a low renal threshold for bilirubin and because canine kidney can convert heme to bilirubin followed by conjugation and excretion.[6,16,17] Heme degradation and bilirubin conjugation by kidney is upregulated in dogs with intravascular hemolysis and hemoglobinuria. Bilirubin is not normally detectable in feline urine, so bilirubinuria in a cat is indicative of conjugated hyperbilirubinemia and hepatobiliary disease.[18]

Urobilinogen is a product of bilirubin degradation by intestinal bacteria. Approximately 20% of intestinal urobilinogen is absorbed into the enterohepatic circulation, and most of this is reexcreted by the liver except for a small amount of absorbed urobilinogen that is excreted in urine through glomerular filtration and tubular secretion.[7] In the past, urobilinogen in the urine has been used as evidence of an intact enterohepatic circulation and to rule out complete extrahepatic bile duct obstruction in icteric patients. However, formation of urobilinogen and its excretion in urine are affected by many other factors including the amount of conjugated bilirubin entering the intestine, activity of intestinal bacteria, intestinal transit time, and various urinary factors. Therefore, qualitative dipstick determination of urine urobilinogen is an unreliable marker of bilirubin metabolism and is not considered diagnostically useful.[1] Causes of spuriously low or negative urine urobilinogen results include abnormal intestinal transit (diarrhea), decreased intestinal bacterial activity (antibiotics), renal insufficiency, dilute urine, acidic urine, urine exposed to light, and urine samples left standing at room temperature.[1] Gastrointestinal hemorrhage can cause false positives, which can be misleading in animals with bile duct obstruction.

Other Serum Chemistry Parameters

In addition to hyperbilirubinemia, increased serum hepatic enzyme activities are expected in most patients with icterus. Increased serum alanine aminotransferase (ALT) and aspartate aminotransferase

(AST) activities reflect changes in hepatocyte membrane permeability, whereas increased serum alkaline phosphatase (ALP) and γ-glutamyltransferase (GGT) activities are a response to cholestasis. In general, hepatic enzymes are expected to be moderately to severely increased in hepatobiliary icterus and normal or only mildly increased in hemolysis, except when severe hemolytic events are complicated by intrahepatic cholestasis from anemic hypoxia, oxidative stress, and systemic inflammatory response. Generally, both ALP and GGT increase to comparable levels in cholestatic hepatic disease except in cats. Cats with idiopathic hepatic lipidosis may have increased ALP and a discordant GGT that remains normal or only minimally increased. Depending on disease and stage of progression, other biochemical abnormalities in cholestatic hepatic disease can include hypoalbuminemia, decreased blood urea nitrogen (BUN), hypercholesterolemia, and electrolyte abnormalities. Pre- and postprandial serum bile acid determinations are more sensitive than serum bilirubin for evaluating liver function in nonicteric dogs and cats. Serum bile acid testing is unnecessary in icteric patients without hemolysis because hyperbilirubinemia provides similar information.[1] The reader is referred to Chapters 25 and 61 for additional information on laboratory diagnostics in hepatic disease.

Other Laboratory Evaluations

Coagulation tests (e.g., activated partial thromboplastin time [aPTT], prothrombin time [PT], protein-induced vitamin K absence [PIVKA], thromboelastography) should be considered because coagulation abnormalities are common in icteric patients, especially with vitamin K–responsive coagulopathy in hepatobiliary icterus, and hypercoagulability or DIC in hemolytic icterus.[1,3] Pancreatic-specific lipase immunoassay (PLI) is indicated when pancreatitis is suspected as a cause of bile duct obstruction and in cats with cholangitis. It may be appropriate to evaluate for extrahepatic sepsis as a cause of functional cholestasis and to test for specific infectious diseases that can involve the liver or cause secondary hemolytic anemia. Older cats with evidence of liver disease should have baseline serum thyroxine concentration determinations to screen for underlying hyperthyroidism. Fluid analysis is important in icteric patients with abdominal effusion to identify neoplastic cells or evidence of gallbladder or bile duct rupture (bile peritonitis), such as the presence of bilirubin crystals or a higher bilirubin concentration in fluid than serum. Bacterial cultures of bile or hepatic specimens also can be helpful.[19]

Diagnostic Imaging

Diagnostic imaging procedures that are most often used for initial evaluation of the icteric patient are abdominal radiography and ultrasonography. Survey abdominal radiography can be used to evaluate liver size, identify abdominal masses or effusions, and detect calcified choleliths that might be a cause of extrahepatic biliary obstruction. In unexplained hemolytic icterus, abdominal radiographs are indicated for diagnosis of metallic objects in the gastrointestinal (GI) tract that could be a cause of zinc toxicosis.

Abdominal ultrasonography is a valuable noninvasive diagnostic tool for differentiating posthepatic biliary obstruction from intrahepatic parenchymal disease. Ultrasonography can be used to evaluate the hepatic parenchyma, bile ducts, and gallbladder, and to identify abdominal effusion (bile peritonitis).[12] Biliary obstruction, bile sludging, gallbladder mucocele, and cholelithiasis are readily identified with ultrasound.[20-26] Hepatic neoplasms, cysts, and abscesses are also usually easily detected. Ultrasonographic findings may also suggest parenchymal abnormalities such as lipidosis, cholangitis, cirrhosis, and lymphoma, or indicate portal hypertension.[12] Ultrasonography can also detect abnormalities in adjacent organs and structures such as the pancreas (carcinoma, pancreatitis), duodenum (neoplasia or foreign body obstructing the duodenal papilla), spleen, kidneys, and lymph nodes. Ultrasound-guided cytology specimens can be collected from any abnormal organ or structure in the abdomen, especially the liver, extrahepatic biliary system, and pancreas in icteric patients. Hepatobiliary nuclear scintigraphy is useful for diagnosing bile duct obstruction, but specialized facilities are needed.[27,28] Computed tomography (CT) and other advanced imaging techniques may be appropriate in some cases.

Hepatic Biopsy

Hepatic biopsy is the single most informative test in hepatic parenchymal disease and is usually required for definitive diagnosis of diseases such as hepatitis, cirrhosis, cholangitis, lipidosis, and neoplasia. Biopsy methods can include fine-needle aspiration (for cytology and culture); percutaneous needle biopsy ("blind" or ultrasound-guided); forceps biopsy by laparoscopy; or excisional biopsy by laparotomy. These procedures are described in Chapters 27, 28, and 61.

Treatment and Management

The appropriate treatment of the icteric patient depends on identifying and treating the underlying cause. In general, prehepatic and hepatic causes of icterus are treated medically, whereas some forms of posthepatic icterus may require surgical intervention.

General Principles

Although icterus is indicative of serious underlying hemolytic or hepatobiliary disease, increased concentrations of bilirubin in plasma, tissues, and urine are not considered to be detrimental in dogs and cats except in rare cases of extreme hyperbilirubinemia (>30 mg/dL) where bilirubin has the potential to injure the kidney or brain (kernicterus). Treatment is therefore directed at eliminating the cause of hyperbilirubinemia in most cases while allowing icterus to resolve on its own. Once the cause of hemolysis is identified and eliminated in patients with prehepatic icterus, erythrocyte turnover returns to normal, the accelerated or premature production of bilirubin ceases, and icterus resolves rapidly. In dogs and cats with hepatic icterus caused by intrinsic disease of the liver, treatment involves (a) specific medical therapy directed at underlying hepatic disease, (b) nonspecific adjunctive therapy with hepatoprotectant medications (see Chapter 46), and (c) therapy to prevent or control the complications of hepatic failure. Treatment of posthepatic icterus caused by extrahepatic bile duct obstruction often, but not always, requires surgical intervention to reestablish bile flow.

Medical

Treatment of hemolytic icterus depends on the inciting cause. In hemolytic crises induced by incompatible blood transfusions, medications, toxins, or envenomation, the hemolysis and icterus are usually self-limiting with supportive care and prevention of further exposure to the inciting factor. In patients with zinc toxicosis, metallic gastrointestinal foreign bodies that contain zinc are removed endoscopically or surgically. When hemolytic icterus is associated with specific erythrocytic infections, such as *Babesia* spp. or hemotropic *Mycoplasma* spp., treatment is aimed at eliminating the infection with appropriate antimicrobial agents. Treatment of icteric cats infected by *C. felis* is not usually successful. Immune-mediated hemolytic anemia is treated with corticosteroids and other

immunosuppressive agents that control immune destruction of erythrocytes, such as azathioprine, cyclosporine, mycophenolate mofetil, or leflunomide, and measures are taken to prevent thromboembolic complications.[11]

Treatments for specific hepatic diseases are described in Sections V and VI. In addition, nonspecific adjunctive medical therapy may be appropriate in cholestatic hepatic diseases. Ursodiol (ursodeoxycholic acid) is proposed to enhance bile flow and improve bile acid composition and water content of bile. The canalicular transport systems for excretion of bilirubin and bile acids are functionally different; however, bile acid excretion enhances bile flow which increases the maximum canalicular transport capacity for bilirubin.[29] This may justify use of ursodiol in nonobstructive icterus to enhance bilirubin excretion while reducing cholestatic hepatocellular injury caused by accumulation of hydrophobic bile acids. In addition, nutraceutical drugs (e.g., vitamin E [α-tocopherol], S-adenosylmethionine [SAMe], and Silybin) with hepatoprotective and antioxidant properties may be appropriate for icteric patients. Finally, medical therapy to prevent or control the complications of hepatic failure is used as needed (see Chapters 46 and 61). This can include nutritional support therapy and treatment for hepatic encephalopathy (diet, antibiotics, lactulose), ascites (diuretics), or gastrointestinal ulceration (proton pump inhibitors for acid control).

Surgical

Most patients with posthepatic obstructive icterus require surgical intervention to decompress the biliary obstruction and restore bile flow.[21,22,25,30-32] This often requires biliary diversion procedures such as cholecystoenterostomy. Choledochal stenting for decompression of extrahepatic biliary obstruction can also be effective.[33,34] When icterus is attributed to disease of the gallbladder (e.g., cholelithiasis, cholecystitis, gallbladder mucocele) treatment usually requires surgical gallbladder removal (cholecystectomy).[20,23,24,35-37] Icteric patients with bilious peritoneal effusion require abdominal surgery to identify and repair the ruptured gallbladder or bile duct and treat bile peritontis.[38]

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CHAPTER 19

Polyphagia and Hyperphagia

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Definition

Polyphagia and hyperphagia are synonyms that refer to excessive food intake or overeating. Polyphagia may be considered pathologic (i.e., secondary to disease) whereas hyperphagia may be physiologic. Both reflect disturbances in normal appetite control. Differentiation and identification of the underlying cause is critical to proper treatment, controlling food intake, and managing body weight.

Appetite Control

Control over food intake and energy balance is regulated by multiple, redundant pathways. Hunger, or the drive to eat, is the dominant effect that is inhibited by various satiety signals. Neuronal and hormonal signals provide feedback to the brainstem and hypothalamic center that controls appetite.[1,2] Gastric and duodenal distention trigger inhibitory signals via the vagus nerve, reducing the desire for food. Gastrointestinal hormones (e.g., cholecystokinin, peptide YY) initiate a cascade effect that among other changes inhibits appetite. In addition hormones (e.g., insulin, glucagon-like peptide) suppress appetite, whereas insulin deficiency contributes to excessive food intake. These effects can be observed in patients with insulinoma and diabetes mellitus.

Gut hormones that promote food intake include ghrelin, which is stimulated by hypoglycemia. Multiple peripheral signals combine to stimulate release of hypothalamic orexigenic neuropeptides, neuropeptide Y, and agouti-related peptide, which promote food intake as well as decrease energy expenditure. Acting at the same hypothalamic neuroreceptor, melanocortins (α-melanocyte-stimulating hormone [MSH]) inhibit food intake and increase energy expenditure via stimulation of thyroid hormone and sympathetic nervous activity.[1,2] Glucocorticoids inhibit action of melanocortins and enhance appetite-stimulating effects of agouti-related peptide. Such polyphagia can be recognized in patients with hyperadrenocorticism.

Chronic regulation of energy intake is driven, in part, by adipose-derived substances such as leptin and adiponectin. The ultimate control over chronic regulation of energy balance and body weight is not fully known.

Disease and drugs can interfere with normal regulatory pathways, contributing to pathologic polyphagia. In addition, environmental and sensory factors can disrupt or override physiologic controls of appetite. Emerging research indicates that sensory properties of food and other pleasant factors involved with food intake stimulate parts of the forebrain recognized as "reward centers."[1-3]

Although the hypothalamus is the primary site for modulating hunger and satiety, the orbitofrontal cortex of the brain plays a key role in processing interacting sensory inputs including sight, smell, taste, and texture of food.[4,5] The forebrain, including the orbitofrontal cortex and nucleus accumbens, appears able to drive food intake despite a lack of hunger or physiologic need for food. Dopamine and opioid receptor pathways in the forebrain drive the desire for food reward, and ingestion of palatable food increases expression of opioid peptides.[3,4] Signals from this reward center can override satiety factors and stimulate food consumption.

Sensory-specific satiety is a decrease in appetite for a particular food rather than for food in general,[5] and is controlled by the orbitofrontal cortex. Recognition of sensory-specific satiety helps explain increased intake that often follows introduction of new foods or new flavors. Dogs and cats, like humans, tend to overeat when presented with a variety of foods.[6] After a time intake will decrease toward or even below energy needs, probably due to sensory-specific satiety as well as physiologic controls of energy balance. However, if novel foods are frequently introduced this stabilization does not take place, and the animal continues to gain weight.[7]

Stress and boredom are additional external factors that can increase food intake. Stress may stimulate appetite via increased release of endogenous corticosteroids or other orexigenic peptides.[8] The role of boredom is less understood but may increase appetite via forebrain mechanisms. Alternate, nonfood stimuli of the reward center may be helpful in managing this type of hyperphagia.

Differential Diagnosis

There are numerous causes of polyphagia and hyperphagia (Box 19-1). Polyphagia may be associated with weight loss, maintenance or gain, whereas physiologic hyperphagia is almost always associated with weight gain.

Evaluation of the Patient

History

Some common causes of hyperphagia can be identified on the patient's history. Pregnancy, lactation, outdoor housing in cold weather, or increases in exercise easily explain increased intake. Cold weather can increase energy requirements significantly. Neutering can cause an increase in food intake with associated weight gain. If no evidence exists to indicate pathologic polyphagia, a detailed dietary history may indicate physiologic or reward-driven hyperphagia (Fig. 19-1).

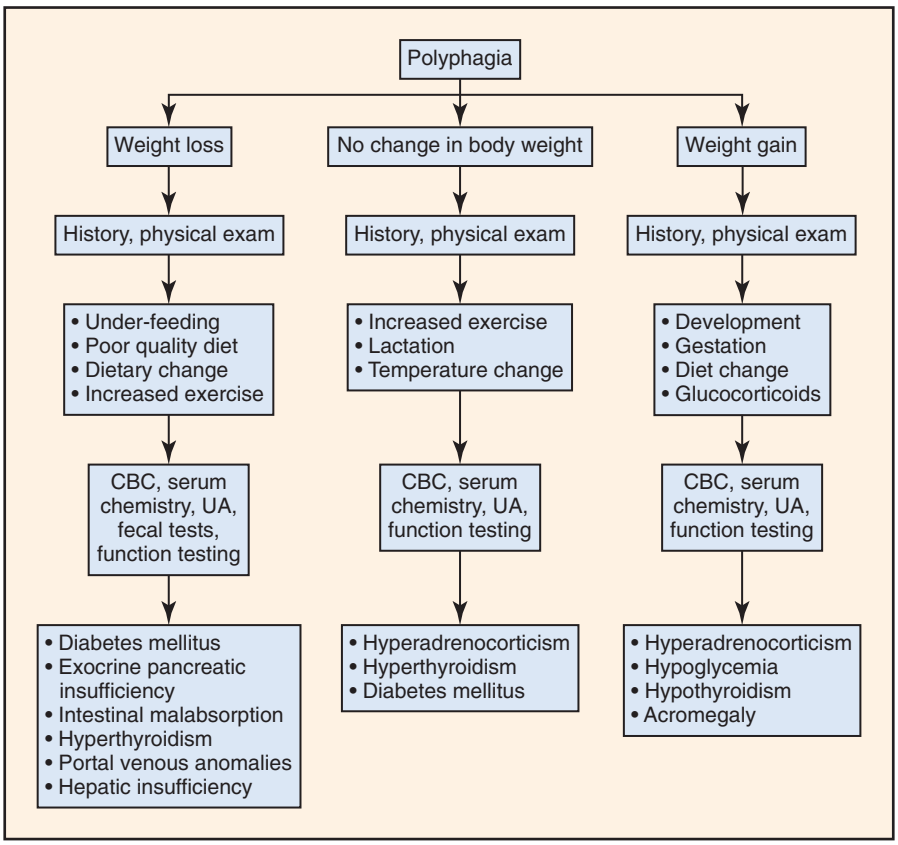

Figure 19-1 Diagnostic approach for the patient with polyphagia as the primary clinical sign. CBC, Complete blood count; UA, urinalysis.

Box 19-1 Common Causes of Hyperphagia and Polyphagia

Hyperphagia	Polyphagia
Cold weather	Diabetes mellitus
Exercise	Hyperadrenocorticism
Pregnancy or lactation	Hyperthyroidism
Neutering	Malabsorption syndromes
Reward driven	Exocrine pancreatic insufficiency
Stress	Drug induced
	Insulinoma
	Central nervous system diseases

Medical history should detect any recent changes in body weight. Polyphagia with weight loss is typically associated with diseases that decrease nutrient digestion and absorption or increase metabolism. Weight gain is common with drug-induced polyphagia (e.g., glucocorticoids) and conditions that increase food intake without altering energy metabolism. Other historical information critical in differentiation of polyphagia include evidence of drug use, polyuria/polydipsia, lethargy, diarrhea, and abnormal behavior (Table 19-1). Drugs recognized to induce polyphagia and weight gain include corticosteroids, anticonvulsants, some antihistamines and antidepressants.

Physical Examination

Physical examination may be normal or simply reflect abnormal body condition. Body weight change may not become manifested until late in the disease progression but is an important

Table 19-1 Differential Diagnoses for Polyphagia

Polyphagia and	Rule Out	Expect Weight
Polydipsia/polyuria	Diabetes mellitus	Loss
	Hyperthyroidism	Loss
	Acromegaly	Loss early/gain late
	Hyperadrenocorticism	Gain
	Sudden acquired retinal degeneration syndrome	Gain
Diarrhea	Exocrine pancreatic insufficiency	Loss
	Inflammatory bowel disease	Loss
	Malabsorption disorders	Loss
	Lymphangiectasia	Loss
	Intestinal parasites	Loss
	Hyperthyroidism	Loss
Ataxia	Central nervous mass lesion	Gain
	Insulinoma	Gain (loss in cats)
Vomiting or regurgitation	Megaesophagus	Loss
	Inflammatory bowel disease	Loss
	Antibiotic-responsive enteropathies	Loss

differentiating sign if present (see Fig. 19-1). Weight gain is common in physiologic hyperphagia, drug-induced polyphagia, and hyperadrenocorticism. Weight loss, especially with atrophy of lean body mass, suggests maldigestion or malabsorption of nutrients, compromised metabolism, or increased metabolic rate. Muscle wasting despite weight gain is suggestive of hyperadrenocorticism. Additional abnormalities may indicate specific underlying conditions. Abdominal palpation in animals with gastrointestinal disease may identify thickened bowel loops, abdominal effusions, masses, or abdominal pain.

Hyperthyroid cats usually have a palpable thyroid nodule and may have cardiac arrhythmias or a heart murmur. A potbellied appearance, symmetric alopecia, hyperpigmentation, and hepatomegaly are suggestive of canine hyperadrenocorticism. Acromegaly in cats and dogs is associated with broadened facial and body features plus prognathism. However, the insidious onset of these changes can make them difficult to recognize until very pronounced.

Central nervous system diseases causing polyphagia may cause ataxia or proprioceptive deficits. A complete neurologic examination should be performed to localize the lesion. Secondary neural signs may occur in patients with hypoglycemia due to insulinoma or hepatic encephalopathy (which rarely can cause polyphagia).

Laboratory Evaluation and Tests

If medical history and physical examination do not confirm a cause for polyphagia, diagnostic testing should be pursued based on clinical signs and weight loss or gain. In animals with polyphagia and weight loss but without other evidence of disease, fecal examination or empirical treatment with metronidazole or fenbendazole may first be attempted to treat presumed intestinal parasitism.

Initial laboratory testing should include hematology, serum biochemistry panel, and complete urinalysis. If gastrointestinal disease is suspected, eosinophilia may suggest undiagnosed intestinal parasites. Lymphocytopenia could be consistent with lymphangiectasia, as can be panhypoproteinemia (see Chapter 57). Chronic diarrhea, weight loss, and hypoproteinemia in the face of polyphagia are most consistent with small intestinal disease (see Chapter 57). Additional tests may be necessary to identify an underlying gastrointestinal cause of polyphagia. For example, intestinal biopsy can often diagnose inflammatory bowel disease or lymphangiectasia. Serum trypsin–like immunoreactivity is sensitive and specific for exocrine pancreatic insufficiency (see Chapter 60).

Endocrine causes of polyphagia can be differentiated on the basis on body weight changes and laboratory values. Hyperthyroidism and diabetes mellitus cause weight loss, while hyperadrenocorticism and insulinomas cause weight gain. Hyperthyroidism commonly produces a stress leukogram, elevations in hepatic enzyme activities, and high basal serum total thyroxine concentrations. Cats with mild hyperthyroidism may have total thyroxine (T_4) concentrations within the normal range, so repeated testing or measurement of serum free T_4 may be needed. Elevated fasting glucose plus polyuria, glucosuria, polyphagia, and weight loss strongly suggests diabetes mellitus. If preliminary findings suggest hyperadrenocorticism, increases in serum alkaline phosphatase, alanine transaminase, cholesterol, triglycerides, and mildly increased blood glucose might be observed. Glucosuria is uncommon but proteinuria common in dogs with hyperadrenocorticism. Specific testing for hyperadrenocorticism includes adrenocorticotropic hormone (ACTH) stimulation, low-dose dexamethasone suppression, and urine cortisol–creatinine tests. However, all of these tests can give false positives. Hypoglycemia with polyphagia is suggestive of insulinoma. Simultaneous, serial insulin and glucose measures or an amended insulin-to-glucose ratio test are used to confirm insulinoma.

Treatment and Management

Treatment varies with underlying disease. Correction of underlying pathology should resolve polyphagia. If underlying pathology cannot be determined or if a patient has drug-induced polyphagia but the drugs cannot be stopped, then weight management will depend on managing caloric intake.

Feeding a low-calorie, high-fiber diet in multiple small meals daily may aid in this regard. Dietary fiber promotes satiety via several routes, including gastric distention through physical bulk and water adsorption; delayed gastric emptying; reduced rate of intestinal transit; and slowed glucose absorption. This latter effect reduces postprandial fluctuations in glucose and insulin and their effects on hypothalamic satiety centers. High-protein diets also are recognized to enhance satiety, so they may be of value in polyphagic patients.[9]

In patients with physiologic hyperphagia and weight gain, client education is needed to alter feeding and behavioral conditions. Palatable foods upregulate expression of hunger signals while blunting the response to satiety signals and activating the "reward" system. Frequent changes in diet (e.g., new flavors, adding flavoring agents or table scraps or other encouragements) contribute to overeating; therefore, these practices should be halted. High-fiber, high-protein, and low-calorie diets can be used to aid satiety while reducing caloric intake and body weight.

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CHAPTER 20

Polyuria and Polydipsia

David J. Polzin

Definition

Polyuria (PU) is defined as excessive urine production and is confirmed by demonstrating that daily urine production exceeds the upper limit of normal. In dogs, daily urine volume should normally not exceed approximately 50 mL/kg/day.[1] Normal daily urine volume is lower in cats. Frequency of voiding is not incl uded in the definition of PU and may be normal or increased in patients with PU. It is essential that PU not be confused with pollakiuria, the frequent voiding of small quantities of urine.

Polydipsia (PD) is consumption of water in excess of the upper limit of normal daily intake. Normal water intake in dogs is usually less than 60 mL/kg/day with an upper limit of 100 mL/kg/day.[1] Because water consumption is easier to measure, it is often used to confirm PD. However, environmental and behavioral factors (e.g., ambient temperature, activity of the animal) may markedly alter water consumption in dogs and should be considered in interpreting these measurements.[2] Normal values for water intake are likely substantially less in cats, but a well-defined cutoff value has not been established.

Diagnosis of PU or PD should ideally be confirmed by measuring water intake and/or urine production rate. Because water intake is more easily and accurately measured than urine output, confirmation of PU or PD is often made by measuring daily water intake. Although PD is usually a reliable surrogate for confirming PU or PD, increased water loss via nonurinary pathways (e.g., diarrhea) may be associated with PD absent PU.

Polyuric patients should have reduced urine specific gravity values; therefore, urine concentration is often used as a surrogate for confirming PU. Patients that persistently produce urine less concentrated than expected (i.e., <1.030 for dogs and <1.035 for cats) should be evaluated for a possible pathologic defect in urine-concentrating ability.[3] In dogs, urine samples obtained in the morning immediately upon arising are typically the most concentrated and thus provide a more reliable estimate of urine concentrating ability.[4] Urinalysis should be performed to determine urine concentration in any patient in which the owner reports increases in water intake or urination, regardless of whether the actual measured water intake exceeds the upper limit for PD. Patients with documented PD that have concentrated urine should be evaluated for nonurinary water losses.

Pathophysiology and Mechanism

General Mechanisms Affecting Water Intake and Urine Volume

Urine concentration and water consumption (thirst) are controlled by interactions between kidneys, pituitary gland, and hypothalamus. Plasma osmolality (primarily sodium concentration) is the primary parameter monitored by this control system. Ingestion of a water load decreases plasma osmolality, while water loss from the body (by any route) increases plasma osmolality. Alterations in plasma osmolality are sensed by receptor cells (i.e., osmoreceptors) in the hypothalamus that affect water intake (via thirst) and excretion (via antidiuretic hormone acting on the kidneys). This system maintains plasma osmolality within a very narrow range.

The normal response to a water load is suppression of antidiuretic hormone (ADH) and thirst. In the absence of ADH, the renal collecting tubules are impermeable to reabsorption of water. In this setting, hypoosmotic tubular fluid leaving the loop of Henle does not equilibrate with renal medullary interstitium resulting in dilute urine, thus allowing elimination of the water load. When PU or PD results from excessive water consumption, plasma osmolality and sodium concentration tend to trend toward the lower end of the normal range.

Correction of a water deficit requires intake and retention of exogenous water. This occurs through increasing thirst and release of ADH in response to an increase in plasma osmolality. Thirst is the primary defense against hyperosmolality. In response to ADH, further loss of water by kidneys is minimized by transient insertion of water-permeable channels (i.e., aquaporin-2) into membranes of renal collecting tubules, thus allowing water to move along its osmotic gradient from lumen of collecting tubules into the hypertonic medullary interstitium producing concentrated urine. When PU or PD results from a defect in urine concentrating ability, plasma osmolality and sodium concentration may trend toward the higher end of the normal range.

In contrast, isoosmotic fluid loss (e.g., many gastrointestinal and urinary fluid losses) typically reduces effective circulating volume without altering plasma osmolality. This decline in effective circulating volume is termed *volume depletion* rather than dehydration. With volume depletion, both sodium and water retention are needed to correct the volume deficit. Sensors and response system

for maintaining effective circulating volume are predominantly focused on modifying renal sodium handling; fluid volume is regulated because water is retained or excreted with sodium.[5] Factors active in this process include the renin–angiotensin–aldosterone system, atrial natriuretic peptide (ANP), ADH, and activation of thirst.

Water Balance and Polyuria and Polydipsia

In the steady state, water intake must equal water output. Water intake includes ingested water, water obtained from food, and water generated endogenously through oxidation of carbohydrates, proteins, and fat. Water output is the sum of urine volume and "insensible losses," which includes water contained in stool as well as evaporative losses from the skin and respiratory tract. These insensible losses typically account for approximately 20 to 25 mL/kg/day; however, they may increase with diarrhea, tachypnea, or increased ambient temperature.[6] When insensible losses increase, water intake may increase without a coincident increase in urine volume.

Urine volume is related to water intake, obligatory solute excretion, and urine-concentrating ability. If water consumption increases or the quantity of solute to be excreted increases (e.g., diabetes mellitus or administration of mannitol), urine volume will increase. Furthermore, as capacity to concentrate urine declines, volume of urine required to excrete the same solute load will increase. For example, if maximum urine concentration is 600 mOsm/L, it will require 500 mL to excrete a solute load of 300 mOsm. However, if the maximum urine concentration is 300 mOsm/L, it will require 1 L to excrete 300 mOsm. This resultant increase in urine volume requires a compensatory increase in water intake.

General Mechanisms Promoting Primary Polyuria

Ability to conserve or excrete water requires (a) the ability to manufacture and appropriately secrete ADH, (b) maintenance of an appropriately hypertonic renal medulla (i.e., functional renal countercurrent mechanism), and (c) ability of kidneys to respond appropriately to ADH when present. Disruption of any of these processes may cause PU. In addition, an excess of nonreabsorbable solute in the glomerular filtrate and renal tubules (e.g., glucosuria in diabetes mellitus or with mannitol infusion) may also impair the urine-concentrating mechanism. In osmotic diuresis, medullary blood flow is enhanced by an unknown mechanism. This results sequentially in decreased renal papillary osmolality and an elevation in both urine volume and sodium excretion, primarily because of a fall in water reabsorption in the descending limb of the loop of Henle and sodium reabsorption in the ascending limb of the loop of Henle. PU may also occur when the thirst center in the anterior hypothalamus is stimulated resulting in PD. Thus, PU may result from four mechanisms: (a) inadequate production of functional ADH (i.e., central diabetes insipidus), (b) lack of appropriate renal response to ADH (i.e., nephrogenic diabetes insipidus), (c) osmotic diuresis, or (d) primary PD. In the first three of these mechanisms, PU is primary and PD is secondary or compensatory. In the last, PD is primary and the PU occurs as a secondary compensation to eliminate excess water consumed. Combinations of these various mechanisms may occur together in the same patient.

Differential Diagnosis

Table 20-1 summarizes various recognized causes of PU and PD. Many of the causes of PU or PD present with other clinical signs or laboratory abnormalities, which readily facilitate their diagnosis (Table 20-2). In most instances, the cause for PU or PD can be determined from information gathered from history, physical examination, a complete blood count, serum chemistry profile, and urinalysis. The most common causes of PU and PD in dogs include renal disease, hyperadrenocorticism, and diabetes mellitus, whereas the most common causes of PU in cats include renal disease, hyperthyroidism, and diabetes mellitus. Gastrointestinal disease and gastrointestinal leiomyosarcoma have been linked to PU and PD.[7-9] Figure 20-1 is an algorithmic approach to diagnosis.

Evaluation of the Patient

History

Before searching for a cause, the presence of PU or PD should be confirmed. A thorough history of the patient's drinking and urinating habits should be obtained. In particular, PU must be differentiated from pollakiuria (i.e., an abnormal increase in the frequency of urination). Patients with PU void large volumes of urine with relatively normal to moderately increased frequency of urination. In contrast, patients with pollakiuria void small quantities of urine at increased frequency. In addition, pollakiuria is often associated with other signs of lower urinary tract disease such as dysuria and stranguria. In rare instances, patients may simultaneously have both PU and pollakiuria. When PU and pollakiuria occur together, they may be of different origins (e.g., PU caused by diabetes mellitus and pollakiuria caused by concurrent urinary tract infection) or emanate from the same condition (e.g., urinary tract infection affecting the kidney causing PU and the bladder causing pollakiuria). Quantifying daily water intake will help support or refute the presence of PD. PU and PD may be confirmed by measuring 24-hour water intake or urine output; however, a 3- to 5-day collection period is recommended to increase reliability. In dogs, daily water consumption in excess of 100 mL/kg confirms PD. Normal water intake for cats is substantially less, but a precise upper limit has not been established. Alternatively, measuring urinary specific gravity may provide evidence of adequate urine-concentrating ability (dogs, 1.030; cats, 1.035), thus providing evidence against PU or PD. However, urine specific gravity values persistently below 1.030 in dogs or 1.035 in cats should be pursued as possible evidence of a defect in urine-concentrating ability, even when daily water intake does not confirm PU or PD.

A complete drug and diet history should be obtained to rule out the possibility of iatrogenic causes for PU or PD. Drugs that may promote PU or PD include diuretics, systemic or topical corticosteroids, and some anticonvulsant medications (e.g., phenobarbital, phenytoin). Diets designed for urolith dissolution or prophylaxis typically promote increased water intake and urine volume because of their high salt and low-protein content. Canned and high-salt diets may be associated with an increase in urine production while dogs and cats consuming dry diets may consume more water because they receive little dietary water; however, their urine volume is typically normal.

Onset, duration, and magnitude of change in water intake and urine volume as well as presence or absence of other clinical signs are of great value in delineating the causation of PU or PD. The patient's species, age, sex (including neutered versus intact), and breed may also provide clues to possible causes for PU or PD. Patients with PU or PD often, but not always, present with clinical signs providing clues to the underlying causes responsible for PU or PD (see Table 20-2). Conditions that may be characterized by PU or PD alone include mild kidney disease (e.g., stages I and II chronic kidney disease [CKD]), pyelonephritis, hyperadrenocorticism, hypercalcemia, leptospirosis, central diabetes insipidus,

Table 20-1 Ruleouts for Polyuria and Polydipsia in Dogs and Cats

Ruleout for PU and PD	Additional Tests Supporting Diagnosis
Renal disease	Glomerular filtration rate (GFR) measurement (creatinine or iothalamate clearance), imaging (ultrasound, radiographs)
Pyelonephritis	Urine culture, renal imaging (ultrasound, excretory urography), pyelocentesis (culture, cytology)
Leptospirosis	Serology and/or polymerase chain reaction (PCR)
Chronic partial urinary obstruction	Urinary tract imaging (ultrasound, contrast radiography)
Renal glucosuria or Fanconi disease	Fractional urinary excretion studies (urine amino acids, bicarbonate, glucose, magnesium, phosphate, potassium, sodium)
Primary nephrogenic diabetes insipidus	Failure to respond to ADH (usually an exclusion diagnosis, typically a congenital disorder)
Postobstructive diuresis	Evidence of recent urinary obstruction, serial declines in serum creatinine and urea nitrogen concentrations
Renal medullary solute washout	Seek underlying cause, response to gradual partial water deprivation
Diabetes mellitus	Serum fructosamine concentration
Hyperadrenocorticism	Adrenocorticotropic hormone (ACTH) response test or low-dose dexamethasone suppression test
Hyperthyroidism (cats)	Free thyroxine (T_4) by equilibrium dialysis, thyroid scan
Hypoadrenocorticism	ACTH response test
Primary hyperaldosteronism	Plasma aldosterone, plasma aldosterone-to-renin ratio, oral fludrocortisone suppression test (urinary aldosterone-to-creatinine ratio)
Central diabetes insipidus	ADH response test, water-deprivation test, imaging (magnetic resonance imaging [MRI] or computed tomography [CT])
Acromegaly	Feline plasma growth hormone concentration (± available), insulin-like growth factor-I concentrations, MRI or CT of the pituitary fossa
Pheochromocytoma	Blood pressure, abdominal ultrasound, urine catecholamine concentrations
Hypercalcemia	Blood ionized calcium concentration
Hypokalemia (marked)	
Hyponatremia (marked)	
Hepatic failure	Fasting and postprandial serum bile acids, imaging (ultrasound, radiographs)
Portosystemic shunt	Fasting and postprandial serum bile acids, imaging (abdominal ultrasound, portography, rectal scintigraphy)
Leiomyosarcoma	Imaging, endoscopy, biopsy
Gastrointestinal disease	Imaging, endoscopy, biopsy
Pyometra	Imaging (ultrasound, radiographs)
Polycythemia	
Pericardial effusion	Echocardiogram
Psychogenic (primary) PD	Multiple urine specific gravity determinations, ADH response test, water-deprivation testing
Paraneoplastic	Imaging (radiographs, ultrasound, CT or MR)
Sudden acquired retinal degeneration syndrome (SARDS)	Retinal examination, electroretinogram
Iatrogenic	

ACTH, Adrenocorticotropic hormone; ADH, anti-diuretic hormone; CT, computerized tomography; GFR, glomerular filtration rate; MRI, magnetic resonance imaging; PCR, polymerase chain reaction; PD, polydipsia; PU, polyuria; SARDS, sudden acquired retinal degeneration syndrome; T_4, thyroxine.

primary (psychogenic) PD, and renal tubular dysfunctions (e.g., primary renal glucosuria, Fanconi syndrome, nephrogenic diabetes insipidus). Note that some diseases may first manifest as only PU or PD, so absence of overt clinical signs do not rule out causes for PU or PD. For example, many dogs with hyperadrenocorticism-associated PU or PD do not present with typical cutaneous lesions.

Physical Examination

A thorough physical examination including assessment of neurologic status, retinal examination, and determination of blood pressure may facilitate identification of the cause for PU or PD. In many patients, physical examination can provide important clues that guide the diagnostic search for underlying causes for PU or PD (see Table 20-2). In addition, assessment of hydration and circulating volume status of the patient is essential to interpretation of renal function and urine specific gravity (urine concentrating ability).

Laboratory Evaluation and Tests

Urinalysis

Urinalysis can provide evidence of a urine-concentrating defect and may also help delineate the cause of PU or PD. Determining the urine specific gravity on several occasions helps define what is typical for this patient. Because urine is most likely to be maximally concentrated first thing in the morning in dogs, urine samples should be obtained at this time if possible.[4]

Urine specific gravity values above 1.030 in dogs and 1.035 in cats are generally inconsistent with PU or PD, although it does not exclude the possibility of intermittent PU or PD. In patients with dehydration or extracellular fluid volume contraction, urine should be adequately concentrated unless ADH activity is inappropriately low, the kidneys are unable to respond to ADH, or an osmotic diuresis is present. Patients with PU or PD will most often have urine specific gravity values between 1.001 and 1.025. The presence of osmotically active substances such as glucose,

Table 20-2 Medical History and Physical Examination Findings Providing Clues to Possible Causes for Polyuria and Polydipsia

Clinical Finding	Possible Ruleouts
Weight loss	Kidney disease, diabetes mellitus, hyperthyroidism, pyelonephritis, malignancy-induced hypercalcemia, hypoadrenocorticism, hepatic disease, pyometra
Polyphagia	Diabetes mellitus, hyperthyroidism, hyperadrenocorticism, acromegaly
Decreased appetite	Kidney disease, pyelonephritis, malignancy-induced hypercalcemia, hepatic disease, hypoadrenocorticism
Vomiting	Kidney disease, hypoadrenocorticism, pyelonephritis, hepatic failure, hypercalcemia, hypokalemia, hyperthyroidism, diabetes mellitus, consumption of excess water
Malaise and/or weakness	Kidney disease, hypoadrenocorticism, pyometra, hypercalcemia, diabetes mellitus, hepatic disease, hypokalemia, hyperadrenocorticism
Behavioral or central nervous system (CNS) signs (seizures, ataxia, stupor, blindness)	Hepatic failure, primary PD, central diabetes insipidus, hyperadrenocorticism, acromegaly, sudden acquired retinal degeneration syndrome (SARDS)
Marked PU or PD	Primary PD, central diabetes insipidus, congenital nephrogenic diabetes insipidus
Middle-aged female, recent estrus	Pyometra
Bilateral alopecia, skin disease	Hyperadrenocorticism or other endocrinologic disorders
Abdominal distention	Hepatic failure, hyperadrenocorticism, pyometra, nephrotic syndrome, bladder enlargement caused by PU
Hepatomegaly	Hyperadrenocorticism, diabetes mellitus, hepatic disease
Small kidneys	Chronic or congenital kidney disease
Hypertension, hypertensive retinopathy	Chronic kidney disease (CKD), hyperthyroidism, diabetes mellitus, hyperadrenocorticism
Uremic breath, uremic stomatitis	Kidney disease
Thyroid or neck mass	Hyperthyroidism, hyperparathyroidism, CKD
Heart murmur	Hyperthyroidism, CKD, acromegaly
Panting, tachypnea	Hyperadrenocorticism, hyperthyroidism, mediastinal mass (lymphoma), pheochromocytoma

CKD, Chronic kidney disease; CNS, central nervous system; PD, polydipsia; PU, polyuria; SARDS, sudden acquired retinal degeneration syndrome.

mannitol, or radiocontrast agents is often associated with urine specific gravity values at the higher end of this range and sometimes above 1.025.

Urinalysis may also provide evidence of the underlying cause for PU or PD. Urine chemistries may reveal evidence of glucosuria, bilirubinuria, or proteinuria. Urine sediment examination may reveal evidence of white blood cells, bacteria, crystals, or casts.

The Minimum Database and Additional Testing

A minimum database consisting of medical history, physical examination, urinalysis, serum chemistry profile, and a complete blood count should be routinely performed on patients with PU or PD. In middle-aged to older cats, a thyroxine (T_4) test should also be considered part of the minimum database. In many instances, this minimum database is sufficient to identify likely causes for PU or PD and further diagnostic tests may be pursued based on these findings (see Tables 20-1 and 20-2).

In both dogs and cats where the minimum database fails to localize the cause of PU or PD, a urine culture should be performed to rule out pyelonephritis. In dogs where the initial database fails to identify the cause for PU or PD, a leptospirosis titer or polymerase chain reaction (PCR) should be included (if locally endemic), and a screening test for hyperadrenocorticism should be considered for middle-aged to older dogs.

Water Deprivation and Antidiuretic Hormone Response Testing

Water deprivation is not indicated as part of the minimum database for patients with PU or PD and should generally be reserved for use only when all other reasonable diagnostic ruleouts have been excluded. As a general rule, water should not be withheld from patients with PU or PD of undetermined origin. When indicated, water deprivation testing should be performed under close supervision because patients with profound PU or PD may dehydrate rapidly (i.e., over several hours). It should never be performed by withdrawing water from the patient overnight. Mechanics of performing water deprivation are described elsewhere.[1,6]

Water deprivation is primarily indicated for differentiating primary PD from central diabetes insipidus (or, rarely, congenital nephrogenic diabetes insipidus) in patients with profound PU or PD and dilute urine. Urine specific gravity values persistently below 1.005 are suggestive of central diabetes insipidus, primary nephrogenic diabetes insipidus (congenital), or primary PD. Occasionally, patients with hyperadrenocorticism or hepatic failure may have urine specific gravity values in this range. It is recommended that water deprivation testing be reserved for patients suspected to have primary PD (see Fig. 20-1). Serum sodium concentration may help differentiate primary PD from primary PU in that the serum sodium concentrations often trend toward the low end of the normal range with primary PD (i.e., dilution induced by drinking of electrolyte-free water). In contrast, serum sodium typically trends from the midrange to high end of the normal range in patients with primary PU and secondary PD.

The goal of water deprivation testing is to stimulate maximum release of endogenous ADH to determine if normal concentration mechanisms are functioning. It is contraindicated in dehydrated patients and azotemic patients. Patients with primary PD should have the capacity to produce concentrated urine when water intake is withheld. However, results of this test may be clouded by

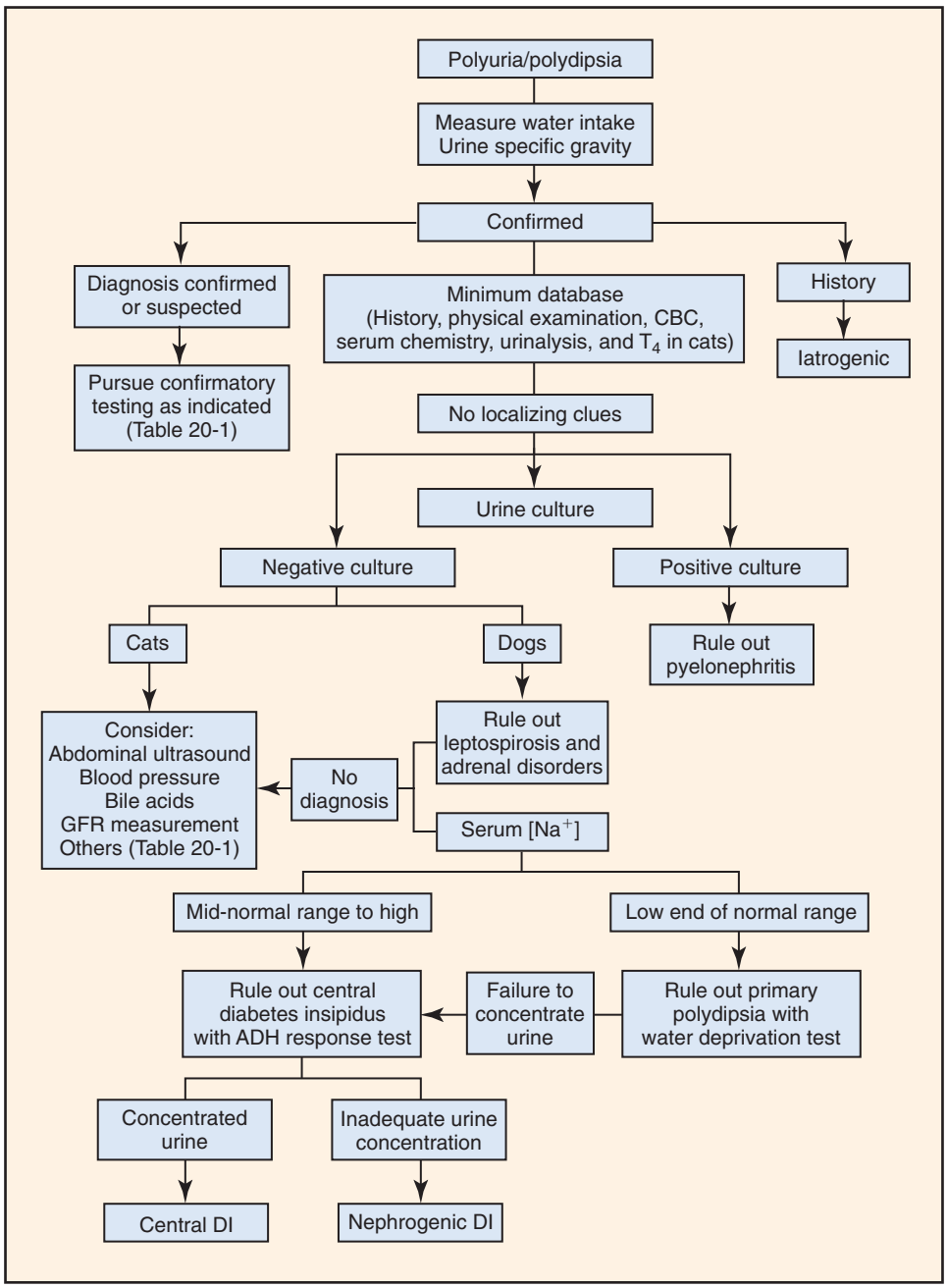

Figure 20-1 Algorithm demonstrating the diagnostic sequence recommended for establishing the diagnosis of PU and/or PD in dogs and cats. Tables 20-1 and 20-2 provide supplemental information useful in applying the algorithm to patients. ADH, Anti-diuretic hormone; CBC, complete blood count; DI, diabetes insipidus; GFR, glomerular filtration rate; T_4, thyroxine.

long-standing PU or PD where washout of renal medullary solute may limit the degree of urine concentration.

At the end of the water-deprivation test, water should be provided and an ADH analogue (e.g., desmopressin [DDAVP]) administered. If the patient has central diabetes insipidus, water deprivation should not result in urine concentration, but the urine should become concentrated after administration of ADH. However, as with primary PD, renal medullary washout may result in a less-robust increase in urine concentration.

An alternative to water-deprivation testing is to provide an ADH analogue to the patient for several days to determine if the urine becomes concentrated. If the urine becomes concentrated, the results suggest central diabetes insipidus. However, they do not completely exclude primary PD. A small risk with this approach is that exogenous administration of ADH will limit the ability to excrete water, and water intoxication may develop if the patient has primary PD and continues to drink excessively,.

Treatment and Management

General Principles

Polyuria and PD are often among the earliest clinical signs revealing presence of disease responsible for PU or PD (see Table 20-1). As such, treatment or management of PU or PD is usually directed at the primary disease responsible for PU or PD. For example, PU or PD caused by feline hyperthyroidism is managed by correcting

the hyperthyroid state. However, it may be impossible to eliminate the primary disease or defect in urine concentrating ability for some causes of PU or PD. For example, urine concentrating capacity cannot be restored for patients with chronic renal disease. In such instances, symptomatic treatment for PU or PD or its consequences may be desirable. Complications of PU or PD that may prompt consideration of symptomatic relief of PU or PD may include inappropriate voiding, nocturia, PU-associated litter box issues, or urinary incontinence.

Serious medical consequences are rare in patients with PU or PD if free access to water is available and the patient is willing and able to drink. Until the mechanism of PU has been established, owners should be discouraged from limiting access to water. In patients where PU or PD is driven by primary PU, dehydration and serious systemic consequences may develop when access to water is limited. If the patient is vomiting or other conditions limiting oral intake are present, fluids may need to be administered parenterally. Administration of parenteral fluids may also be required when dehydration persists despite ongoing PD.

Medical

Although medical therapy for PU or PD is generally directed at the underlying cause, in some conditions the primary cause for PU or PD cannot be eliminated and a defect in urine concentrating ability persists. In patients with limited urine concentrating ability, quantity of urine produced is largely determined by quantity of solute excreted in the urine. This is because solute excretion can only be increased by increasing urine concentration or increasing volume of water in which the solute is dissolved. However, by reducing the quantity of solute to be excreted, the magnitude of PU or PD can be diminished. This reduction in solute may be accomplished either by reducing the quantity of solute resulting from dietary intake or by reducing the quantity of sodium delivered to the distal nephron by enhancing proximal renal reabsorption of sodium. Potential benefits of such therapy may be to reduce magnitude of PU as well as its clinical consequences (e.g., nocturia, inappropriate voiding, litter box issues, urinary incontinence, PD).

Principal solutes present in urine are urea and sodium (salt). In patients with chronic renal disease, the magnitude of PU or PD may be reduced by feeding a diet containing reduced quantities of protein (the metabolic precursor of urea) and salt. However, this approach to management of PU or PD is only likely to be effective in patients where at least part of the mechanism of PU or PD is solute diuresis. Such patients typically have urine specific gravity values that are isosthenuric (1.008 to 1.012) or greater. In patients with congenital nephrogenic diabetes insipidus, magnitude of PU may be reduced by administration of thiazide diuretics, which induces a small degree of volume contraction. This in turn promotes enhanced proximal renal tubular reabsorption of sodium and water.

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CHAPTER 21

Regurgitation

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Definition

Regurgitation is the most important clinical sign of esophageal disease and should be differentiated from *dysphagia* and *gagging* of more proximal gastrointestinal disorders, and from vomiting of more distal gastrointestinal disorders. Regurgitation differs from *vomiting* in that it is characterized by the passive retrograde evacuation of undigested food from the esophagus. *Vomiting* is characterized by coordinated activities of the gastrointestinal, musculoskeletal, and nervous systems culminating in active evacuation of digested or partially digested food from the gastrointestinal tract.[1] *Vomiting* usually signifies disease caudal to the gastroesophageal sphincter. Severity of clinical signs with esophageal disease is dependent upon the pathogenesis of the disease. For example, animals with vascular ring anomaly may have severe regurgitation, but the appetite is usually excellent because of secondary malnutrition. On the other hand, animals with inflammatory esophageal disease may have *anorexia*, *dysphagia*, *odynophagia* (pain on swallowing), and *salivation* without much evidence of regurgitation. The latter group clearly presents a diagnostic challenge because of the differing clinical signs. For example, signs referable to aspiration pneumonia, *coughing* and *dyspnea*, may be the major presenting complaint in some animals. A good history usually elicits the other signs of esophageal disease in those patients.

Pathophysiology and Mechanisms

Transport of ingested liquids and solids from oral cavity to stomach is the major function of the esophagus. Anatomic structures that permit this function are striated muscle of the cranial esophageal sphincter (cricopharyngeus), striated and smooth muscle of the esophageal body, and smooth muscle of the caudal esophageal (gastroesophageal) sphincter. An important species difference between dogs and cats is in the musculature of the esophageal body. The full length of the canine esophageal body is composed of striated muscle, whereas the distal one-third to one-half of the feline esophageal body is composed of smooth muscle. Striated muscle of the cranial esophageal sphincter and esophageal body is innervated by somatic branches (glossopharyngeal, pharyngeal, and recurrent laryngeal) of the vagus nerve arising from the brainstem nucleus ambiguus. Smooth muscle of the esophageal body and caudal esophageal sphincter is innervated by autonomic branches (esophageal) of the vagus nerve arising from the dorsal motor nucleus of the vagus (see Figure 13-1).[2]

Anatomic and physiologic differences in canine and feline esophagus have been highlighted in several previous studies.[3-6] During fasting elevated pressures of the cranial and caudal esophageal sphincters prevent movement of food and chyme into the esophageal body from the oral cavity and stomach, respectively. When an animal swallows the cranial esophageal sphincter relaxes to permit movement of liquids and solids into the proximal esophageal body. Swallowing also initiates a wave of peristaltic contractions (primary peristalsis) in the esophagus that transports food into the distal esophageal body. Primary peristaltic contractions are reinforced by a secondary wave of contraction (secondary peristalsis) physiologically mediated by intraluminal distention. The caudal esophageal sphincter relaxes in advance of the propagated pressure wave to permit food to empty into the stomach. Once the bolus of food has passed into the stomach, the caudal esophageal sphincter resumes its high resting pressure.

Inflammation (esophagitis, gastroesophageal reflux, esophageal fistulae), *hypomotility* (idiopathic megaesophagus, dysautonomia, diverticula), and *obstruction* (stricture, hiatal hernia, neoplasia, intussusception, foreign bodies, vascular ring anomalies) are the major pathophysiologic processes involving the esophagus of dogs and cats.[7] With mild esophagitis and hypomotility lesions, the esophagus may undergo healing without further complication. In more severe cases the esophagus may respond with extensive fibrosis, muscular hypertrophy, esophageal narrowing, and/or loss of neural regulation (i.e., flaccidity). Luminal flow is directly related to the fourth power of esophageal radius so that even small diminutions result in significant reductions in esophageal transit.

Differential Diagnosis

Esophagitis

Esophagitis is an acute or chronic inflammatory disorder of esophageal mucosa that occasionally involves underlying submucosa and muscularis. It most often results from chemical injury from swallowed substances, esophageal foreign bodies, or gastroesophageal reflux. Esophageal mucosa has several important barrier mechanisms to withstand caustic substances, including stratified squamous epithelium with tight intracellular junctions, mucus gel, and surface bicarbonate ions. Disruption of these barrier mechanisms results in inflammation, erosion, and/or ulceration of the underlying structures.[8]

Gastroesophageal Reflux

Gastroesophageal reflux is a disorder of the caudal esophageal sphincter permitting reflux of gastrointestinal fluids or ingesta into the esophagus. Varying degrees of esophagitis result from prolonged contact of gastric acid, pepsin, trypsin, bile salts, and duodenal

bicarbonate with esophageal mucosa. The frequency of reflux and composition of the refluxed material determines the severity of the esophagitis. Gastric acid alone produces a mild esophagitis, whereas combinations of acid and pepsin or trypsin, bicarbonate, and bile salts produce a severe esophagitis.[9]

Esophageal Fistulae

An esophageal fistula is an abnormal communication between the esophagus and adjacent structures. Most esophageal fistulae involve the lungs or airway structures (e.g., esophagopulmonary, esophagobronchial, or esophagotracheal fistulae). Occasionally, esophageal fistulae expand into the pleural space or cervical tissues.

Idiopathic Megaesophagus

Idiopathic megaesophagus is the most common cause of regurgitation in the dog.[10] Aside from dysautonomia, megaesophagus is a rare finding in the domestic cat. The disorder is characterized by esophageal hypomotility and dilation, progressive regurgitation, and loss of body condition. Several forms of the syndrome have been described, including congenital, acquired secondary, and acquired idiopathic megaesophagus.

Dysautonomia

Dysautonomia is a generalized autonomic neuropathy that was originally reported in cats in the United Kingdom, but that has now been documented in dogs and cats throughout Western Europe and the United States.[11,12] Clinical signs reflect a generalized autonomic dysfunction but megaesophagus, esophageal hypomotility, and regurgitation are fairly consistent findings. Pathologically, degenerative lesions are found in autonomic ganglia, intermediate gray columns of the spinal cord, and some sympathetic axons. No definitive etiology has ever been established despite an intensive search for genetic, toxic, nutritional, and infectious etiologic agents.

Esophageal Diverticula

Esophageal diverticula are circumscribed sacculations in the esophageal wall that interfere with normal esophageal motility patterns. Both congenital and acquired forms have been described. Congenital diverticula have been attributed to abnormalities in embryologic development that permit herniation of mucosa through a defect in the muscularis. Acquired diverticula are subdivided into either traction or pulsion forms, depending upon pathogenesis. Traction diverticula tend to develop in the cranial and midesophageal body and result from periesophageal inflammation and fibrosis. Adhesions to adjacent tissue (e.g. lung, bronchus, lymph node) distort the esophageal lumen and create sacculations. Abscess development from grass awn migration is a common cause of traction diverticula in the western United States. Pulsion diverticula develop in association with increases in intraluminal esophageal pressure, abnormal regional esophageal motility, or when normal peristalsis is obstructed by a stenotic lesion.[13]

Esophageal Stricture

Esophageal stricture is an abnormal narrowing of the esophageal lumen. The most important etiologies of stricture are chemical injury from swallowed substances, esophageal foreign bodies, esophageal surgery, and intraluminal or extraluminal mass lesions (neoplasia or abscesses). Anesthesia, poor patient preparation, and poor patient positioning during anesthesia place some animals at risk for gastroesophageal reflux, esophagitis, and subsequent stricture formation.[14] Cats appear to be particularly susceptible to doxycycline-associated esophagitis and esophageal stricture.[15]

Hiatal Hernia

Two types of hiatal hernia have been recognized in the dog and cat: (a) sliding hiatal hernia, in which the abdominal segment of the esophagus and parts of the stomach are displaced cranially through the esophageal hiatus; and (b) paraesophageal hiatal hernia, in which the abdominal segment of the esophagus and caudal esophageal sphincter remain in a fixed position but a portion of the stomach herniates into the mediastinum alongside the thoracic esophagus. Sliding hiatal hernia is the most common form and may occur as a congenital or acquired lesion in the dog and cat.

Esophageal Neoplasia

Esophageal cancer accounts for less than 0.5% of all cancers in the dog and cat.[13] Tumors of the esophagus may be of primary esophageal, periesophageal, or metastatic origin. The most common primary esophageal tumors in the dog are osteosarcomas and fibrosarcomas, particularly in areas of *Spirocerca lupi* endemicity. *Spirocerca* esophageal granulomas may undergo metaplastic or neoplastic transformation to fibrosarcomas and osteogenic sarcomas. Squamous cell carcinoma is the most common primary esophageal tumor in the cat. Less commonly reported primary esophageal tumors of the dog and cat include leiomyo(sarco)mas, scirrhous carcinomas, melanomas, and adenocarcinomas. Metastatic lesions appear to be the most common esophageal tumors in dogs and cats and include thyroid, pulmonary, and gastric carcinomas.

Esophageal Foreign Bodies

Esophageal foreign bodies are a frequent clinical problem in dogs and cats. The most common esophageal foreign bodies found in dogs are bones, bone fragments, and monetary coins, whereas play objects are more commonly found in cats. Many foreign bodies are regurgitated or transported into the distal gastrointestinal tract, but others remain lodged in the esophageal body. Those that are too large to pass through the esophagus cause mechanical obstruction. The severity of esophageal damage is dependent upon foreign body size, angularity or sharp points, and the duration of obstruction.[16]

Vascular Ring Anomalies

Vascular ring anomalies are congenital malformations of major arteries of the heart that, because of altered anatomic relationships, entrap the esophagus and trachea. Persistent right aortic arch, persistent right or left subclavian arteries, persistent right dorsal aorta, double aortic arch, left aortic arch and right ligamentum arteriosum, and aberrant intercostal arteries have been described in both dogs and cats.[13] Persistent right aortic arch is the most common vascular ring anomaly found in dogs and cats.

Gastroesophageal Intussusception

Gastroesophageal intussusception is a rare condition of young dogs (most younger than 3 months of age) resulting from invagination of stomach into the esophagus, with or without other abdominal organs (e.g., spleen, duodenum, pancreas, omentum).[17] Many affected animals have preexisting esophageal disease, most importantly idiopathic megaesophagus. The role of idiopathic megaesophagus in the pathogenesis of gastroesophageal intussusception is not well understood, but it may be that the greatly enlarged capacity of a dilated esophagus accommodates invagination of the stomach through the diaphragmatic hiatus. Gastroesophageal intussusception is a true gastrointestinal emergency that may culminate in death if untreated.

Evaluation of the Patient

History

A careful history is useful in differentiating clinical signs of esophageal disease from oral, pharyngeal, and gastric disease, and in planning diagnostic tests needed in evaluation of the patient. Signs consistent with esophageal disease include regurgitation, odynophagia (painful swallowing), dysphagia (difficulty in swallowing), multiple swallowing attempts, excessive salivation (particularly with inflammatory disorders), and changes in appetite (ravenous appetite with motility disorders or reduced appetite with inflammatory disorders).

Physical Examination

Physical examination findings may be minimal in some animals with primary esophageal disease. Severe regurgitation and malnutrition may result in mild to moderate cachexia. Fever and pulmonary crackles or wheezes occur in association with aspiration pneumonia. An occasional foreign body or esophageal dilation may be detected during examination. Physical examination is important from the standpoint of excluding other gastrointestinal or systemic disease.

Laboratory Evaluation and Tests

Figure 21-1 outlines an approach to diagnosis of regurgitation associated esophageal disease. Initial laboratory testing should include routine hematology, serum biochemistry, urinalysis, and fecal parasitologic examination. This database will be useful in excluding systemic or metabolic disease as a cause of secondary esophageal signs. In the absence of systemic or metabolic disease, hypoproteinemia (associated with malnutrition) and leukocytosis (associated with esophageal inflammation or aspiration pneumonia) are the only laboratory abnormalities that are sometimes encountered. Hyponatremia and hyperkalemia may be evident in animals with Addison's disease and secondary megaesophagus.

Survey radiography, contrast radiography, fluoroscopy, and esophageal endoscopy are diagnostic methods currently available in modern veterinary practice. Survey radiography of the neck and thorax should be performed in all animals suspected of having

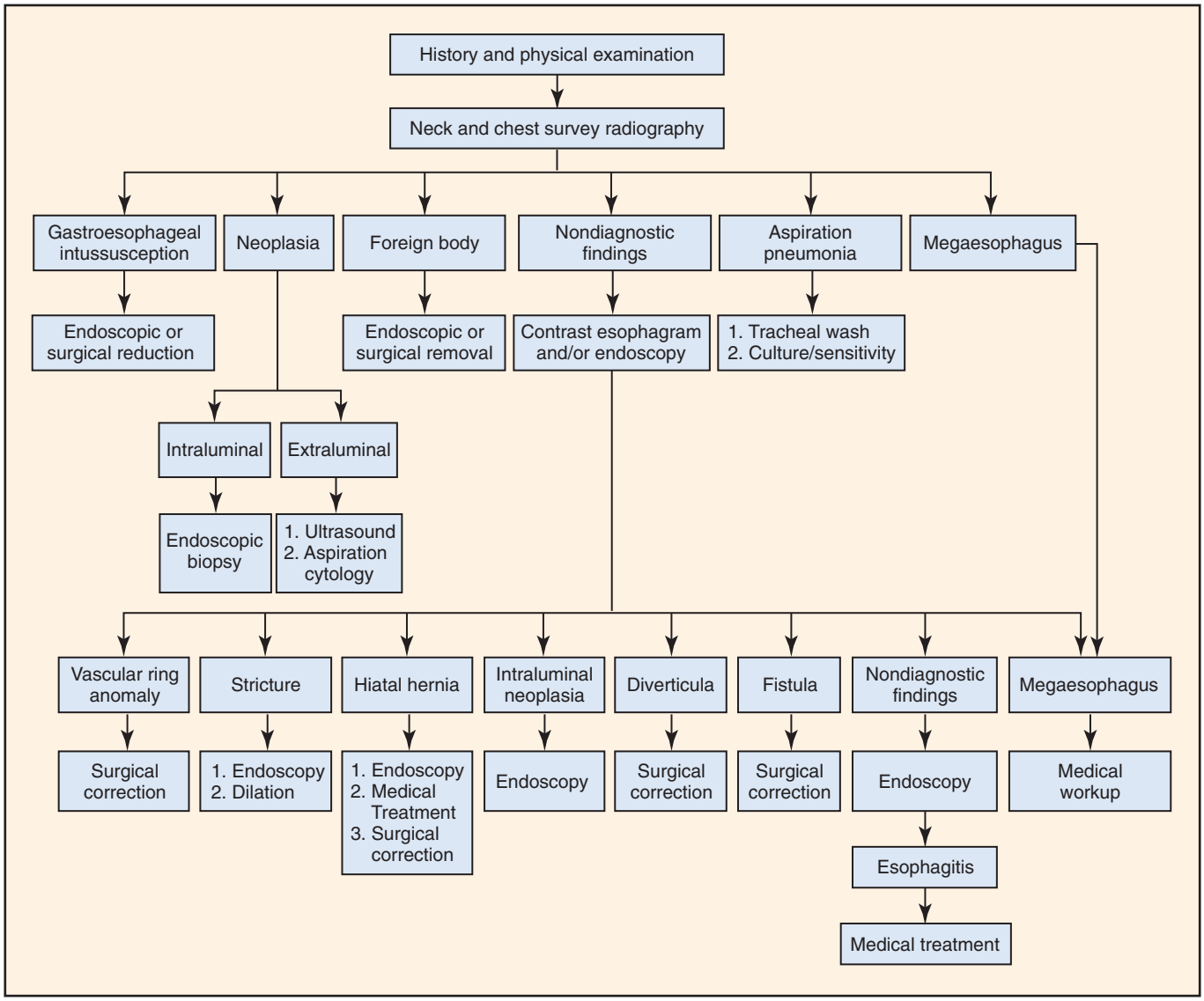

Figure 21-1 General diagnostic and therapeutic approach to regurgitation.

esophageal disease. Definitive diagnosis or evidence in support of a diagnosis may be obtained with survey radiographs in many cases, including esophageal foreign body, megaesophagus, neoplasia, hiatal hernia, and gastroesophageal intussusception. Thoracic radiographs will also identify some of the complications of esophageal disease, including aspiration pneumonia, pleural effusion, mediastinitis, and pneumothorax.

Contrast radiography and fluoroscopy can be performed to identify esophageal lesions or to confirm a tentative diagnosis. Disorders not readily diagnosed by survey radiography (e.g., radiolucent foreign body, esophagobronchial fistula, esophagitis, diverticula, and stricture) may be more readily diagnosed by contrast radiography. Dynamic contrast studies (i.e., videofluoroscopy) should be used instead of static barium radiographs whenever possible. In addition to structural information, dynamic studies will provide some information about esophageal motility. Contrast studies may be performed using barium paste (80% to 100% weight/volume), barium suspension (30% weight/volume), barium-coated meals, or iodinated contrast agents. The choice of a specific contrast agent depends upon which esophageal disease is suspected.

Esophageal endoscopy has become a very useful tool in diagnosis and treatment of esophageal disease. Usually performed after survey radiographic assessment, endoscopy and biopsy are particularly useful in diagnosing esophageal stricture, esophagitis, intraluminal mass, foreign body, and diverticula.[18] Endoscopy may also be used therapeutically to remove foreign bodies, to dilate esophageal strictures, or to place gastrostomy feeding tubes.

Ultrasonography has proved useful in diagnosis of periesophageal masses or other mediastinal disease. Esophageal manometry is useful for diagnosing cricopharyngeal achalasia, generalized esophageal motility disorders, and caudal esophageal sphincter incompetence, but the technique is currently only performed at major referral centers and university teaching hospitals. Nuclear scintigraphy and esophageal pH monitoring have also been used to diagnose esophageal motility disorders and gastroesophageal reflux, respectively.

Treatment and Management

General Principles

Animals with inflammatory conditions of the esophagus may be managed on an outpatient basis. Oral food intake should be withheld for 2 to 3 days in cases of mild esophagitis. Animals with more severe esophagitis (e.g., complete anorexia, dehydration, aspiration pneumonia) may require hospitalization. Food and water should be withheld in such cases, and animals may need additional nutritional maintenance either by enteral or total parenteral nutrition.

Medical (Drugs and Diet)

Because dietary fat delays gastric emptying and reduces caudal esophageal sphincter pressure, animals should be fed fat-restricted diets. Pet owners should also avoid late-night feedings because this would tend to reduce caudal esophageal sphincter pressure during sleep. In addition to nutritional considerations, rational medical therapy for this disorder includes diffusion barriers (e.g., sucralfate), gastric acid secretory inhibitors (e.g., cimetidine, ranitidine, famotidine, or omeprazole), and prokinetic agents (e.g., metoclopramide). Diffusion barriers are perhaps the most important medical therapy in gastroesophageal reflux. Sucralfate (0.5 to 1.0 g PO, TID) protects against mucosal damage from gastroesophageal reflux and promotes healing of existing esophagitis. Refractory cases of gastroesophageal reflux should also be medicated with acid secretory inhibitors and/or prokinetic agents. The H_2 histamine receptor antagonists such as cimetidine (5 to 10 mg/kg PO or IV, TID-QID), ranitidine (1.0 to 2.0 mg/kg PO or IV, BID-TID), and famotidine (0.1 to 0.5/mg/kg PO or IV, BID) inhibit gastric acid secretion and reduce the amount of acid reflux. Omeprazole (1 to 2 mg/kg PO, QD), an H^+,K^+-adenosine triphosphatase (ATPase) inhibitor, pantoprazole (1 mg/kg IV), lansoprazole (1 mg/kg IV), esomeprazole (1 mg/kg IV) could also be used to inhibit gastric acid secretion. Metoclopramide (0.2 to 0.4 mg/kg PO, TID-QID) and erythromycin (0.5 to 1.0 mg/kg PO, BID-TID) may be useful in treating gastroesophageal reflux because they increase caudal esophageal sphincter pressure. Serotonin (5-HT_4) agonists like cisapride also increase tone in the caudal esophageal sphincter, but cisapride has since been withdrawn from several international markets.[13]

Surgical

Surgical excision and repair provide the most successful outcomes in animals with esophagobronchial fistula, esophageal diverticula, vascular ring anomalies, some esophageal neoplasia, gastroesophageal intussusception, and hiatal herniae. Surgical cardiomyotomy (myotomy of the caudal esophageal sphincter) has been recommended in the past as a therapeutic measure in the belief that canine megaesophagus is similar to human achalasia. Because most studies have reported normal caudal esophageal sphincter tone and appropriate relaxation with swallowing, cardiomyotomy cannot be recommended for treatment of this disorder. Indeed, animals treated with myotomy generally have had poorer outcomes than untreated animals.

Nonsurgical

Esophageal strictures are best managed with mechanical dilation. Dilation may be achieved with balloon dilation catheters or bougienage tubes. Balloon dilations are safer and more effective in applying radial forces to expand the stricture site. Anecdotal opinion suggests that balloon dilations may be safer and more effective in applying radial forces to expand the stricture site. One recent study suggests that bougienage may be applied with increased risk of esophageal pathology or perforation (see Chapter 55).[14,19]

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CHAPTER 22

Salivation

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Definition

True ptyalism is an increase in production of saliva by one or more salivary glands. Pseudoptyalism is the inability of the patient to swallow normal amounts of saliva due to a disease process. There are many causes of ptyalism and pseudoptyalism, including oral trauma, oral cavity disease, toxin ingestion, salivary gland disorders, neoplasia, gastrointestinal tract disorders, metabolic and systemic disease, infectious diseases, neurologic disease, developmental anomalies, and behavioral responses. Excessive salivation is considered a normal finding in some dog breeds (e.g., Saint Bernard, Dogue de Bordeaux, and Mastiff).

Pathophysiology and Mechanisms

Excessive salivation is a common clinical finding in patients with disease of the oral cavity, and is usually as a consequence of pain, inflammation, and obstruction (see Chapter 54). Trauma patients, such as those with mandibular fracture, have concurrent disruption in the normal mechanisms of swallowing. Ingested toxins may have both direct noxious effects on saliva production and indirect effects through inflammation of mucosal surfaces. Primary salivary gland disorders (e.g., necrosis, inflammation, cancer) usually provoke an increase in secretion of saliva, although some salivary disorders may be associated with a decrease in saliva production. Neoplasia affecting structures of the oral cavity, oropharynx, and esophagus will interfere with normal swallowing mechanisms resulting in pseudoptyalism. True ptyalism is a common clinical sign with gastrointestinal, metabolic, and systemic disease, and involves activation of humoral and neural pathways for nausea and vomiting (see Chapter 23). Many of the infectious diseases, including viral, bacterial, rickettsial, and protozoal infections, can have direct or indirect effects on saliva production. Central nervous system disorders either increase salivation (e.g., meningitis) or interfere with normal swallowing function (e.g., trigeminal neuropathy).

Differential Diagnosis

The DAMNIT system of disease classification can be used to systematically consider the most important differential diagnoses for ptyalism[1-11] and pseudoptyalism:

- **D,** *Degenerative, Drug-Induced, and Developmental*—Some drug-induced disorders of ptyalism result from ingestion of unpleasant tasting medications (e.g., metronidazole in cats), whereas others (e.g., erythromycin in dogs) activate the humoral pathway for nausea, salivation, and vomiting. Developmental anomalies such as lip folds and malocclusions will often be accompanied by pseudoptyalism.
- **A,** *Anatomic, Allergic, Autoimmune*—Generalized idiopathic megaesophagus and gastric dilation/volvulus syndrome have documented distal effects on normal swallowing function resulting in pseudoptyalism. Some of the autoimmune disorders, such as pemphigus vulgaris, involve the mucous membranes as well as the skin resulting in both true ptyalism and pseudoptyalism.
- **M,** *Metabolic, Mechanical*—Any of the metabolic disorders (e.g., renal, hepatic, endocrine) may be accompanied by humoral activation of nausea, salivation, and vomiting. True fever and hyperthermic reactions directly stimulate panting, salivary secretion, and evaporative cooling. Bony fragments and other foreign bodies lodged in the soft palate, oropharynx, and proximal esophagus directly stimulate salivary secretion.
- **N,** *Nutritional, Neoplastic, Neurologic*—Incubation of pancreatic enzyme supplements in the food of dogs with exocrine pancreatic insufficiency may induce a severe inflammatory response of the oral cavity and true ptyalism. Cancers of the oral cavity, particularly squamous cell carcinomas in cats, induce true and pseudoptyalism (Fig. 22-1). Central nervous system disorders such as facial paralysis, seizure disorders, vestibular disease, and cranial nerve lesions may interfere with normal swallowing function. An unusual form of phenobarbital-responsive ptyalism has been reported in the dog that has been analogized to limbic epilepsy. Although poorly understood, behavioral responses or reactions may interfere with normal swallowing function (Fig. 22-2).
- **I,** *Inflammatory, Infectious, Immune-Mediated*—Caudal stomatitis in cats (see Fig. 22-3) and chronic ulcerative paradental stomatitis in dogs (Figs. 22-4 and 22-5) are important causes of true ptyalism. Severe untreated oral, esophageal, and gastric inflammation may progress to erosion and ulceration inducing both true and pseudoptyalism. Viral infections (e.g., rabies, pseudorabies, calicivirus, and herpes viruses), bacterial infections (e.g., tetanus, botulism, *Bordetella*), and periodontal disease (Fig. 22-6) may be associated with voluminous aqueous or mixed aqueous-mucoid salivary secretions. Almost any disease of the salivary gland (e.g., sialocele, foreign body, abscessation, trauma, necrosis, neoplasia, hyperplasia,

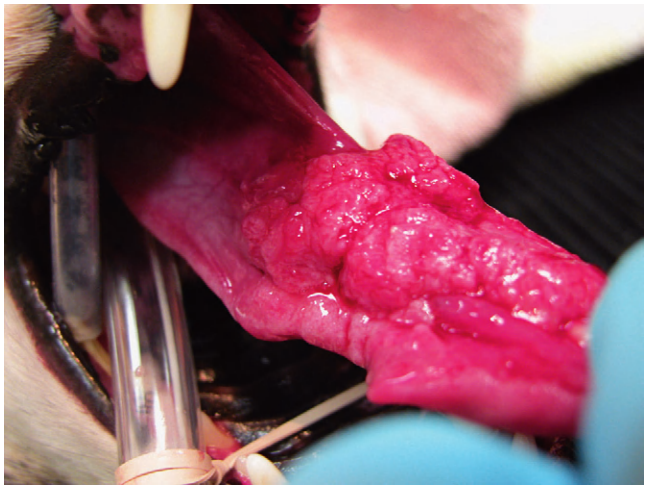

Figure 22-1 Intraoral photograph illustrating a lingual neoplastic mass.

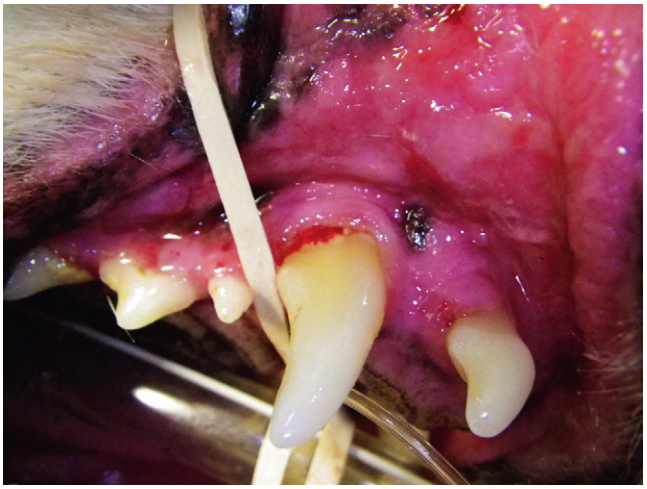

Figure 22-4 Intraoral photograph illustrating severe chronic ulcerative paradental stomatitis (CUPS) in a dog.

Figure 22-2 Ptyalism induced by anxiety associated with a visit to the veterinary hospital.

Figure 22-5 Chin dermatitis secondary to chronic ulcerative paradental stomatitis (CUPS)-associated hypersalivation in a dog.

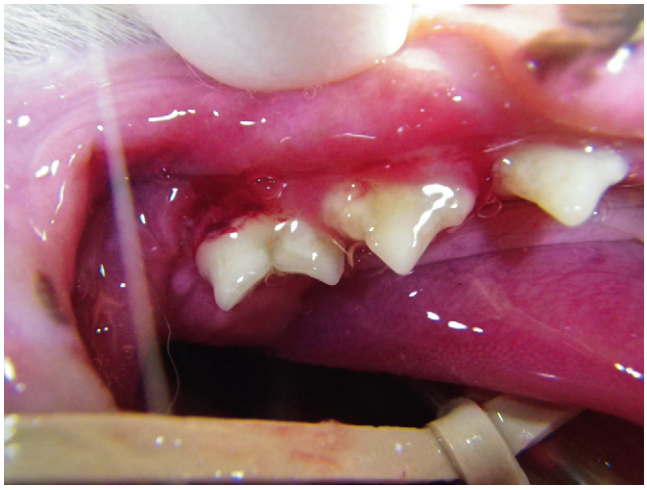

Figure 22-3 Intraoral photograph illustrating severe caudal stomatitis in a cat with secondary hypersalivation.

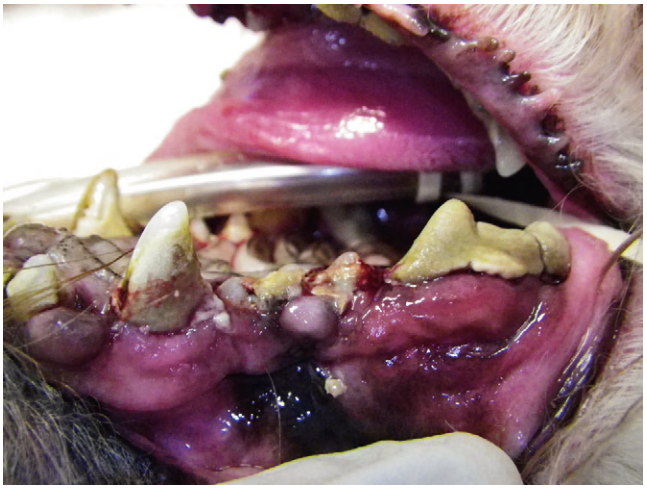

Figure 22-6 Intraoral photograph of a dog with severe periodontal disease and secondary ptyalism.

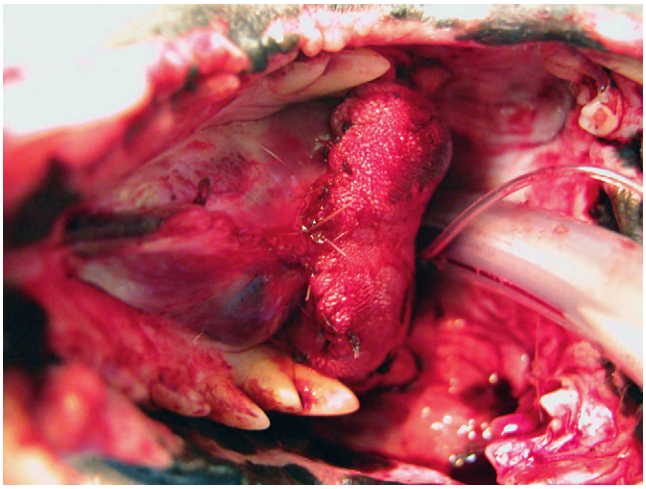

Figure 22-7 Postglossectomy image of the patient in Figure 22-1.

necrotizing sialometaplasia) is associated with moderate to severe true ptyalism.

- **T,** *Traumatic, Toxic*—Mandibular and maxillary fractures, temporomandibular joint luxation, and traumatic and electrical injuries stimulate salivary secretion from one or more of the salivary glands. Postmaxillectomy, mandibulectomy, and glossectomy patients (Fig. 22-7) all have predictable true and pseudoptyalism. Excessive salivation will regress with soft tissue and bony healing. Organophosphates, toxic mushrooms, caustic material, and insect bites are all associated with true ptyalism.

Evaluation of the Patient

History

Obtaining a thorough history will be essential to diagnosing the cause of true or pseudoptyalism. Important questions should include:

1. What is the age of the patient?
   Common causes for younger patients include foreign body or toxin ingestion, as well as burn injuries. Younger pets are also more likely to be affected by a viral infection or congenital abnormality. Older pets are more likely to be affected with metabolic, immune-mediated, and neoplastic diseases.
2. Is the condition acute, subacute, or chronic?
   Acute onset is more likely caused by viral infections, toxin exposures, and oral trauma. A more gradual onset is usually a result of severe periodontal disease, neoplasia, or metabolic disorders.
3. Are there concurrent clinical signs with particular reference to the gastrointestinal and respiratory tracts?
   Is the patient showing clinical signs of vomiting, coughing, gagging, or regurgitation? Vomiting associated with ptyalism generally has a gastrointestinal, neurologic, or metabolic origin. Idiopathic megaesophagus should be suspected in cases where regurgitation is reported. Gagging and coughing may be associated with foreign bodies or neoplasia of the oral cavity or oropharynx.
4. Does the animal have difficulty with prehension, mastication, bolus formation, or swallowing of water or food?
   Oral pain may interfere with feeding behavior because of the animal's reluctance to mobilize the structures of swallowing. Temporomandibular joint luxations and mandibular fractures can result in malocclusions that prevent closure of the mouth. Difficult swallowing (dysphagia) can result from any number of painful or neurologic disorders (see Chapters 13 and 54).
5. Is there any known exposure to toxins?
   Work around the household, including new carpeting, painting, construction, or carpet cleaning, should be queried. The use of flea and tick products or other chemicals should also be questioned.
6. Is the patient currently being treated with any other medications?
   A thorough inventory of medications and supplements should be developed, particularly complementary and alternative therapies.
7. Has there been any recent surgery or other nonsurgical trauma?
   Animal fights, other injuries, and dental, oral, and gastrointestinal surgeries should be queried.

Physical Examination

Complete physical and oral exams should be performed on the patient (Fig. 22-8). Oral cavity should be noted and detailed, including missing teeth, oral masses, fractured teeth, severe inflammation, and periodontal disease. The tongue should be elevated to look for sublingual swelling. Lymph nodes and salivary glands should be palpated for irregularities and size. Range of motion of the mandible should be assessed while simultaneously noting crepitus or discomfort. Neurologic exam of the head and neck should be performed particularly if clinical signs of gagging and dysphagia, are described. Assessing color and consistency of saliva may help to narrow the list of differential diagnoses. Presence of blood or purulent material in saliva suggests infection, neoplasia, and trauma as more likely diagnoses. Some patients may have severe pain associated with inflammation, foreign body, infection, or cancer involving structures of the oral cavity, thereby preventing direct observation without analgesia, sedation, or anesthesia.

Laboratory Evaluation and Tests

Cytology and culture of the saliva are generally unrewarding because of the complex nature and mixed flora of the oral cavity.[7] A minimum database should be obtained, including complete blood count, serum chemistry, serum thyroid hormone concentrations, and urinalysis. The initial data base may identify need for further medical investigation including function tests or imaging studies. Lesions of the oral cavity should be surgically biopsied under general anesthesia and submitted for histopathology. It is important to obtain a biopsy sample that contains a good representation of the lesion. While the patient is under anesthesia, intraoral dental radiographs should be obtained to look for evidence of disease below the gum line. Advanced imaging of head and neck via magnetic resonance imaging (MRI) or computerized tomography (CT) may be needed to rule out complicated causes of ptyalism. Additional diagnostic tests may be required once oral and maxillofacial disorders have been excluded from the list of differential diagnoses. These may include thoracic and abdominal radiographs, abdominal ultrasound, and endoscopy.

Treatment and Management

Syndromes of hypersalivation are quite often secondary to disease processes unrelated to structures of the oral cavity and oropharynx. In these cases, treatment and management should address the underlying cause (outlined in Chapters 54 to 61).

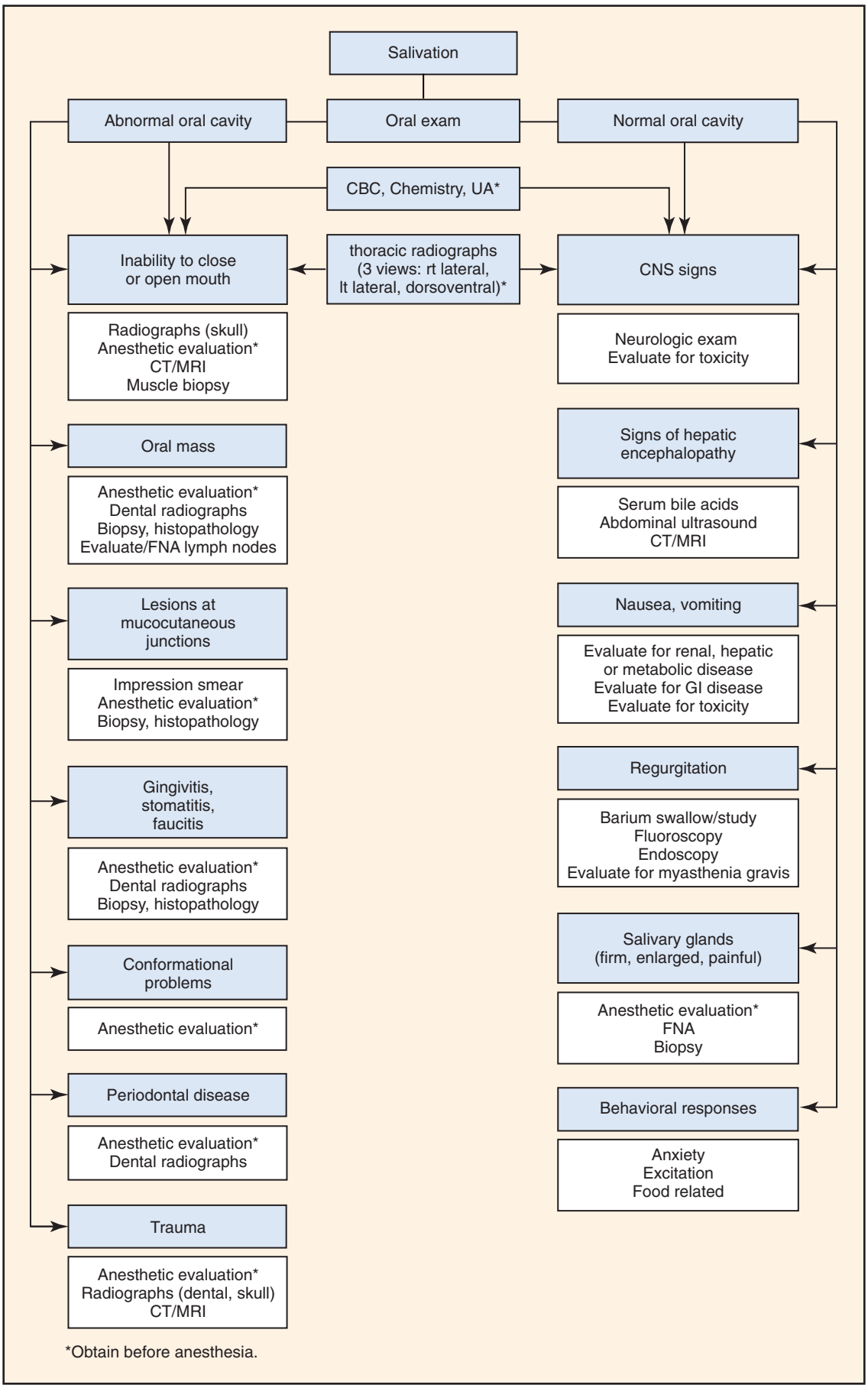

Figure 22-8 Algorithm for diagnosing salivation. CBC, complete blood count; chem, serum chemistry; CNS, central nervous system; CT, computed tomography; FNA, fine-needle aspiration; GI, gastiointestinal; MRI, magnetic resonance imaging; UA, urinalysis.

In cases where salivary glands are the primary cause of ptyalism, surgical removal of one or more of the affected glands is the treatment of choice.[8,9] Short-term treatment of hypersalivation may be achieved medically with the use of a muscarinic antagonist such as atropine or glycopyrrolate.[10] Cheiloplasty can be performed to help eliminate excessive drooling caused by lip malformation, mandibulectomy, glossectomy, or neurologic disorders of swallowing.[11]

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CHAPTER 23

Vomiting

Robert J. Washabau

Definition

Vomiting or emesis is a complex reflex pathway that has evolved to protect animals from ingested toxins, but it holds greater importance because of the large number of medical conditions that may cause or be associated with it (Box 23-1).[1,2] Emesis may occur with such diverse conditions as systemic (septicemia, multiple organ failure), metabolic (uremia, liver failure), and endocrine (hyperthyroidism, hypoadrenocorticism) disease, as well as with inflammatory, infectious, neoplastic, obstructive, and toxicologic disorders of the gastrointestinal tract, pancreas, liver, and biliary tract. In each of these circumstances, vomiting is believed to be activated through a neural or humoral mechanism.[3,4]

Pathophysiology and Mechanisms

Physiology of Vomiting: Humoral and Neural Pathways

The first mechanistic studies of vomiting were carried out by Borison and Wang in the early 1950s.[3,4] Borison and Wang postulated a two-component model of vomiting involving activation of a humoral or neural pathway (Fig. 23-1). In the Borison–Wang model, vomiting was postulated to occur through activation of chemoreceptor trigger zone (CRTZ) by bloodborne substances (*humoral pathway*), or through activation of emetic center by vagosympathetic, CRTZ, nucleus tractus solitarius, vestibular, or cerebrocortical neurons (*neural pathway*). Through a complicated series of experiments, Borison and Wang showed that activation of CRTZ by circulating emetogenic substances (e.g. uremic toxins, cardiac glycosides, endotoxins, and apomorphine) could be abolished by CRTZ antagonism, but not by vagotomy, sympathectomy, or emetic center antagonism. At the same time, neural activation of emetic center by gastrointestinal disease (e.g., inflammation, infection, obstruction, toxicity, etc.) could be abolished by vagotomy, sympathectomy, and emetic center antagonism, but not by CRTZ antagonism. Thus, vomiting was most easily explained by two independent mechanisms—one mechanism involving an essentially neural pathway, the other mechanism operating through a humorally dependent pathway.[3,4] The Borison–Wang two-component model has helped to explain many of the vomiting disorders of animals and humans. The model is not without challenge. It has been suggested that there are parallel mechanisms for initiation of emesis in response to any stimulus, and it is the sum of the inputs that drives the emetic response.[5] In other words, emesis need not be simply an either/or response. The concept of a discrete emetic center has also been seriously challenged. Based on more recent electrophysiologic studies, a model of sequential activation of a series of effector nuclei (e.g., nucleus tractus solitarius, retrofacial nucleus, dorsal motor nucleus of the vagus) has been proposed that doesn't require a discrete emetic center.[5] Despite contemporary reexamination, there still is good agreement on two general patterns of emesis, one humoral and the other neural.

The essential component of the *humoral* pathway is the CRTZ located within the area postrema, which is sensitive to activation by bloodborne substances. The CRTZ is located anatomically outside of the blood–brain barrier and is readily perfused by substances in systemic circulation. Receptors within the CRTZ may be activated by many endogenous (e.g., uremic, hepatoencephalopathic, or endotoxins) or exogenously derived (e.g., digitalis glycosides, *cis*-platinum, apomorphine) bloodborne substances. Many pharmacologic approaches to antiemetic therapy have been based on receptor interactions at the CRTZ, emphasizing the *humoral* pathway of emesis.[1,4]

Although many antiemetic agents are based on CRTZ pharmacology, many spontaneous vomiting disorders result from activation of the *neural* pathway. Vomiting associated with primary gastrointestinal tract disease (e.g., inflammation, infection, malignancy, toxicity) results from activation of an afferent neural pathway, nucleus tractus solitarius neurons, and the emetic center. Efferent information transmitted back to the gastrointestinal tract stimulates motor correlates of vomiting (i.e., retrograde duodenal and gastric contractions, relaxation of the gastroesophageal sphincter, gastroesophageal reflux, opening of the proximal esophageal sphincter, evacuation of gastrointestinal contents).[6,7] A *neural* pathway can also be involved in vomiting associated with motion sickness. Although there are important species differences,[8-10] motion within the semicircular canals is transduced to vestibulocochlear neurons that ultimately synapse in the CRTZ (dog) or emetic center (cat). Finally, a *neural* pathway involving cerebrocortical neurons are very likely involved in vomiting disorders associated with anxiety or anticipation, but their importance in companion animals has not yet been established.

Pharmacology of Vomiting: Neurotransmitters and Receptors

Chemoreceptor Trigger Zone

Neurochemical studies have demonstrated several neurotransmitters (e.g., dopamine, norepinephrine, 5-hydroxytryptamine [5-HT], serotonin), acetylcholine, histamine, substance P, enkephalins), their respective receptors or binding sites (e.g., D_2 dopaminergic, α_2 adrenergic, 5-HT_3 serotonergic, M_1 cholinergic, H_1 and H_2 histaminergic, NK_1 neurokininergic, ENK_μ and ENK_δ enkephalinergic), and their respective synthetic or degradative enzymes (e.g., dihydroxyphenylalanine [DOPA] decarboxylase, dopamine

Box 23-1 Etiology of Vomiting Disorders in Companion Animals

Abdominal, Alimentary Disorders
Infection
Inflammation
Malignancy
Toxicity
Obstruction
Ulceration
Intussusception
Foreign bodies
Motility disorders

Abdominal, Extraalimentary Disorders
Peritoneal disorders (e.g., peritonitis)
Urinary tract disorders (e.g., bladder rupture)
Reproductive disorders (e.g., pyometra)
Splenic disorders (e.g., splenitis)
Nutrition
Dietary indiscretion
Food hypersensitivity reactions

Metabolic Disorders
Uremia
Liver failure
Electrolyte disorders (K^+, Ca^{2+}, Mg^{2+})
Acid–base disorders

Endocrine Disorders
Diabetes mellitus (ketoacidosis)
Hyperthyroidism
Hypoadrenocorticism

Systemic Disorders
Septicemia
Endotoxemia
Multiple organ failure

Nervous System Disorders
Encephalitis/meningitis
Hydrocephalus

Exogenous Medications
Digitalis glycosides
Erythromycin
Chemotherapy
Apomorphine
Xylazine
Nonsteroidal antiinflammatory drugs (NSAIDs)

Toxicity
Ethylene glycol
Heavy metals–copper, zinc, lead
Strychnine

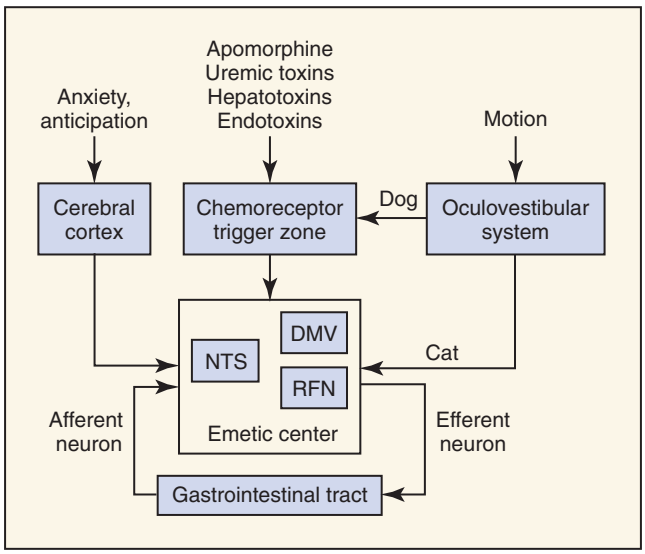

Figure 23-1 Physiology of vomiting: humoral and neural pathways. *Humoral pathway*—Vomiting is initiated through activation of the chemoreceptor trigger zone by bloodborne substances. *Neural pathway*—Vomiting is initiated through activation of the emetic center by vagosympathetic, chemoreceptor trigger zone, nucleus tractus solitarius (NTS), vestibular, or cerebrocortical neurons. DMV, Dorsal motor nucleus of vagus; RFN, retrofacial nucleus.

β-hydroxylase, 5-hydroxytryptophan decarboxylase, choline acetyltransferase, histidine decarboxylase, aminopeptidase N, enkephalinase) (Fig. 23-2).[11]

Some neurotransmitter-receptor signal transduction pathways are probably more important than others. For example, apomorphine (a D_2-dopamine receptor agonist) is a potent emetic agent in the dog, but it does not readily induce emesis in the cat.[12] This finding has two important implications: (a) CRTZ D_2-dopamine receptors may not be as important in mediating humoral emesis in the cat, and (b) D_2-dopamine receptor antagonists (e.g., metoclopramide) may not be effective antiemetic agents in the cat. Xylazine, an α_2-adrenergic agonist, is a more potent emetic agent in the cat than in the dog.[12,13] Xylazine's effect suggests that α_2-adrenergic antagonists may be more useful antiemetic agents than D_2-dopamine antagonists in the cat.[9] Cancer chemotherapy (e.g., *cis*-platinum, doxorubicin, cyclophosphamide) induced–emesis is mediated by activation of 5-HT_3 receptors in the CRTZ of the cat,[11,14-16] whereas visceral and vagal afferent 5-HT_3 receptors may be more importantly involved in the dog.[17] Antagonists of the 5-HT_3 receptor are efficacious in prevention of emesis associated with *cis*-platinum and other chemotherapy in cats[14-16] and dogs.[18] NK_1-receptor antagonists represent a unique new class of antiemetic agents that are based on substance P pharmacology at the CRTZ as well as the nucleus tractus solitarius. This group of antiemetic agents may have advantages over other antiemetic classifications in that they may inhibit vomiting through both pathways (humoral and neural).[19,20] Finally, although histamine and H_1- and H_2-histaminergic receptors have been demonstrated in the CRTZ of the dog, they have not yet been demonstrated in the cat. Histamine is a potent emetic agent in the dog, but the cat seems resistant to its emetic effects.[11,12] H_1-histaminergic antagonists (e.g., diphenhydramine, dimenhydrinate) are ineffective antiemetic agents for motion sickness in the cat.[10]

Emetic Center

Emetic center pharmacology is complicated; some experimental results may not be reflective of pharmacology at one site. At the present time 5-HT_{1A}, α_2-adrenergic, and NK_1 receptors are the only documented receptors involved in regulation of emesis at the level of the emetic center for which there are clinically available antiemetic agents. It has been shown that 5-HT_{1A}-receptor agonists (e.g., flesinoxan, 8-OH-DPAT, buspirone) suppress emesis associated with motion sickness in cats.[21] The emetic center α_2-receptor as well as the CRTZ α_2-receptor may be antagonized by a pure α_2-antagonist (e.g., yohimbine) or by mixed α_1/α_2 antagonists (e.g., prochlorperazine, chlorpromazine).[13] It is likely, however, that most of the antiemetic effect of the α-receptor antagonists results from antagonism at the level of the CRTZ.[21,22]

Vestibular Apparatus

Muscarinic M_1 receptors and acetylcholine have been demonstrated in the vestibular apparatus of the cat. Mixed M_1/M_2 antagonists (e.g., atropine) and pure M_1 antagonists (e.g., pirenzepine) inhibit motion sickness in the cat. It is not clear whether the antiemetic effect of these drugs is solely a result of M_1-receptor antagonism at the vestibular apparatus. Other sites (e.g., cerebral cortex, reticular formation, area postrema) of antagonism are possible.[11] More recently, NK_1 receptors have been shown to be involved in pathogenesis of motion sickness, and NK_1-receptor antagonists (e.g., maropitant) prevent motion sickness in both dogs and cats.[23,24]

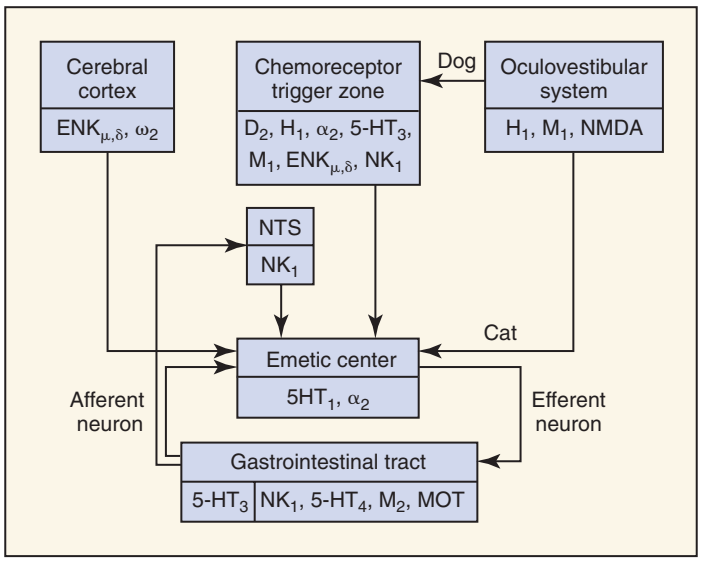

Figure 23-2 Pharmacology of vomiting—neurotransmitters and receptors. α_2, Alpha$_2$-adrenergic receptor; D_2, dopamine$_2$ receptor; ENK$_{\mu,\delta}$, enkephalin $_{\mu,\delta}$ receptor; H_1, histamine$_1$ receptor; 5-HT_{1A}, 5-hydroxytryptamine$_{1A}$ receptor; 5-HT_3, 5-hydroxytryptamine$_3$ receptor; 5-HT_4, 5-hydroxytryptamine$_4$ receptor; M_1, muscarinic$_1$ cholinergic receptor; M_2, muscarinic$_2$ cholinergic receptor; MOT, motilin receptor; NK_1, neurokinin$_1$ receptor; NMDA, N-methyl D-aspartate; NTS, nucleus tractus solitarius; ω_2, benzodiazepine ω_2 receptor.

Cerebral Cortex

Opioids, cannabinoids (e.g., nabilone) and benzodiazepines (e.g., diazepam, lorazepam) have been used to reduce anticipatory nausea and vomiting in human beings undergoing cytotoxic drug therapy. Cerebrocortical opioid and benzodiazepine receptors have been implicated but have not been well characterized pharmacologically. The importance of these receptors in pathogenesis of nausea and vomiting disorders in the dog and cat has not yet been established.[4,11,12]

Gut Afferents

There are a number of different mechanisms by which stimuli arising from the gastrointestinal tract activate the vomiting reflex. Ingested toxins, cell degeneration or necrosis, inflammation, luminal distention, chemotherapy, and radiation therapy all induce emesis. Of the many receptors found in the gastrointestinal tract, 5-HT_3 receptors likely play an important role in initiation of emesis.[11] It is now well established that cytotoxic drugs provoke 5-HT release from enterochromaffin cells in the gastrointestinal tract, which then activates 5-HT_3 receptors in afferent vagal fibers (dog)[17] or CRTZ (cat).[14,15] Vomiting induced by 5-HT release and 5-HT_3 receptor activation is abolished by pretreatment with 5-HT_3 antagonists (i.e., ondansetron, granisetron, tropisetron, dolasetron).[14,18] Metoclopramide is a weak antagonist of 5-HT_3 receptors but does not seem to be very effective in preventing chemotherapy-induced emesis.[25] It remains to be determined whether other gastrointestinal tract pathologies (e.g., inflammation, infection, malignancy, toxicity) are mediated via 5-HT_3 receptor activation.

Gut Efferents

Vagal efferent and myenteric neurons initiate complex excitation and inhibition of visceral smooth muscle (e.g., retrograde duodenal and gastric contractions, relaxation of the gastroesophageal sphincter, gastroesophageal reflux, opening of the cricoesophageal sphincter, and evacuation of gastrointestinal contents) that culminates in emesis. A number of receptors have been identified on myenteric neurons and gastrointestinal smooth muscle cells that regulate gastric emptying and/or intestinal transit. These include 5-HT_4 serotonergic (neuronal),[26] D_2-dopaminergic (neuronal),[27] M_2-cholinergic (smooth muscle),[28] and motilin (smooth muscle; dog only)[29] receptors. Cisapride and other 5-HT_4 agonists facilitate gastric emptying by activating presynaptic neuronal 5-HT_4 receptors.[20,26] Metoclopramide is a weak gastric prokinetic agent in the dog and cat and is believed to facilitate gastric emptying via agonism of 5-HT_4 serotonergic receptors[26] or via antagonism at D_2-dopamine receptors.[27] Canine gastric emptying is also regulated by motilin, a hormone that is released episodically from gastrointestinal endocrine cells. Motilin initiates phase III of the migrating myoelectric complex and facilitates gastric emptying during the fasting state. Low doses of erythromycin (0.5 to 1.0 mg/kg q8h PO, IV) stimulate motilin release and facilitate gastric emptying in the dog.[29-31] The role of motilin in regulation of feline gastric emptying is incompletely understood. Motilin-like macrolide antibiotics increase tone in feline caudal esophageal sphincter,[32] but their role in the regulation of gastric, intestinal, and colonic motility is incompletely understood.

Differential Diagnosis

Emesis may occur with such diverse conditions as systemic (e.g., septicemia, multiple organ failure), metabolic (e.g., uremia, liver failure), and endocrine disease (hyperthyroidism, hypoadrenocorticism), as well as disorders of the gastrointestinal tract (e.g., inflammatory bowel disease, gastrointestinal malignancy and obstruction, pancreatitis, and hepatobiliary disorders) (see Box 23-1).

Evaluation of the Patient

History

A complete and detailed history is the first step in establishing a correct diagnosis of a vomiting disorder. The patient's signalment will usually establish some level of probability for many of the differential diagnoses. For example, adrenocortical insufficiency would be an important differential diagnosis for a 2-year-old dog presented with an acute history of vomiting and muscular weakness, with or

without diarrhea. Similarly, acute onset of vomiting in an unvaccinated puppy should alert the veterinarian to the possibility of an infectious disease (e.g., parvoviral or distemper viral gastroenteritis). Chronic vomiting in an 11-year-old dog, on the other hand, would elicit a different set of differential diagnoses.

Following consideration of the patient's signalment, history taking should ascertain vaccination status, travel history, and any recent dietary changes. Previous medical problems, medication history, and possible ingestion of toxic substances or foreign bodies should also be ascertained. These pieces of information can be useful in formulating a list of differential diagnoses. Next, the veterinarian should be convinced that the pet owner is describing vomiting and not some other sign. Coughing associated with inflammatory disorders of the upper airway will often be described as vomiting by many pet owners. Gagging is also occasionally confused with vomiting. A careful history taking will usually discriminate coughing and gagging from vomiting. Pet owners will also often confuse regurgitation and dysphagia with vomiting. Regurgitation is the passive evacuation of ingested food from pharynx and/or esophagus; premonitory signs of retching and abdominal contractions seen with vomiting are not observed with regurgitation. The description of regurgitation by a pet owner would suggest a more proximal disorder of the pharynx or esophagus. Dysphagia or difficulty in swallowing would also suggest a more proximal disorder of the pharynx.

History taking should then elicit the duration, frequency, and time of vomiting episodes, as well as the relationship of vomiting to food and water consumption. Disorders of vomiting that are of short duration are usually self-limiting and not worthy of extensive investigation; chronic vomiting histories are more serious and certainly require a more detailed investigation. Frequent vomiting usually occurs as result of systemic, metabolic, or endocrine disorders or severe inflammatory disorders of the primary gastrointestinal tract. Vomiting that occurs in the immediate postprandial period is usually suggestive of overeating, excitement, or disorders of the esophageal body or esophageal hiatus (e.g., hiatal hernia). Conversely, vomiting of undigested or partially digested food 8 or more hours postprandially suggest a distal gastric (corpus, antrum, and pylorus) motility disorder or obstruction. Vomiting of water would be more suggestive of a proximal gastric (cardia, fundus) motility disorder. Vomiting during early morning hours often may result from gastroesophageal reflux.

Physical characteristics of the vomitus, including color, amount, odor, consistency, and presence or absence of blood or bile should be ascertained. Undigested food in the vomitus implies an esophageal etiology while digested food (chyme) implies a gastric or intestinal etiology for the vomiting. Blood in the vomitus implies disruption of gastrointestinal mucosa; blood may appear as frank red clots or as a dark brown "coffee grounds" material resulting from acid proteolysis. Bile in the vomitus usually suggests only that the pylorus has permitted bile reflux. However, bile salts increase permeability of the gastric mucosal barrier resulting in a syndrome of bile reflux gastritis. Bilious vomiting, therefore, might provide a clue to the pathogenesis of the disorder. A fecal odor has been described with lower intestinal (jejunoileal) obstruction.

Physical Examination

Examination of mouth and pharyngeal structures often provides important clues to the pathogenesis of vomiting (e.g., uremic breath or ulcers, icteric mucous membranes, severe pharyngitis or pharyngeal string foreign bodies). Physical examination finding of generalized lymphadenopathy suggest neoplasia or a systemic inflammatory disease as the pathogenesis of the vomiting. Hence, all lymph nodes should be carefully palpated to determine if they are enlarged or painful. Fever on physical examination would likewise suggest an inflammatory pathogenesis for the vomiting disorder. Extreme bradycardia or other rhythm disturbance detected upon cardiac auscultation might be an important sign of a metabolic disturbance such as adrenocortical insufficiency or septic shock. The abdomen should then be carefully palpated for effusion (e.g., peritonitis), masses (e.g., carcinomatosis or other malignancy), pain (e.g., peritonitis, pancreatitis, or nephritis), gaseous or fluid distention of the intestine (e.g., obstruction), kidney size and shape (e.g., end-stage fibrotic kidneys or nephritis), liver size (e.g., hepatitis), uterine distention (e.g., pyometra), and urinary bladder size (e.g., bladder obstruction). Rectal examination might also provide some evidence of pain or hematochezia (e.g., colitis), worms (e.g., hook or whipworms), or painful prostatomegaly (e.g., prostatitis or prostatic neoplasia). Finally, examination of the central nervous system should be considered, especially in animals in which the cause of vomiting is not so obvious. Some animals with intervertebral disk disease will experience nausea and vomiting because of pain.

Laboratory Evaluation and Tests

If a definitive diagnosis is not established from history and physical examination, additional diagnostic tests may be warranted, including complete blood count, serum chemistry, urinalysis, fecal parasitologic examination, and abdominal imaging. Peripheral eosinophilia in a complete blood count would suggest systemic mast cell disease, intestinal parasitism, or adrenocortical insufficiency. Leukopenia and neutropenia might be observed in the acute phase of a viral gastroenteritis. Leukocytosis might suggest an inflammatory disorder like acute pancreatitis. The serum chemistry will often help identify systemic, metabolic, and endocrine causes of vomiting. For example, (a) azotemia and hyperphosphatemia suggest that the vomiting has resulted from chronic renal failure; (b) hyperglycemia, acidosis, glucosuria, and ketonuria suggest diabetic ketoacidosis; (c) hyponatremia and hyperkalemia suggest adrenocortical insufficiency; (d) lipasemia suggests acute pancreatic necrosis; (e) increases in serum hepatic enzyme activities (alanine aminotransferase [ALT], aspartate aminotransferase [AST], alkaline phosphatase [ALP]) suggest primary hepatic disease; and (f) hypercalcemia suggests parathyroid or other malignancy. Urinalysis is useful in differentiating prerenal and primary renal azotemia while fecal examination may provide evidence of intestinal helminth infestation. Survey abdominal radiographs are indicated in the initial workup of a vomiting disorder. Abdominal radiographs provide useful information about the abdominal alimentary and extraalimentary structures. The decision to perform additional tests is based on response to empirical therapies and initial test results. Further tests might include adrenocorticotropic hormone (ACTH) stimulation, hepatic function tests, serum pancreatic enzymes, thoracic radiography, contrast radiography, abdominal ultrasonography,[33] computed tomography (CT)/magnetic resonance imaging (MRI), gastrointestinal endoscopy, laparoscopy, and laparotomy. Figure 23-3 is an algorithm for the medical investigation of vomiting disorders.

Treatment and Management

General Principles

Each vomiting patient is likely to have a unique clinical presentation; some are benign and require little in the way of intervention while others require extensive stabilization, therapy, and rehabilitation. Efforts should be made to identify and eliminate inciting agents; sustain blood and plasma volume; restore blood pressure;

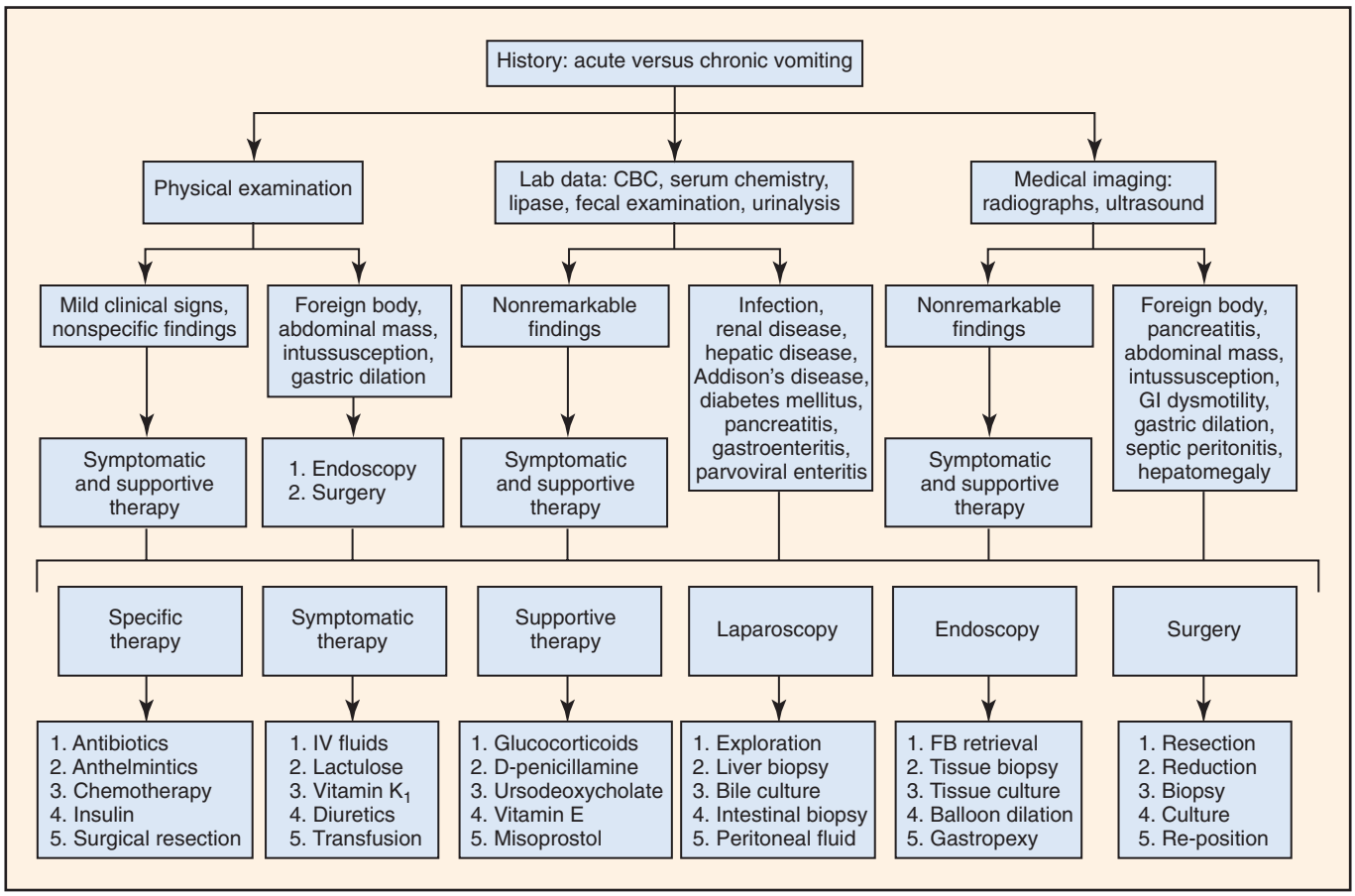

Figure 23-3 Diagnostic approach to vomiting disorders in dogs and cats. FB, Foieign body; IV, intravenous.

correct acid–base, electrolyte, and fluid deficits; and treat complications as they develop.

Nutrition

Short periods of fasting are appropriate to reduce severity and frequency of the central emetic response. Fasting in cats should be implemented only in those instances in which there is severe vomiting and risk of aspiration pneumonia. As obligate carnivores, cats develop fat mobilization and hepatic lipidosis during even short periods of starvation. With chronic vomiting disorders, esophagostomy, gastrostomy, and enterostomy tubes may be placed to facilitate nutrition in anorectic animals (see Chapter 33).

Fluids

Severe vomiting will likely result in serious fluid, electrolyte, and acid–base disturbances. The goal of fluid therapy is to restore volume and composition of body fluids to normal and, once this is achieved, to maintain external fluid and electrolyte balance so that input by treatment matches fluid losses (see Chapter 48). Electrolyte solutions can be divided into replacement and maintenance solutions. Replacement solutions provide 130 to 147 mEq/L of sodium, similar to values in extracellular fluid. Maintenance electrolyte solutions provide 40 to 77 mEq/L of sodium, about one-half or less of values in the extracellular fluid. Supplementation of replacement fluids may be required to correct acid–base imbalance and potassium deficits, particularly in animals suffering from vomiting and diarrhea. In the absence of cardiopulmonary disease, intravenous fluids can be safely administered to dogs and cats at 90 mL/kg/h. Animals with mild volume depletion can be treated with lower fluid rates (10-20 mL/kg/h, as needed).

Antiemetic Agents

Antiemetic therapy should be formulated on the basis of most likely underlying pathogenesis (i.e., neural or humoral pathway). The NK_1 neurokinin antagonists, α_2 adrenergic antagonists, 5-HT_3 serotonergic antagonists, and D_2 dopaminergic antagonists appear to be the most effective antiemetic agents in the dog and cat, although the D_2 dopaminergic antagonists appear to be less efficacious in the cat (Table 23-1). The reader is referred to Chapter 35 for more definitive outline of rational antiemetic therapy.

Anti-Secretory Agents

Histamine H_2 receptor antagonists and H^+,K^+-adenosine triphosphatase (ATPase) inhibitors are the best clinical examples of gastric acid secretory inhibitors. It may be difficult to impossible to determine pathogenesis of gastric injury in an individual animal. Most cases will likely result from the combined effects of acid injury and disruption of the gastric mucosal barrier. Acid suppression and restitution of the gastric mucosal defense mechanisms are the cornerstones of treatment (see Chapter 45).

Prokinetic Agents

Gastrointestinal prokinetic agents should be considered in patients that fail to respond to dietary and antiemetic therapy. Combination antiemetic and prokinetic therapy are particularly effective in refractory vomiting patients. The most effective prokinetic agents

Table 23-1 Antiemetic Classifications

Classification	Examples	Sites of Action	Dosage	Side Effects
α_2-Adrenergic antagonists	Prochlorperazine	CRTZ, emetic center	0.1 to 0.5 mg/kg q6-8h SQ, IM	Hypotension, sedation
	Chlorpromazine	CRTZ, emetic center	0.2 to 0.4 mg/kg q8h SQ	Hypotension, sedation
	Yohimbine	CRTZ, emetic center	0.25 to 0.5 mg/kg q12h SQ, IM	Hypotension, sedation
D_2-dopaminergic antagonists	Metoclopramide	CRTZ, GI smooth muscle	0.2 to 0.4 mg/kg q6h PO, SQ, IM, IV	Extrapyramidal signs
	Domperidone	CRTZ, GI smooth muscle	0.1 to 0.3 mg/kg q12h IM, IV	Extrapyramidal signs
	Prochlorperazine	CRTZ, emetic center	0.1 to 0.5 mg/kg q6-8h SQ, IM	Hypotension, sedation
	Chlorpromazine	CRTZ, emetic center	0.2 to 0.4 mg/kg q8h SQ, IV	Hypotension, sedation
H_1-histaminergic antagonists	Diphenhydramine	CRTZ	2 to 4 mg/kg q8h PO, IM	Sedation
	Dimenhydrinate	CRTZ	4 to 8 mg/kg q8h PO	Sedation
	Prochlorperazine	CRTZ, emetic center	0.1 to 0.5 mg/kg q6-8h SQ, IM	Hypotension, sedation
	Chlorpromazine	CRTZ, emetic center	0.2 to 0.4 mg/kg q8h SQ, IV	Hypotension, sedation
M_1-cholinergic antagonists	Pirenzepine	Vestibular apparatus, CRTZ	25 to 50 mg q24h PO	None reported
	Aminopentamide	Multiple CNS and PNS sites	0.01 to 0.03 mg/kg q8-12h PO, SQ	GI dysmotility
	Prochlorperazine	CRTZ, emetic center	0.1 to 0.5 mg/kg q6-8h SQ, IM	Hypotension, sedation
	Chlorpromazine	CRTZ, emetic center	0.2 to 0.4 mg/kg q8h SQ, IV	Hypotension, sedation
5-HT_3 serotonergic antagonists	Ondansetron	CRTZ, vagal afferent neurons	0.5 to 1.0 mg/kg q12h PO, IV	Sedation, head shaking
	Granisetron	CRTZ, vagal afferent neurons	0.1 to 0.5 mg/kg q12h PO, IV	Sedation, head shaking
	Tropisetron	CRTZ, vagal afferent neurons	0.5 to 3.0 mg/kg q12h PO	Sedation, head shaking
	Dolasetron	CRTZ, vagal afferent neurons	0.6 to 1.0 mg/kg q12h PO, IV	Sedation, head shaking
5-HT_4 serotonergic agonists	Cisapride	Myenteric neurons	0.1 to 0.5 mg/kg q8-12h PO	Cardiac arrhythmia
$ENK_{\mu,\delta}$-enkephalinergic	Butorphanol	CRTZ	0.2 to 0.4 mg/kg q12h IM	Sedation antagonists
NK_1 neurokinin antagonists	Maropitant	CRTZ, emetic center	1.0 mg kg q24h SQ	Injection irritant

CRTZ, Chemoreceptor trigger zone; GI, gastrointestinal; 5-HT, 5-hydroxytryptamine; IM, intramuscular; IV, intravenous; PO, per os; q, every; SQ, subcutaneous.

are the 5-HT_4 serotonergic agonists, of which cisapride, tegaserod, and mosapride are the best examples. D_2-Dopaminergic antagonists, motilides, and cholinomimetic agents have also been used to stimulate propagating gastrointestinal motility in companion animals (see Chapter 52).

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CHAPTER 24

Weight Loss and Cachexia

Cynthia R. Ward

Healthy animals typically maintain their body weight within a remarkably stable range given the differing levels of caloric intake and energy expenditure that may occur daily. Significant, unintentional weight loss is usually a sign of disease. In patients who tend to mask early signs of disease, it may be the first clue of pathology. Loss of greater than 5% body weight should prompt diagnostic evaluation. Weight loss is considered a negative predictor in the outcome of many chronic diseases; therefore, it must be recognized and addressed.[1]

Definition

Weight Loss

Weight loss occurs when energy expenditures and caloric loss exceed caloric intake. The main controllers of these processes, appetite and metabolism, are regulated by an intricate network of neural and hormonal factors. These signals are primarily integrated in the arcuate nucleus of the hypothalamus, which maintains homeostatic control over food intake, levels of activity, and basal energy expenditure.[2] This area of the brain is relatively accessible to circulating signals and can respond to peripheral and central inputs. Peripherally secreted hormones, primarily insulin and leptin, give information relating to long-term energy stores in the body. Insulin, secreted by the pancreatic B cells, regulates storage of absorbed nutrients and acts as an adiposity signal to the brain.[3] Adiposity signals are cytokines produced and secreted by adipose tissue in proportion to the body fat content. Leptin secreted by adipocytes informs the brain of adipose energy reserves, and appetite is adjusted accordingly.[4] Signals relating to recent nutritional condition are provided by the vagal neural system that relates information about gastric distention and nutrients in the portal circulation.[5]

Enteroendocrine cells in the gut produce numerous hormones that are also integrated in the hypothalamus to control metabolism. These include satiety peptides cholecystokinin (CCK), glucagon-like peptide-1 (GLP-1), and oxyntomodulin that are produced in the small intestine in response to food in the gut lumen.[6-8] Peptide YY (produced in ileum and colon) and pancreatic polypeptide (produced by pancreatic cells) are released in response to feeding and signal satiety as well.[9-11] Ghrelin, produced primarily in the stomach, is secreted during fasting and stimulates appetite.[12]

When faced with a decrease in caloric intake, otherwise normal animals respond with a corresponding decrease in energy expenditure. Although body weight is lost, muscle protein is preserved while adipose tissue is broken down providing energy. The net result is fat loss over muscle loss. If adequate calories are later ingested, normal body weight and condition should be restored.

Cachexia

The terms *weight loss* and *cachexia* are often used interchangeably with cachexia usually referring to more severe weight loss that is associated with disease. Cachexia is technically different than simple weight loss, being a metabolic disorder of increased energy expenditure that cannot be resolved by merely providing extra calories.[13] It differs from simple weight loss in that the normal physiologic mechanisms supporting muscle preservation despite increased energy demands are lost.[14] Thus, protein and adipose tissue provide energy in the cachexic animal resulting in disproportionate muscle wasting in the animal. Cachexia occurs with severe debilitating disease, including malignancy, renal failure, heart failure, and chronic inflammatory diseases.[15] Cachexia is a significant predictor of mortality in human medicine.[16]

Although the pathogenesis of cachexia is not fully understood, cytokines have been implicated as major mediators.[17] Systemic inflammation from cell injury or activation of the immune system can trigger release of cytokines into circulation. Proinflammatory cytokines (e.g., interleukin [IL]- 1 and -2, interferon-γ, tumor necrosis factor [TNF]-α) are commonly implicated in the pathogenesis of cachexia.[18-20] These cytokines can activate proteolytic systems that cause hypercatabolism as well as activate tissue factors (e.g., IL-1, TNF-α) responsible for decreased protein synthesis and enhanced lipolysis.[20-22] The result of these processes is negative energy balance, muscle wasting, and weight loss. Other hormones implicated in cachexia are testosterone, insulin-like growth factor 1, myostatin, glucocorticoids, and catecholamines.[23-27]

Differential Diagnosis

The list of differential diagnoses for weight loss and cachexia is extensive. Major causes of weight loss include inadequate caloric ingestion, absorption, or digestion; caloric loss; increased metabolic rate; or cachexia. Inadequate calories available for ingestion occurs when animals are underfeeding or eat nutritionally incomplete diets. Dental pain, prehension or swallowing abnormalities, regurgitation, vomiting, or gastrointestinal obstructions can prevent adequate calories from being digested. Malabsorption, maldigestion, and diabetes mellitus are examples of weight loss as a result of an inability

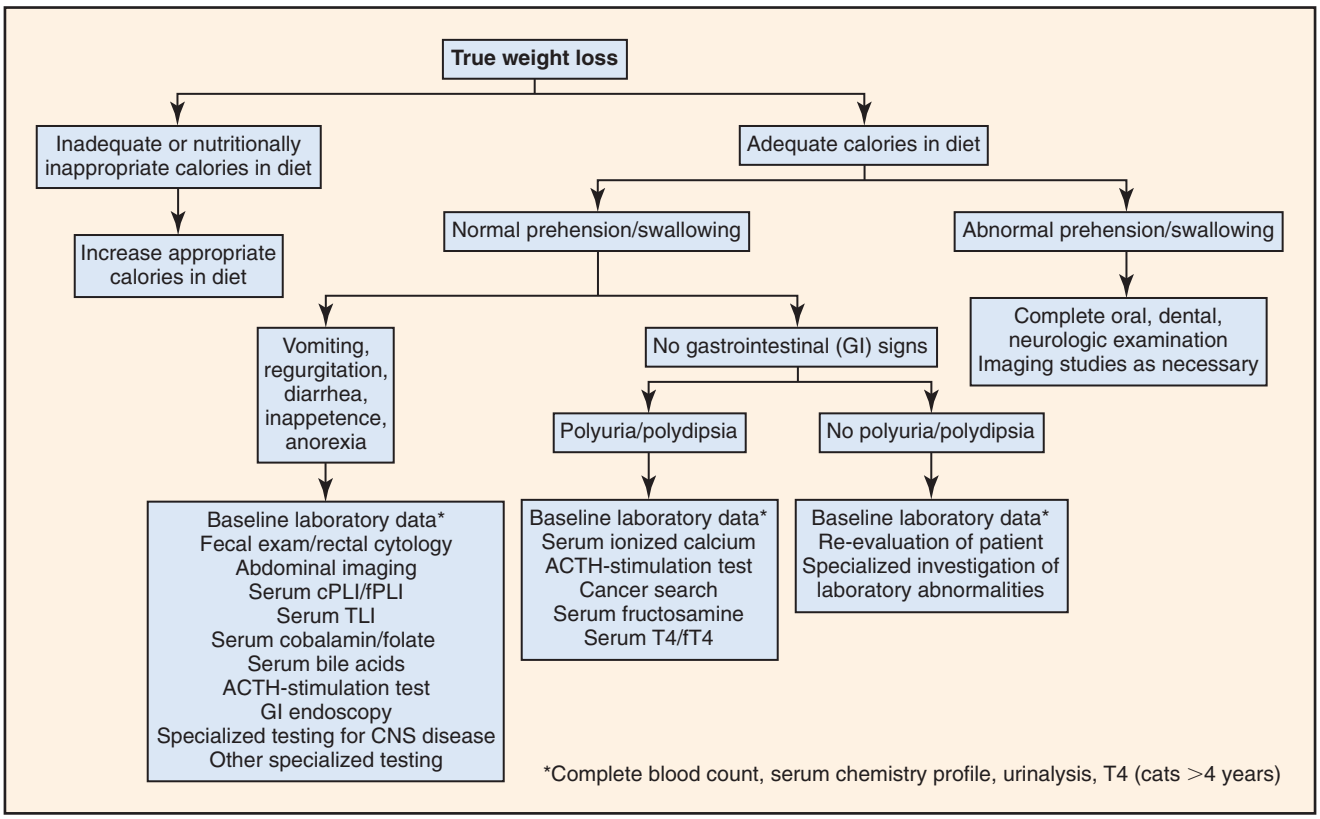

Figure 24-1 Algorithm for the diagnosis and treatment of weight loss. ACTH, Adrenocorticotropic hormone; CNS, central nervous system; cPLI, canine pancreatic-specific lipase; fPLI, feline pancreatic-specific lipase; TLI, trypsinogen-like immunoreactivity.

to absorb or process adequate calories. Caloric loss can occur from protein-losing diseases (e.g., protein-losing nephropathy, exudative skin lesions). Hyperthyroidism, extreme exercise, cold weather, lactation, and cachexia caused by chronic illness can produce weight loss from increased metabolism causing excess calorie usage.

Evaluation of the Patient

History

Weight loss may be the initial presenting complaint, part of other clinical signs, or unnoticed by the owner. A detailed history is important in patients with weight loss, and an algorithm for the diagnosis and treatment of weight loss is shown in Figure 24-1. Initially it is important to determine whether true weight loss has occurred because owners can be mistaken about weight changes in their pets. Medical records should be evaluated for previous weight measurements and compared to the current weight. These data should be compared to the current body condition of the animal. In addition to normal historical questioning, a detailed dietary history including type and amount of food given should be obtained to determine whether the animal is receiving sufficient calories to maintain its weight. Diets high in cellulose content and other indigestible material are examples of inappropriate calories in the diet. The practitioner should carefully question the owner about the animal's appetite and about other animals in the household who may be competing for food. Weight loss can occur in the face of a normal, increased, or decreased appetite. Malabsorption, maldigestion, hyperthyroidism, and diabetes mellitus are examples in which weight loss may occur with or without a decrease in appetite. The animal's ability to prehend and swallow food should be ascertained. Vomiting, regurgitation, and quantity and consistency of feces should be noted. The owner should be questioned about other clinical abnormalities in the animal. Environmental conditions, including any recent changes in weather or housing, should be noted to determine whether there is an impediment to the animal's ability to obtain sufficient food.

Physical Examination

To determine true weight loss, the animal must be weighed on an accurate and appropriate scale (e.g., pediatric scales should be used for small dogs and cats). If possible, the animal should be weighed on the same scale at each visit. Physical examination should include careful examination of the animal's body condition and hydration status. A body condition score should be recorded. Muscle mass should be noted as compared to fat. The mouth should be carefully examined for neural, oral, or dental disease that may produce avoidance of food because of pain or inability to prehend food. Nasal discharge can be important because some animals, especially cats, will not eat appropriately unless they can smell their food. Abdominal palpation should be thorough and all peripheral lymph nodes evaluated for signs of malignancy. A rectal examination with inspection of fecal matter should be performed in dogs.

Laboratory Evaluation and Tests

A complete blood count (CBC), serum biochemistry profile, total thyroxine (T_4) (cat), and urinalysis should be performed on animals exhibiting weight loss or cachexia unless the cause is obviously a lack of nutrition. Then a diagnostic plan is based on the history, physical examination, and clinical pathology data. This may include fecal examination, rectal cytology, abdominal/thoracic imaging,

infectious disease testing, biopsies of enlarged lymph nodes or masses, bone marrow examination if malignancy or disseminated histoplasmosis are suspected, or examination of the gastrointestinal (GI) tract. Cerebrospinal fluid analysis and central nervous system (CNS) imaging should be considered in difficult, unresolved cases of anorexia.

Treatment and Management

Because weight loss and cachexia are constitutional signs of disease, identification and successful treatment of underlying disease processes is necessary to resolve the clinical condition. Simple caloric replacement will not totally reverse weight loss in cachexic animals because they are hypermetabolic.

If the animal will eat normally, a dietary plan should be prepared to ensure sufficient caloric intake to support the animal's metabolic activity. Extra calories should be provided to compensate for weight loss. Calculation of caloric needs is outlined in Chapter 30. Feeding tube placement (Chapters 32 and 33) should be considered for animals with physical or behavioral impediments to food delivery to the stomach. Total or peripheral parenteral nutrition (Chapter 33) should be considered for animals with severe vomiting, pancreatitis, or other disease that prevents normal digestion. Appetite stimulants (e.g., cyproheptadine, mirtazapine) may be effective in hastening resolution of behaviorally induced inappetence.

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CHAPTER 25

Laboratory Approach

STOMACH AND SMALL INTESTINE

Jan S. Suchodolski

Gastrointestinal (GI) diseases occur commonly in companion animals. Because of their nonspecific clinical signs, GI disorders pose a diagnostic challenge for the clinician. Collecting an initial database consisting of hematology, serum biochemistry, and urinalysis aids in determining extragastrointestinal causes of the observed clinical signs, and may be useful in the exclusion of systemic and metabolic disorders, the assessment of the severity of the disease, and of the hydration status of the patient. Assessing serum thyroxine (T_4) concentrations and feline leukemia virus (FeLV) and feline immunodeficiency virus (FIV) status are useful adjunct tests in cats with chronic GI disease.

Diagnostic imaging, especially a combination of ultrasonography and radiography, can be helpful for evaluation of patients for obstructions or neoplasia. Endoscopic examination and biopsy of the GI tract is currently regarded as the gold standard and yields information about macroscopic lesions and changes in histologic appearance of the mucosa; however, this approach is invasive. Furthermore, histologic interpretation of biopsy specimens can be highly variable among individual pathologists.[1]

Several specialized laboratory procedures are available for the diagnostic workup of patients with GI disease. Many of these tests can be either used as bedside diagnostics or can be performed by a reference laboratory. These tests include serum markers of GI function and inflammation and the evaluation of fecal samples for infectious agents. These tests are helpful for the diagnosis of GI disease and assessment of severity, and can be employed before proceeding to more invasive diagnostic procedures.

Detection of Bacterial Pathogens

Specific enteropathogens (e.g., *Clostridium perfringens*, *Clostridium difficile*, *Salmonella* spp., *Escherichia coli*, *Campylobacter* spp., or *Yersinia enterocolitica*) are associated with GI disease in dogs and cats. However, most of these enteropathogens are commensals in the GI tract and have been isolated at similar frequencies from diarrheic and nondiarrheic animals.[2] This complicates the clinical interpretation when presumptive enteropathogens are identified. Therefore adjunct laboratory testing for the presence of virulence genes (e.g., *E. coli* virulence factors), and/or toxins (e.g., *C. perfringens* and *C. difficile*) can be helpful in determining the clinical importance of isolated enteropathogens.

Various methods are available for the detection of enteropathogens, including bacterial culture, molecular tools (e.g., polymerase chain reaction [PCR]), or immunoassays (either antigen testing or serology). The analytical sensitivity of each method is influenced by how samples are collected, stored, and shipped. Detailed instructions for sample collection and submission should be obtained for each particular assay. It is important to note that there is generally a lack of standardization with regards to cultivation methods and PCR assays. In particular, DNA extraction and PCR protocols vary substantially among reference laboratories. These differences can have a substantial impact on the analytical sensitivity and specificity of bacterial culture and PCR assays.

Culture-dependent methods should be employed if a specific pathogen is suspected (e.g., *Salmonella* spp.). Isolating enteropathogens allows identification of an active infection by viable organisms, and also allows antibiotic susceptibility testing of the isolates. Individual isolates can be typed for epidemiologic surveys of specific strains and their virulence factors. In contrast, PCR detects DNA or RNA rather than the living cell. Although PCR tests are considered to have a higher sensitivity (in theory a single target copy can be amplified), the extraction of DNA from complex environments such as the intestine remains challenging. Improper DNA extraction from highly complex material, such as fecal samples, may result in residual PCR inhibitors and false-negative PCR results. As a result of the high sensitivity of PCR assays, DNA contamination is an important problem with the potential to lead to false-positive results. Therefore it is recommended that a laboratory with expertise in molecular analysis, which has validated the particular assay for the respective target organism, be selected.

Detection of *Helicobacter* spp.

A high prevalence of *Helicobacter*-like organisms (HLOs) has been reported in the stomach of dogs and cats, with up to 100% of healthy animals being positive in some studies.[3] HLOs are also highly prevalent in the intestine and can be found occasionally in the liver. *Helicobacter pylori*, the clinically most important *Helicobacter* species in man, is typically not isolated from companion animals and has been identified so far only in colony cats. The most commonly observed HLOs in pet cats and dogs are *Helicobacter felis*, *Helicobacter heilmannii*, *Helicobacter salomonis*, *Helicobacter bilis*, *Flexispira rappini*, *Helicobacter bizzozeronii*, and *Helicobacter baculiformis*. Animals usually harbor several different *Helicobacter* spp. The detection of

Helicobacter spp. is based on invasive or minimally invasive methodologies.

Minimally Invasive Methods

Minimally invasive methods allow the detection of *Helicobacter* spp., but do not allow assessment of concurrent GI disease associated with *Helicobacter* spp. Serologic tests have a relatively low sensitivity. Most commercial serologic assays test for immunoglobulin (Ig) G and IgM specific for the human pathogen *H. pylori*, and these assays therefore have little value in companion animals. Antibodies will circulate for several months after eradication of the organism and thus antibody tests have limited use for monitoring therapeutic success.[4] The ^{13}C-urea breath test is based on the detection of metabolic activity of *Helicobacter spp*. The organisms produce the enzyme urease, which catalyzes the metabolism of orally administered ^{13}C-urea. In turn, ^{13}C is released from the urea, incorporated into $^{13}CO_2$, and can be quantified in either breath or blood samples. This method is the diagnostic test of choice in humans and is also used to evaluate the success of treatment. A ^{13}C-urea breath and blood test has been evaluated for use in dogs, but is not offered commercially at this time.[5] Using PCR, *Helicobacter* DNA can also be detected in fecal samples, but the sensitivity of this approach is unclear in companion animals.[6]

Invasive Tests

Gastroscopy not only allows for the detection of *Helicobacter* spp. but also provides information about the presence of gastric lesions. Gastroscopy allows for direct visualization of the gastric mucosa. *Helicobacter* spp. have a typically patchy distribution in the mucosa, and it is recommended that biopsy specimens or impression smears be obtained from several areas of the stomach.[7] However, the cultivation of *Helicobacter* spp. from biopsy specimens is of low sensitivity. *Helicobacter* spp. can be detected in biopsies (Fig. 25-1) by means of histochemical stains (e.g., Warthin-Starry or modified-Steiner stains), immunohistochemistry, fluorescence in-situ hybridization (FISH), PCR, or commercially available rapid-urease tests.[8,9] It is important to note that the rapid-urease tests (e.g., CLOtest, Kimberly-Clark) may require up to 24-hour incubation before displaying a color change indicating a positive test result, especially if the patient has received acid-suppressing therapy. Brush cytology of the mucosa is a highly sensitive method for the detection of *Helicobacter* spp. The material obtained is spread across a microscope slide and stained with May-Grünwald-Giemsa, Gram, or Diff-Quick stain.[8]

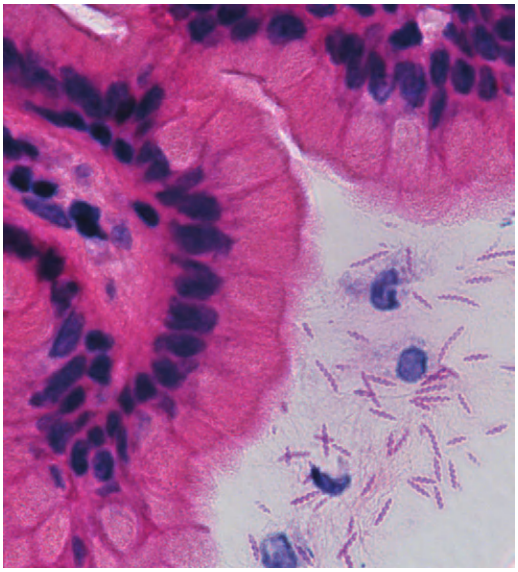


Figure 25-1 *Helicobacter* spp. adjacent to the gastric epithelium in a healthy dog. (Hematoxylin and eosin [H&E] stain; ×100.) (Picture courtesy of Dr. Jose Garcia-Mazcorro, GI Lab, Texas A&M University.)

Diagnosis of *Clostridium perfringens*–Associated Diarrhea

Bacterial culture for the isolation of C. *perfringens* has little diagnostic value as C. *perfringens* is a commensal that can be detected by PCR in up to 100% of dogs and cats.[10] The development of C. *perfringens*–associated diarrhea has been primarily related to the presence of various toxins, especially C. *perfringens* enterotoxin (CPE). A subset of C. *perfringens* organisms carries the gene coding for CPE. When sporulation occurs (this is poorly understood, but suspected triggers include dietary changes or antibiotic use), the enterotoxin is released in high quantities and may potentially cause changes in intestinal permeability leading to diarrhea. Enterotoxigenic C. *perfringens* can be detected by PCR assays that target the CPE gene; however, our recent unpublished studies reveal that 20% of healthy cats, 37% of healthy dogs, and 37% of diarrheic dogs and cats harbor the CPE gene. Similar results with no significant differences in the prevalence of enterotoxigenic C. *perfringens* between healthy and diarrheic dogs have been reported in the literature.[11] Furthermore, of those animals that carry enterotoxigenic C. *perfringens*, the expressed enterotoxin can only be detected in a small proportion of cases. Because of this, and because of the high rate of enterotoxigenic C. *perfringens* carriage in healthy animals, it is recommended that combined testing for the CPE gene by PCR and for the C. *perfringens* enterotoxin by fecal enzyme-linked immunosorbent assay ([ELISA]; e.g., C. *perfringens* enterotoxin test; Techlab, Blacksburg, Virginia) should be performed.[11] Other enterotoxin tests such as the reverse passive latex agglutination (RPLA) assay have a lower analytical sensitivity and are not recommended. Also, enumeration of C. *perfringens* endospores is not considered to be a reliable test for diagnosing C. *perfringens*–associated diarrhea in dogs. In one study, no association was established between C. *perfringens* endospore counts and the detection of CPE, and no difference was observed in the number of observed C. *perfringens* endospores between diarrheic and nondiarrheic dogs.[2]

Diagnosis of *Clostridium difficile*–Associated Diarrhea

Isolation rates for C. *difficile* range between 0% and 40%, and this organism has been isolated in similar frequencies from diarrheic and nondiarrheic dogs.[2,12] Approximately 50% of C. *difficile* organisms harbor toxin A and B genes. Consequently, the significance of detecting C. *difficile* organisms in dogs with diarrhea remains unclear. Currently the most accurate method for diagnosis of C. *difficile*–associated diarrhea is the detection of the organism (either by culture or by antigen testing for glutamate dehydrogenase) in combination with the detection of toxins A and B by ELISA.

The tissue culture cytotoxin-B assay detects the presence of toxin B and is considered the most sensitive (94% to 100%) and specific (99%) test for the diagnosis of C. *difficile*–associated diarrhea.[13] It is, however, technically challenging and requires a 2- to 3-day turnaround time. The latex particle agglutination (LPA) assay and RPLA assay have a high rate of false-positive and false-negative results and are not recommended. Various immunologic assays have

been developed that allow the detection of either toxin A or B or both toxins simultaneously. While most *C. difficile* strains contain toxin A (enterotoxin) and toxin B (cytotoxin), the occurrence of toxin A^-/toxin B^+ strains has been reported. Consequently, it is recommended to use immunoassays that target both toxins. Commercially available human ELISAs that measure both toxins (Premier ToxinA/B and the Techlab ToxinA/B) show a high sensitivity (93%) and specificity (95%) when testing cultured isolates of *C. difficile*. Both ELISAs show a lower sensitivity (27% to 33%) when canine fecal samples are tested directly for the presence of both toxins.[13] Although a positive toxin ELISA result is suggestive of *C. difficile*–associated diarrhea in animals with compatible clinical signs, confirming the presence of the organism improves the diagnostic accuracy. In man, it is recommended that up to three consecutive samples be tested if the first result is negative.

Detection of *Campylobacter* spp.

The normal GI tract harbors various spiral shaped bacteria, including *Campylobacter*, *Helicobacter*, *Spirochaetes*, and *Anaerobiospirillum*.[10] It is not possible to reliably distinguish these organisms on fecal smear examination. At least 14 different *Campylobacter* spp. have been identified in the GI tract of dogs and cats, and most animals harbor multiple species.[14,15] *Campylobacter upsaliensis* and *Campylobacter helveticus* have been reported as the most prevalent *Campylobacter* spp. in dogs and cats, respectively.[14,15] In contrast, *Campylobacter jejuni* and *Campylobacter coli*, the most commonly identified pathogens in man are infrequently isolated from dogs and cats, with prevalence rates ranging between 1% and 10% in most studies.[15,16] Because various *Campylobacter* spp. are part of the normal intestinal ecosystem, species-specific assays able to identify the potentially pathogenic and zoonotic *C. jejuni* or other *Campylobacter* spp. of interest must be used instead of broad-range culture or detection assays.

Salmonella spp.

Bacterial culture has typically a higher sensitivity for the detection of *Salmonella* spp. compared with PCR that is performed on DNA extracted directly from fecal samples. If fecal samples are initially enriched in tetrathionate broth for up to 24 hours before DNA extraction, PCR has a comparable sensitivity to culture.

Escherichia coli

E. coli is a normal inhabitant of the GI tract of dogs and cats.[10] However, diarrheic dogs more commonly harbor *E. coli* possessing specific virulence genes.[17] These include enteropathogenic *E. coli* (EPEC), enterotoxigenic *E. coli* (ETEC), verocytotoxin-producing *E. coli* (VTEC), enterohemorrhagic *E. coli* (EHEC), and enteroinvasive *E. coli* (EIEC). Consequently, molecular assays for the detection of these virulence genes must be employed to detect pathogenic strains of *E. coli*.

Recently, adherent and invasive *E. coli* (AIEC) strains were associated with the development of histiocytic ulcerative colitis in Boxer dogs, which responds to antimicrobial therapy.[18] The AIEC strains can be identified using FISH in mucosal biopsies.

Viral Enteritis

Parvovirus

The diagnosis of parvovirus infection requires a rapid result to initiate immediate treatment. Commonly used in-clinic immunoassays (e.g., SNAP Parvo Test, IDEXX Laboratories) have high positive and negative predictive values for the detection of canine parvovirus (CPV)-2 and can also detect feline panleukopenia virus.[19,20] New studies also show that these assays identify all three CPV types—2a, 2b, and 2c.[19] However, low virus loads may remain undetected with in-house immunoassays and PCR assays have been shown to have a superior analytical sensitivity.[21] Samples from animals that are suspected to have parvovirus infection, but have a negative SNAP test result, can be submitted to a reference laboratory for assessment by PCR or electron microscopy. A disadvantage of the in-house SNAP test is that it cannot differentiate vaccine strains from infectious strains of CPV-2.

Detection of Gastrointestinal Parasites in Feces

Fecal Examination Techniques

Testing for GI parasites is an important part of the diagnostic workup of patients with signs of GI disease. Successful identification of parasites is highly dependent on the quantity (2 to 5 g of feces is optimal) and quality (i.e., freshness) of feces obtained and the storage conditions of the sample. Additional factors determining success include the technique used (e.g., fecal smear, fecal flotation, antigen testing, or PCR) and the expertise of the examiner.

For in-house testing it is important to design a standard operating procedure to ensure that each procedure will be performed in a consistent, systematic, and reproducible manner. All fecal examination techniques have technical limitations. Therefore, negative results do not exclude the possibility of parasite infection, but may reflect low analytical sensitivity of the method used, absence of organisms in the aliquot examined, or intermittent shedding of organisms (e.g., *Giardia*).

Fecal examination techniques include direct fecal smears, fecal flotation with or without centrifugation, sedimentation techniques, antigen testing, and PCR assays. Generally, centrifugal flotation and antigen testing are considered to have the highest analytical sensitivity.

Direct fecal smears (wet mounts; a small amount of feces is mixed with saline yielding a layer that is thin enough to read newsprint through) may be useful for recovery of motile trophozoites (e.g., *Giardia* and *Tritrichomonas foetus*), but should only be performed on very fresh fecal samples (<10 minutes). Adding a drop of Lugol iodine may improve the detection of trophozoites. Additional slides can be prepared and stained (e.g., Diff-Quik) for cytologic examination (e.g., presence of neutrophils, bacterial spores). A disadvantage of direct smears is that only a low sample volume can be analyzed, resulting in a low sensitivity for the detection of intestinal parasites.

Fecal flotation techniques allow the separation of parasites from fecal debris because of the difference in specific gravity of parasite forms (Fig. 25-2). If the flotation solution has a higher specific gravity than the parasite form (e.g., eggs, oocysts, cysts), these will rise to the surface and can be identified (Table 25-1). Because flotation techniques allow the concentration of parasites, a higher sample volume (1 to 5 g) can be analyzed, improving the analytical sensitivity. Fecal flotation should be prepared on fresh feces (<2 hours). Flotation can be performed either as a passive separation technique (e.g., commercial kits including Fecalyzer, Ovassay) or as a centrifugation technique with either a fixed rotor or a swinging bucket rotor. Centrifugation techniques show a consistently higher recovery compared with passive techniques and are currently recommended for routine use in practice. In one study, a direct smear technique failed to identify whipworm eggs 93% of the time.[22] A passive flotation technique (e.g., Ovassay) yielded false-negative results in 30% of samples, while the centrifugation technique using Sheather's Sugar Solution yielded false-negative results in only 5%

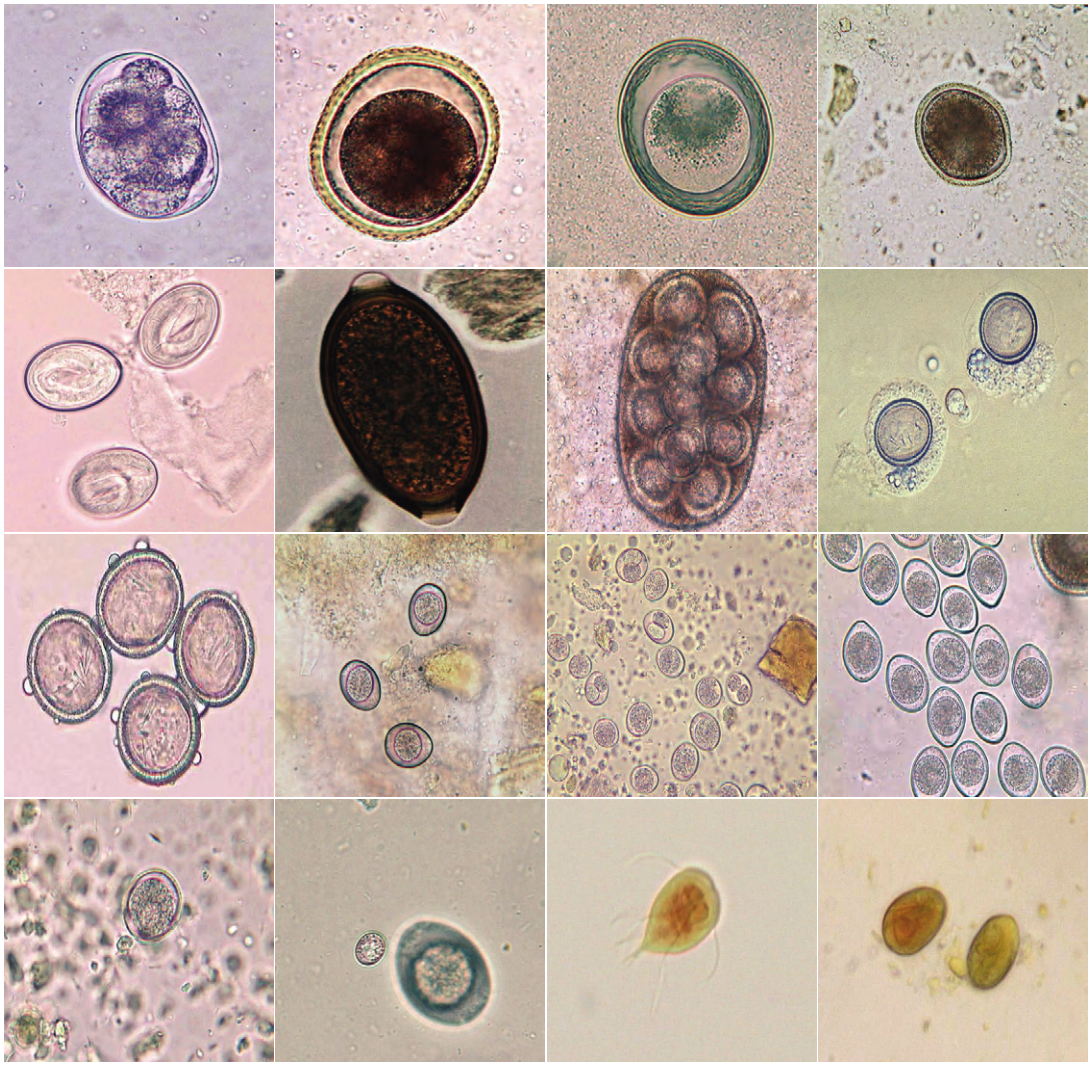


Figure 25-2 Commonly observed parasite eggs, oocysts, and trophozoites in fecal samples. Row 1, left to right: *Ancylostoma caninum* egg, *Toxocara canis* egg, *Toxascaris leonina* egg, *Toxocara cati* egg. Row 2, left to right: *Physaloptera* spp. eggs, *Trichuris vulpis* egg, *Dipylidium caninum* egg basket, *Echinococcus granulosus* eggs. Row 3, left to right: *Taenia* spp. eggs, nonsporulated oocysts of *Isospora canis*, nonsporulated oocysts of *Isospora ohioensis*, nonsporulated oocysts of *Isospora felis*. Row 4, left to right: nonsporulated oocysts of *Isospora rivolta*, *Toxoplasma gondii* unsporulated oocysts compared with *Isospora felis* in the background, *Giardia* spp. trophozoite, *Giardia* spp. cysts (iodine stain). (All photos courtesy of Dr. Byron L. Blagburn, College of Veterinary Medicine, Auburn University.)

of the samples examined.[22] Similar results were also observed for other parasite types. The recovery of parasites using commercially available passive flotation kits (e.g., Ovassay) can be improved if the flotation solution is applied for at least 20 minutes.

Box 25-1 summarizes the standard procedure for the centrifugal flotation technique. The specific gravity of the flotation solution plays a critical role in the identification of parasites. The higher the specific gravity of the parasite egg, the higher must be the specific gravity of the flotation solution to allow the ova to rise to the surface. For example, eggs of *Physaloptera* spp. (specific gravity 1.14) and *Taenia* spp. (specific gravity 1.23) have a higher specific gravity than the commonly used $ZnSO_4$ solutions (specific gravity 1.18), thus they will likely remain undetected. Table 25-2 lists the specific gravity of commonly used flotation solutions, and Table 25-1 lists the specific gravity of common parasite eggs. A specific gravity hydrometer may be used to measure the correct specific gravity of the solution. The use of a micrometer to measure the size of cysts and eggs may help identify parasites (see Table 25-1). The use of centrifugation and Sheather's Sugar Solution (specific gravity 1.27; commercially available from Jorgensen Laboratories) is currently recommended as the most efficient method for the recovery of the most common parasite eggs and oocysts.[23]

Diagnosis of Parasites of the Esophagus and Stomach During Fecal Examination

Spirocerca lupi eggs are barrel shaped and elongated with parallel sides (Fig. 25-3). Compared with other parasite eggs they are small (see Table 25-1), typically measuring 20 to 37 × 11 to 18 μm, and contain a larva when laid. The current gold standard for the detection of *S. lupi* is esophageal endoscopy and is required for differentiation between neoplastic and nonneoplastic *S. lupi* nodules.[25] Thoracic radiography is up to 86% sensitive if signs of thoracic vertebrae spondylitis, an undulating aortic border, and a caudal mediastinal mass are included.[24] The reported sensitivity for the

Table 25-1 Characteristics of Important Gastrointestinal Parasites

Parasite	Host	Diagnosis	Size of Reproductive Product (in μm)	Specific Gravity
Nematodes				
Ancylostoma caninum	Dogs	Flotation	70 × 45	1.06
Ancylostoma braziliense	Dogs and cats	Flotation	70 × 45	1.06
Uncinaria stenocephala	Dogs and cats	Flotation	80 × 45	1.06
Ancylostoma tubaeforme	Cats	Flotation	70 × 45	1.06
Toxocara canis	Dogs	Flotation	85 × 75	1.09
Toxocara cati	Cats	Flotation	75 × 65	1.10
Toxascaris leonina	Dogs and cats	Flotation	82 × 70	1.06
Trichuris vulpis	Dogs	Flotation	80 × 38	1.15
Ollulanus tricuspis	Cats	Worms in vomitus	n/a	n/a
Physaloptera spp.	Dogs and cats	Endoscopy[1]	50 × 35	1.24
Spirocerca lupi	Dog	Endoscopy/radiograph, centrifugal flotation with $NaNO_3$ (1.22 SG)[1]	20-37 × 11-18	Unknown
Cestodes				
Taenia spp.	Mostly dogs[2]	Flotation	37 × 32	1.23
Echinococcus spp.	Dogs	Flotation[3]	Similar to *Taenia* spp.	1.23
Dipylidium caninum	Dogs and cats	Flotation	45 × 45	Unknown
Trematodes				
Platynosomum fastosum	Cats	Sedimentation	45 × 30	Unknown
Heterobilharzia americana	Dogs	Sedimentation in saline or PCR	80 × 100	Unknown
Protozoa				
Isospora spp.	Dogs and cats	Direct smear or flotation	15 to 50 in diameter, variable	Unknown
Giardia intestinalis	Dogs and cats	Immunofluorescence assay (IFA), $ZnSO_4$ centrifugal flotation, immunoassay	Trophozoites 14 × 8; cysts 11 × 9	Unknown
Toxoplasma gondii	Cats	Serology	10 to 12 in diameter	N/A
Cryptosporidium parvum	Dogs and cats	IFA, immunoassay	4 to 6 in diameter	N/A
Tritrichomonas foetus	Cats	PCR, culture, or direct smear	Variable	N/A

[1]Eggs difficult to find even with centrifugal flotation or sedimentation.
[2]*Taenia taeniaeformis* in cats.
[3]Cannot distinguish eggs from *Taenia* spp.

Table 25-2 Specific Gravities of Flotation Solutions

Solution	Specific Gravity*	Preparation in Water
Water	1.00	N/A
Sodium chloride	1.18	350 g per 1 L
Magnesium sulfate	1.20	450 g per 1 L†
Zinc sulfate	1.18	331 g per 1 L
Sodium nitrate	1.18	338 g per 1 L
Sheather's sucrose¶	1.27	454 g per 355 mL w/ 6 mL formaldehyde†

*Verify specific gravity with hydrometer.
†Water must be heated to get substance into solution.
¶Recommended flotation solution.

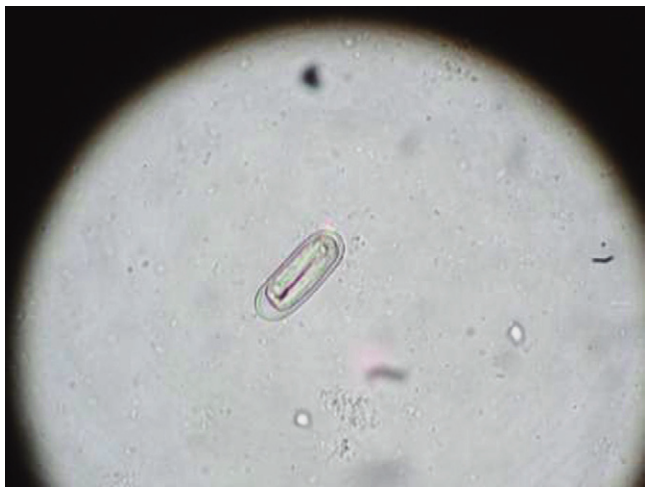


Figure 25-3 *Spirocerca lupi* egg containing a larva. The eggs are small and barrel-shaped. The reported sensitivity for the detection of eggs in feces is low and was highest (67%) when using a centrifugal flotation technique with $NaNO_3$ (specific gravity 1.22). Endoscopy is the recommended method for the detection of *Spirocerca lupi* (×400). (Picture courtesy of Dr. Jevan Christie, University of Pretoria, South Africa.)

Box 25-1 Procedure for Fecal Examination Using a Centrifugation Technique

1. Two to 5 g of feces (preferably abnormal stool) are mixed with 10 mL of flotation solution.
2. This emulsion is poured through a tea strainer or a cheese cloth into a fecal cup. Straining is important to remove the heavy fecal matter.
3. The emulsion is poured into a 15-mL conical centrifugation tube. The amount of flotation solution to be added depends on the rotor used (swinging bucket or fixed angle).

- *Swinging bucket rotor:* flotation solution is added to create a slightly positive meniscus (but do not overfill the tube to avoid spilling of parasite eggs).
  - Cover slip is placed on top of the tube *before* centrifugation.
  - Tube is centrifuged for 5 minutes at 280 g (1200 rpm).
  - The tube (with coverslip) is removed and let stand for 10 minutes.
- *Fixed angle rotor:* the tube is filled only ¾ full with flotation solution.
  - Tube is centrifuged for 5 minutes at 280 g (1200 rpm).
  - After centrifugation, more flotation solution is carefully added with a pipette down the side of the tube until the positive meniscus is created on top of the tube.
  - The coverslip is now placed on top of the tube and let stand for 10 minutes.

4. The coverslip is removed after 10 minutes and placed on a glass slide. The entire glass slide should be systematically scanned using ×10 magnification (i.e., 100 diameters). The ×40 magnification can be used for identification and measurement of parasites. It is important to standardize the procedure (including microscopic examination) for consistent results.

detection of eggs in feces is low and was highest (reaching 67%) using a centrifugal flotation technique with $NaNO_3$ (specific gravity 1.22).[25]

Stomach worms can cause vomiting, anorexia, melena, and anemia. The small stomach worm of cats (*Ollulanus tricuspis*; size 0.7 to 0.9 cm) can be detected during microscopic examination of vomitus or gastric lavage solution. *O. tricuspis* is sometimes also observed in dogs. Eggs of the large stomach worm of dogs and cats (*Physaloptera* spp.) have a high specific gravity (see Table 25-1) and are therefore difficult to detect in fecal smears or by fecal flotation using standard flotation solutions. However, as a result of the size and appearance of the worms (1 to 6 cm in length, cream to white colored, often coiled), they can be sometimes visualized in vomitus or during endoscopic examination.

Diagnosis of Parasites of the Small and Large Intestine

Giardia spp.

A centrifugation technique using Sheather's Sugar Solution is currently considered the best method for performing routine fecal flotation in practice; however, the sugar solution may distort or even destroy *Giardia* cysts, making them more difficult to diagnose for an inexperienced examiner. Therefore, the use of $ZnSO_4$ (specific gravity 1.18 to 1.2) may be a better method for diagnosis of *Giardia* spp. in practices that do not routinely analyze fecal samples. However, even the use of $ZnSO_4$ requires an experienced examiner and false negatives can occur. The in-clinic *Giardia* SNAP test

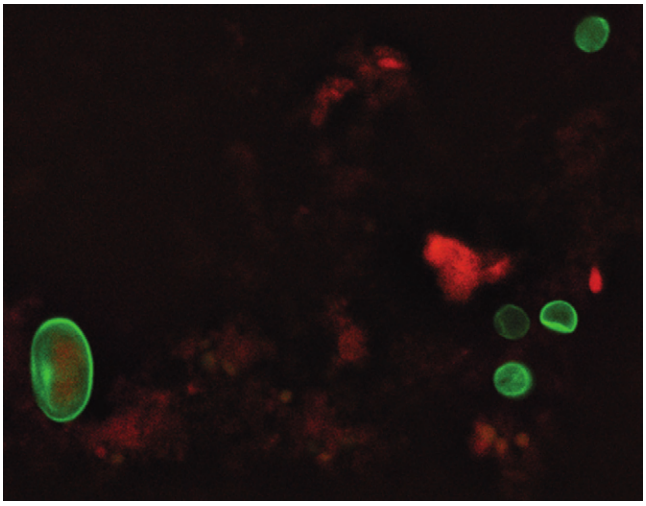


Figure 25-4 Immunofluorescence assay (IFA) for the simultaneous detection of *Giardia* and *Cryptosporidium* spp. in canine or feline fecal samples. The assay utilizes fluorochrome-labeled antibodies directed against *Giardia* (large green oval structure on the *left*) and *Cryptosporidium* (smaller green four round structures on the *right*). Fecal debris is stained red (×100). (Picture courtesy of Dr. Yasushi Minamoto, GI Lab, Texas A&M University.)

(IDEXX SNAP *Giardia* test) has a comparable sensitivity to $ZnSO_4$ centrifugation and ameliorates the need for identification of *Giardia* cysts based on morphology. However, false-negative results can occur and the combination of the SNAP *Giardia* test and $ZnSO_4$ centrifugation performed on the same sample may show the highest sensitivity.[23] *Giardia* cysts are shed intermittently and a single negative result on either or both of these tests does not rule out a *Giardia* infection. Therefore, the examination of three consecutive fecal samples over a period of 7 days (or pooled samples from consecutive defecations) examined using both $ZnSO_4$ and the *Giardia* SNAP test may achieve 94% accuracy.[26] It is important to note that the number of recovered cysts is typically independent of the clinical disease. Cysts are shed intermittently and it is not possible to draw conclusions about the severity of the disease.

The detection of *Giardia* antigen using a fluorochrome-labeled monoclonal antibody (immunofluorescence antibody test [IFA]; Merifluor *Cryptosporidium/Giardia* Direct Immunofluorescence Test Kit; Meridian Bioscience Inc, Cincinnati, Ohio) is often used as the gold standard for the diagnosis of a *Giardia* infection (Fig. 25-4).[27,28] A recent study compared IFA with $ZnSO_4$ flotation centrifugation, the in-clinic IDEXX SNAP *Giardia* test, and a commercial ELISA for *Giardia* antigen (*Giardia* II Test Direct ELISA; Techlab Inc, Blacksburg, Virginia). The authors found discordant results, suggesting that at the observed prevalence rates in a clinical setting (estimated prevalence rate: 4% to 10%), the in-house tests have poor positive predictive values but good negative predictive values.[27] This would suggest that when used in practice, these assays are helpful in ruling *out* giardiasis, but are incapable of ruling *in* the diagnosis.[27] These results also indicate that the in-house methods should not be used as screening tools in healthy animals, as false-positive results may occur, leading to an improper diagnosis and treatment.[27]

The use of a nested PCR assay for the detection of *Giardia* from fecal samples has been reported, and has shown good sensitivity for detecting *Giardia duodenalis* in cats.[29] The nested PCR allows determination of the genotype (also called assemblage) of the organisms, which is useful for epidemiologic studies.[29,28]

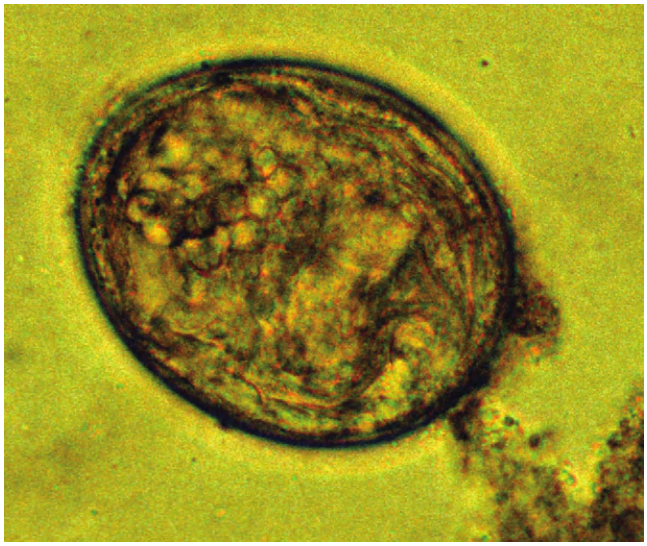


Figure 25-5 *Heterobilharzia americana* egg as visualized using sodium chloride precipitation. (Photograph courtesy of Dr. Thomas Craig, Texas A&M University.)

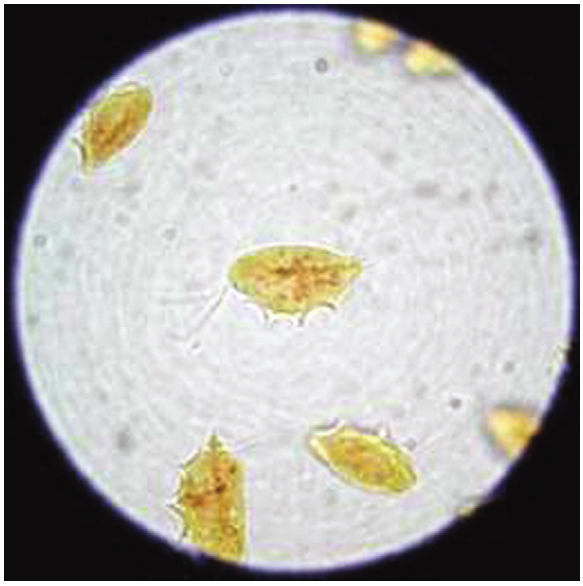


Figure 25-6 ***Tritrichomonas foetus*.** Appearance of an individual *T. foetus* organism stained with Lugol iodine solution. Three anterior flagellae and an undulating membrane that runs the length of the body can be seen. (Image reproduced with permission from www.fabcats.org; photo by Dr. A. Sparkes.)

Cryptosporidium spp.

Cryptosporidium oocysts can be isolated using centrifugal flotation with sucrose, but this technique showed a low sensitivity of 21.4% in one study.[30] The oocysts have a spheroid shape and because of their very small size (4 to 6 μm in diameter), they can easily be missed on fecal smears. An acid-fast stain will stain the oocysts red on fecal smears. The currently recommended test for detection of *Cryptosporidium* spp. is an IFA that will also simultaneously identify *Giardia* cysts (Merifluor *Cryptosporidium*/*Giardia* Direct Immunofluorescence Test Kit; Meridian Bioscience Inc, Cincinnati, Ohio). This test requires a fluorescence microscope and is offered by major reference laboratories. Figure 25-4 illustrates the size comparison between *Cryptosporidium* oocysts and *Giardia* cysts using the IFA.

A PCR test has been described, showing a higher analytical sensitivity for *Cryptosporidium parvum* in feline fecal samples compared with IFA.[31] In a study of dogs and cats with diarrhea, 24.3% were positive for *Cryptosporidium* on PCR, while only 2.7% were positive on IFA.[32] Commercially available in-clinic immunoassays have a low analytical sensitivity (42.9% to 71.4%) compared with IFA, but have been shown to have acceptable specificity (>96%) for detecting *Cryptosporidium* spp. in feline fecal samples.[30]

Canine Schistosomiasis

Canine schistosomiasis, also named bilharziasis, is caused by the trematode *Heterobilharzia americana*. Nutria, raccoons, and other vermin are the natural reservoirs for *H. americana*. Transmission is via penetration of the skin by cercariae in water sources containing the snail intermediate host. Clinical signs of infected dogs include lethargy, weight loss, hyporexia, vomiting, and diarrhea.[33] Diagnosis can be made on visualizing a granulomatous response to the migrating eggs in the hepatic or intestinal tissue at necropsy or histopathology. Parasite eggs can be demonstrated using saline fecal sedimentation (Fig. 25-5).[34] Canine schistosomiasis can also be diagnosed with an immunoassay detecting antigen in feces or urine that was originally developed for use in humans or by a fecal PCR assay specific for *H. americana*.[33]

Tritrichomonas foetus

T. foetus, a flagellated protozoan, has been identified as a pathogen in cats, causing diarrhea after both experimental and natural infection.[35] Trichomonads do not form cysts, but they reproduce by binary fission and are transmitted directly between hosts as trophozoites (Fig. 25-6). Pathogenic and nonpathogenic species of trichomonads can be found in the GI tract of dogs and cats. Diagnosis of a *T. foetus* infection can be made by the visualization of trophozoites on a direct fecal smear, by culture or PCR analysis of fecal material, or by observation of organisms in colonic mucosal biopsy specimens. The best results for all the detection methods are obtained if diarrheic stools are examined. Direct fecal smear examination has a low sensitivity (<14%) and low specificity (*T. foetus* can be misdiagnosed as *Giardia* spp. or the nonpathogenic *Pentatrichomonas hominis*). For the cultivation of organisms, the in-house culture system (In Pouch TF; Biomed Diagnostics, San Jose, California) should be inoculated with approximately 50 mg of freshly voided, loop or flush-collected feces, and then incubated at 25°C (77°F) for up to 12 days.[36] The pouch must be evaluated under a microscope every couple of days. *Giardia* spp. and *P. hominis* organisms do not survive in the culture media for longer than 24 hours and thus positive cultures are strongly suggestive of *T. foetus* infection.[36] The reported sensitivity for culture is 1000 *T. foetus* organisms per 50 mg of feces. *T. foetus* DNA can be amplified from fecal samples by PCR.[37] A nested PCR assay has been reported as the most sensitive method for detecting *T. foetus* in fecal samples (10 *T. foetus* organisms per 50 mg of feces).

Assessment of Gastrointestinal Function and Pathology

Gastrointestinal Permeability Testing

Various GI diseases can cause epithelial damage that will lead to an increase in intestinal permeability and subsequently to the translocation of antigens and/or pathogens through the intestinal mucosa. For the assessment of GI permeability exogenous nonmetabolizable markers, such as polyethylene glycol (PEG), mono- and

disaccharides, or radiolabeled substances are administered orally.[38-40] An increased recovery of those markers (e.g., lactulose, 51-chromium-labeled ethylenediaminetetraacetate [^{51}Cr-EDTA]) in serum or urine indicates an increase in GI permeability, while a decreased recovery of other markers indicates a decreased absorptive capacity of the marker (e.g., methylglucose).[39] Traditional probes such as ^{51}Cr-EDTA and PEG do not undergo metabolism or bacterial degradation in the GI tract and remain intact during their passage through the gut. Therefore the increased appearance of such probes in serum or urine indicates an increased permeability of the GI tract, but it is not helpful in localizing a specific site of the GI tract. In contrast, the various sugar probes are metabolized or undergo bacterial degradation in different parts of the GI tract. Therefore, a mixture of sugar probes can be used to help localize the site of increased GI permeability. For example, orally administered sucrose is too large to penetrate the intact gastric mucosa and is broken down by brush border enzymes upon entering the small intestine. Therefore, sucrose is typically not recovered in urine or serum of healthy animals with an intact gastric mucosa. However, an increase in the urine or serum concentration of sucrose is indicative of an increased gastric permeability suggestive of gastric mucosal damage. In contrast, the sugar probes lactulose and mannitol will survive the passage through the stomach and proximal small bowel, but will undergo bacterial degradation in the distal small intestine and colon. Therefore, changes in their recovery suggest an altered permeability in the small intestine. Sucralose is resistant to bacterial degradation in the colon and is also not absorbed in the GI tract. An increase in serum or urine sucralose can therefore be indicative of increased GI permeability in any part of the intestine. If sucralose is used in combination with other sugar probes, it can serve as a marker for large bowel permeability (i.e., increase in sucralose concentration but normal concentration of small intestinal sugar probes).

Rhamnose (R) and lactulose (L) are commonly used as markers for small intestinal permeability. The monosaccharide rhamnose crosses the epithelium passively through small pores in the intestinal cells (transcellular uptake). The disaccharide lactulose crosses the epithelium through larger pores located near the tight junctions of the intestinal cells (paracellular uptake). These larger pores occur less frequently than the smaller pores that allow penetration of monosaccharides. In animals with an intact intestinal epithelium, less lactulose in relation to rhamnose (expressed as lactulose/rhamnose [L/R] ratio) will cross the intestinal mucosa and can be recovered in serum or urine. Intestinal disorders cause a decrease in the total epithelial surface area in the intestine, causing a reduction in the transcellular pores and an increase in the permeability of the tight junctions. This results in an increase in the L/R recovery ratio. For the evaluation of small intestinal absorptive capacity, the monosaccharides xylose (X) and methylglucose (M) are commonly used, as they both are absorbed through a carrier-mediated transport. The two different markers are often measured together to assess intestinal damage, as xylose is absorbed by fructose carriers and methylglucose is absorbed by glucose carriers in the small intestine.[38,40]

Measurement of permeability may be helpful in disorders that are not accompanied by histopathologic changes in the GI mucosa. For example, increases in intestinal permeability have been reported in dogs with small intestinal bacterial overgrowth (SIBO), gluten-sensitive enteropathy, intestinal ischemia–reperfusion injury, nonsteroidal antiinflammatory drug–induced damage, and diet-responsive diarrhea.[41,42] However, intestinal permeability testing was not useful as an indicator of clinical disease activity in dogs with chronic enteropathies.[38] There is currently a lack of standardization for the various methods used for the assessment of intestinal permeability among laboratories. Furthermore, only few studies have been performed in clinical patients, and the interpretations of the results of GI permeability testing have not been well elucidated for routine clinical settings.

Evaluation of Intestinal Protein Loss

Protein-losing enteropathy (PLE) is defined as a heterogeneous group of diseases in which plasma proteins are lost into the GI lumen. Any GI disease, if severe enough, can lead to intestinal protein loss. Common causes for PLE include inflammatory enteropathies (e.g., inflammatory bowel disease [IBD]), infectious enteritis (bacterial, parasitic, or fungal enteritis), lymphangiectasia, intestinal neoplasia (e.g., lymphoma), intussusception, immunoproliferative disease, and small intestinal dysbiosis.[43] Although most animals with GI protein loss display panhypoproteinemia, it is not uncommon to encounter patients with hypoalbuminemia but without hypoglobulinemia. This is a result of an increased globulin production caused by concurrent or underlying disease (e.g., histoplasmosis, ehrlichiosis, chronic skin disease, immunoproliferative small intestinal disease in the Basenji). Therefore, it is crucial to determine serum albumin concentrations in addition to total plasma protein. Other causes of protein loss such as protein-losing nephropathy and hepatic insufficiency must be excluded.[43]

ELISAs for the measurement of fecal α_1-PI (α_1-proteinase inhibitor) have been validated for cats and dogs and are useful in assessing protein loss through the GI tract.[44,45] α_1-PI is a serum proteinase inhibitor, and is present in the lumen of the GI tract in trace amounts. α_1-PI has a similar molecular mass (approximately 60 kDa) to albumin. When GI disease is severe, α_1-PI is lost together with albumin into the lumen. Albumin is usually rapidly degraded by proteolytic enzymes, but α_1-PI is a proteinase inhibitor that is resistant to proteolytic enzymes and can be measured in feces as an intact molecule. α_1-PI serves as an indicator of loss of plasma proteins into the GI tract.

If intestinal protein loss is suspected in patients with concurrent renal or hepatic disease, the measurement of fecal α_1-PI concentration may help distinguish PLE from other causes of protein loss. Measurement of fecal α_1-PI can also be useful in animals with hypoalbuminemia that do not have signs of GI disease and where renal or hepatic causes of protein loss have been excluded. Fecal α_1-PI may be increased before protein loss is severe enough to lead to hypoalbuminemia. It should be noted that puppies and kittens younger than 1 year of age have significantly higher concentrations of fecal α_1-PI.

Other methods for the measurement of enteric protein loss involve determining the recovery of intravenously administered radioactively labeled substances (e.g., ^{51}Cr-albumin) in fecal samples.[46] Although considered the gold standard, those tests have the obvious disadvantage of the use of radioactivity.

Minimally Invasive Markers for Assessment of Gastric and Intestinal Inflammation and Damage

Serum Gastrin

A commercially available chemiluminescence immunoassay for use in humans (Immulite 2000, Siemens Diagnostics) has been validated for measurement of serum gastrin concentrations in dogs and cats.[47] Serum should immediately be separated from blood cells, frozen, and shipped on ice. The measurement of serum gastrin is useful in cats and dogs with unexplained gastric erosion or ulceration and mucosal hyperplasia. A several-fold and persistent increase (multiple consecutive samples should be evaluated after a 12- to

24-hour fast) in serum gastrin concentration in animals with concurrent clinical signs is suggestive of a gastrinoma. Normal fasting serum gastrin concentration makes gastrinoma unlikely. If serum gastrin is not markedly increased and a gastrinoma is suspected, a secretin stimulation test can be performed. However, it should be noted that, at least in dogs, the administration of a proton pump inhibitor can lead to massive increases of serum gastrin concentrations. Thus, such medication should be discontinued for at least 10 days before measurement of serum gastrin concentration,

Inflammatory Markers

Fecal calprotectin (also called calgranulin A/B or S100A8/A9) and calgranulin C (S100A12) have been reported to be increased in serum and/or plasma in human patients with various inflammatory disorders and are also sensitive and specific fecal markers for human IBD. Species specific assays for dogs have been developed and show promise for the assessment of intestinal inflammation in this species.[48,49] The clinical utility of these assays is under investigation. *N*-methylhistamine is a stable metabolite of histamine and has been used as a marker for mast cell activity and systemic release of histamine in human IBD. The use of *N*-methylhistamine in dogs and cats as a marker for GI disease is currently under investigation.

C-reactive protein (CRP) is a sensitive but nonspecific inflammatory marker and has been shown to correlate with the degree of experimentally induced damage to the gastric mucosa and with the clinical activity index in canine IBD.[50,51] New studies have evaluated the index of variability for CRP, suggesting that the use of population-based reference range is not appropriate for evaluating changes in CRP concentrations in individual patients (Ruaux CG, research abstract, ACVIM Forum 2010). Therefore, for assessment of the severity of GI disease, serial CRP measurements should be performed, and modest changes in serum CRP concentrations may indicate of the severity of GI disease.

Citrulline

Citrulline is an amino acid that is synthesized mostly by intestinal enterocytes and also to some degree by hepatocytes. Citrulline has been used as a marker of functional enterocyte metabolic mass. For example, human studies have demonstrated a correlation between fasting plasma citrulline concentrations and the functional length of the small intestine in patients with short bowel syndrome.[52] Plasma citrulline concentration has been shown to be significantly decreased in dogs with parvovirus enteritis, indicating that citrulline is a potential marker for spontaneous acute and severe intestinal failure.[53]

Occult Blood Testing

Fecal occult blood tests are used to detect blood in stools before visible melena occurs. Several assays are commercially available and are based on different test principles (e.g., guaiac or o-toluidine fecal occult blood tests). Their clinical use in dogs and cats is limited as they have poor sensitivity and specificity. Because the assay is not specific for a patient's hemoglobin, but can also react with any dietary hemoglobin, false-positive test results occur frequently. Therefore, to increase the specificity of occult blood testing, patients must ideally be on a meat-free diet for at least 3 days before fecal samples are collected.[54] However, it should be noted that the effect of diet is much smaller on tests based on o-toluidine when compared with those based on guaiac. Tests performed on three consecutive bowel movements may help to avoid false-negative results. Manual stool collection may cause iatrogenic blood contamination.

Miscellaneous Tests

An increased plasma L-lactate concentration (>6.0 mmol/L) has been shown to be a negative prognostic marker for postoperative survival time in dogs following gastric dilation volvulus.[55] Serum pepsinogen concentrations have been measured in humans to assess gastric inflammation and *H. pylori* infection. However, serum pepsinogen and serum gastric lipase concentrations were not useful in detecting gastric lesions in dogs or cats.[56]

Evaluation of Gastrointestinal Motility

The assessment of GI motility remains challenging, mostly because of the lack of practical and reproducible minimally invasive test procedures.[57] Scintigraphy is considered the gold standard for evaluation of gastric emptying but requires the use of a radioactive probe. Alternatively, radiopaque markers, such as barium-impregnated polyethylene spheres (BIPSs), have been introduced as an alternative. Both these markers have the disadvantage that, depending on their size, they only mimic emptying of either solid or liquid food.[58] Ultrasonography is a reliable and quantitative method for assessing the emptying time of liquids and solids when performed by an experienced ultrasonographer. A minimally invasive method to assess gastric emptying time in dogs and cats is the ^{13}C-octanoic acid breath test.[59] This test allows labeling of a complex meal with ^{13}C-octanoic acid, a medium-chain fatty acid that is absorbed in the duodenum. In liver ^{13}C is released and oxidized. A rise in $^{13}CO_2$ in the expiratory air or in blood indicates that gastric emptying has occurred.

The use of a wireless capsule (SmartPill), originally designed for use in humans, has been reported for assessment of GI motility in dogs.[60] The capsule measures 13 × 26 mm and is given orally to dogs. The capsule records pH, pressure, and temperature along its passage through the GI tract. These parameters allow calculation of gastric emptying time, small intestinal and/or colonic transit time, and also the total GI transit times. This system appears reproducible in dogs, and changes in GI motility in response to dietary modification and motility altering drugs have been demonstrated. Because of the size of the capsule, it leaves the stomach at the onset of the interdigestive migrating motor complexes (MMCs) after all liquids and solids have already been propelled into the small intestine. Because of the size of the capsule, this method cannot be used in cats and only in dogs of more than 15 kg body weight.

Assessment of Intestinal Function and Pathology

Serum Cobalamin and Folate

The uptake of cobalamin (vitamin B_{12}) and folate from the small intestine is dependent on several factors and can therefore be used as an indirect marker for the assessment of GI disease. Disorders that may affect serum cobalamin and/or folate concentrations include small intestinal inflammation, exocrine pancreatic insufficiency (EPI), and small intestinal dysbiosis (also referred to as small intestinal bacterial overgrowth [SIBO] or antibiotic-responsive diarrhea [ARD]). As a consequence of different sites of absorption, specific changes in serum cobalamin and folate concentrations can yield information on the localization and potentially the severity of intestinal disease (Table 25-3). Serum concentrations of cobalamin and folate should be assessed in any dog or cat with clinical signs of GI disease.

Cobalamin

Cobalamin is an essential, water-soluble vitamin and an important cofactor for many biochemical reactions. Canine and feline diets contain plentiful cobalamin, making a dietary insufficiency unlikely.

Table 25-3 Interpretation of Serum Cobalamin and Folate Concentrations in Dogs and Cats with Gastrointestinal Diseases

	Serum Folate	Serum Cobalamin
Increased	Dogs: small intestinal bacterial overgrowth Cats: clinical significance unknown Increased dietary intake of folic acid Vitamin supplementation	Clinical significance unknown in dogs and cats Recent parenteral administration (<4 weeks) of cobalamin
Decreased	Proximal or diffuse small intestinal disease (e.g., IBD, lymphoma, fungal disease)	Distal or diffuse small intestinal disease involving the ileum (e.g., IBD, lymphoma, fungal disease) Small intestinal bacterial overgrowth Exocrine pancreatic insufficiency Hereditary cobalamin malabsorption Low dietary intake (vegetarian diet)

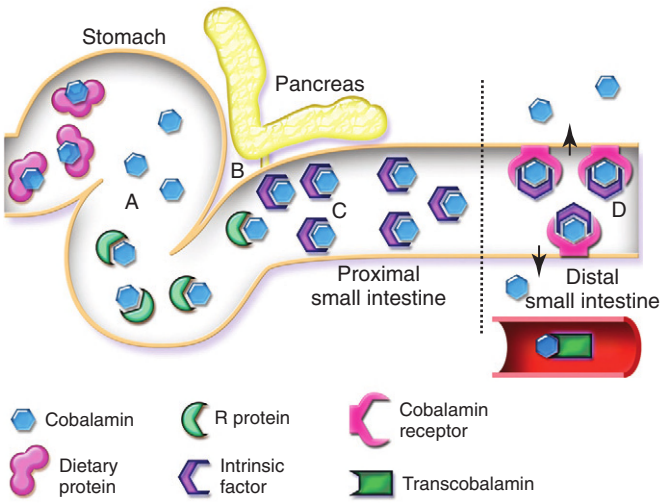


Figure 25-7 Absorption of dietary cobalamin. A, In the diet, cobalamin is bound to dietary protein. After digestion of these proteins in the stomach by pepsin and hydrochloric acid, cobalamin is released and immediately bound to R-protein, which is secreted in saliva and gastric juice. **B**, Pancreatic enzymes (i.e., trypsin and chymotrypsin) digest R-protein, again releasing cobalamin. **C**, Intrinsic factor, produced mostly in the pancreas in dogs and exclusively in the pancreas in cats binds to cobalamin and serves as a transporter to the distal small intestine (i.e., ileum). **D**, Cobalamin/intrinsic factor complexes are absorbed by specific receptors located in the ileal mucosa. (Reprinted from Suchodolski J, Steiner J. Laboratory assessment of gastrointestinal function. *Clin Tech Small Anim Pract* 18:207, 2003. With permission from Elsevier.)

However, patients that are fed an exclusively non-fortified vegetarian diet for longer periods may develop cobalamin deficiency unless supplementation occurs.

The physiologic mechanism of cobalamin absorption is complex and requires a functioning digestive system (Fig. 25-7). Dietary cobalamin is bound to animal-based protein. After digestion of these carrier proteins in the stomach, the cobalamin is immediately bound to R-protein, a cobalamin transporter secreted in saliva and gastric juice. Pancreatic enzymes (i.e., trypsin and chymotrypsin) digest the R-protein in the small intestine, and the free cobalamin is bound by intrinsic factor. The exocrine pancreas is a major source of intrinsic factor in dogs and appears to be the exclusive source of intrinsic factor in cats.[61] This is in contrast to humans where intrinsic factor is produced predominantly in the stomach. Intrinsic factor/cobalamin complexes are then absorbed by specific mucosal receptors located in the ileum.

Major disorders that interfere with cobalamin uptake are EPI, distal or diffuse small intestinal disease, and excess bacterial utilization of cobalamin in bacterial dysbiosis. Aberrations in the small intestinal microbiota may lead to increased competition for cobalamin resulting in decreased absorption by the host. Bacteria in the gut may compete with receptors located in the distal small intestine and prevent cobalamin uptake by enterocytes. *Bacteroides* spp. are the principal organisms involved because they can utilize cobalamin-intrinsic factor, whereas other bacteria can only bind free cobalamin, which is present in lower concentrations in the gut. The reported sensitivity of serum cobalamin for the diagnosis of SIBO is 25% to 55%.[62]

Any long-standing and severe intestinal disease (e.g., IBD, lymphoma, or fungal disease) affecting the ileum may also lead to damage of mucosal cobalamin receptors. This can cause cobalamin malabsorption with a subsequent depletion of body stores of cobalamin, and ultimately lead to a decreased serum cobalamin concentration.

Abnormalities of both vitamins are common in dogs and cats with EPI. Therefore, EPI should be ruled out in patients with GI signs and a decreased serum cobalamin concentration. Serum cobalamin must bind to intrinsic factor in order to be absorbed by receptors located in the distal ileum. Because the exocrine pancreas is the exclusive source of intrinsic factor in cats and the main source in dogs, EPI will lead to decreased secretion of intrinsic factor and, therefore, decreased uptake of cobalamin. Cats with EPI almost always have subnormal serum cobalamin concentrations. Similar subnormal cobalamin concentrations have been described in excess of 80% in dogs with EPI.[63]

The measurement of serum concentrations of cobalamin is only an indirect test for assessing cobalamin deficiency. Cobalamin deficiency leads to accumulation of serum or urine methylmalonic acid (MMA), the concentrations of which are often dramatically increased in patients with cobalamin deficiency and have been shown to decrease with cobalamin supplementation.[64] It has also been shown that some patients with low normal serum cobalamin concentrations have increased MMA concentrations, indicating cobalamin deficiency on a cellular level.[64] Therefore, cobalamin deficiency may even be present when serum cobalamin concentration is in the low end of the reference interval (<350 ng/L) and parenteral cobalamin supplementation should be considered in patients with compatible clinical signs. The measurement of MMA concentration is technically challenging and currently only available through few laboratories. Very young puppies (up to 13 weeks) have been shown to have lower serum cobalamin concentrations than adult dogs. Also, a hereditary form of cobalamin deficiency has

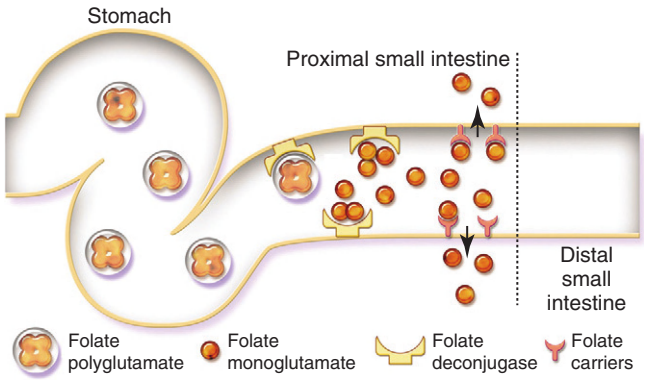


Figure 25-8 Absorption of folate. Dietary folate is usually present in the poorly absorbable polyglutamate form. Folate deconjugase, a brush-border enzyme secreted in the jejunum, removes all but one glutamate residue from the molecule. Specific carriers for folate monoglutamate in the proximal small intestine will promote folate uptake. Disease processes located in the proximal small intestine can lead to damage of folate carriers resulting in a decreased serum folate concentration. (Reprinted from Suchodolski J, Steiner J. Laboratory assessment of gastrointestinal function. *Clin Tech Small Anim Pract* 18:208, 2003. With permission from Elsevier.)

been reported in both dogs and cats, and affected animals present usually at a young age (6 to 12 weeks).[65]

Folate

Folate is a water-soluble vitamin that, similar to cobalamin, is abundant in canine and feline diets, making nutritional deficiency unlikely. Dietary folate is typically present in the poorly absorbable polyglutamate form. In the proximal small intestine, the brush-border enzyme folate deconjugase removes all but one glutamate residue from the molecule (Fig. 25-8). The uptake of folate monoglutamate occurs through specific carriers located in the proximal small intestine. Folate uptake is increased at a slightly acidic pH. Because erythrocytes contain high concentrations of folate hemolysis may lead to falsely increased serum folate concentrations.

In dogs increased serum folate concentrations can be indicative of small intestinal dysbiosis (SIBO/ARD). Resident bacteria in the distal small intestine (i.e., ileum) and in the large intestine can produce large quantities of folate. Because the carriers responsible for folate uptake are located exclusively in the proximal small intestine, folate produced in distal sections of the intestine cannot be absorbed. However, if folate-producing bacteria proliferate in the proximal small intestine, the bacterial folate can be absorbed by the host resulting in increased serum folate concentrations. The reported sensitivity of serum folate for the diagnosis of SIBO in dogs ranges from 50% to 66%, while no such data are available for cats.[62] Increases in serum folate concentrations are also often observed in dogs with EPI. Reduced pancreatic secretions, which normally help to suppress bacterial colonization in the small intestine, may lead to bacterial overgrowth in the small intestine. In contrast to dogs, cats with EPI often have a concurrent chronic enteropathy that may damage folate receptors in the proximal small intestine, leading to decreased serum folate concentrations.

Serum Cobalamin and Folate Concentrations in Patients with Small Intestinal Disease

Serum concentrations of cobalamin and folate are often abnormal in animals with EPI, and exocrine pancreatic function should be assessed in every animal with chronic GI disease. If serum trypsin-like immunoreactivity (TLI) is normal, then changes in serum cobalamin and folate are highly suggestive of small intestinal disease. The specific receptors for cobalamin and folate are located in different parts of the small intestine. Inflammatory disorders (e.g., IBD, lymphoma, fungal disease), especially if they are severe and chronic, may damage these receptors and can cause, depending on the localization of inflammation, subnormal serum concentrations of one or both vitamins.[66] A low serum folate concentration suggests proximal small intestinal disease, while low serum cobalamin suggests ileal disease. If both vitamins are decreased, this is indicative of a diffuse and potentially severe disease process.

Assessment of serum cobalamin and folate are helpful tools for the diagnosis of small intestinal dysbiosis (SIBO/ARD), although they have a poor sensitivity and specificity.[62] Serum cobalamin may be decreased and serum folate may be increased in animals with SIBO/ARD. If both vitamins are altered, then this is highly suggestive of small intestinal dysbiosis. However, changes may be evident only in chronic disease.

Assessment of Small Intestinal Dysbiosis

A definitive diagnosis of small intestinal dysbiosis is difficult to obtain. A tentative diagnosis can be made based on the combination of clinical signs, altered serum cobalamin and folate concentrations, and by a successful antibiotic therapeutic trial. However, other conditions, such as undetected intestinal pathogens, may also respond to antibiotic therapy, and an improvement after therapy does not necessarily confirm the presence of small intestinal dysbiosis. The measurement of serum cobalamin and folate concentrations is probably the most useful aid for the diagnosis of SIBO for the clinician, although both have a poor sensitivity and specificity for the diagnosis of SIBO.[62] Serum cobalamin may be decreased and serum folate may be increased; if both serum vitamin concentrations are altered this is considered highly suggestive of SIBO.

Quantitative cultures of duodenal juice have been considered the gold standard for SIBO. It is now well established that there is no correlation between bacterial counts and disease status, as in some studies healthy dogs had higher bacterial counts in the duodenum compared with dogs with suspected SIBO.[62] New studies have shown that each dog harbors a very unique small intestinal microbiota, making the determination of a normal or abnormal microbiota difficult.

Many other tests have been proposed for the evaluation of suspected small intestinal dysbiosis, including the measurement of serum unconjugated cholic acid (SUCA) concentration, the ^{13}C-xylose absorption test, the ^{13}C-bile acid absorption test, urinary indican test, or the hydrogen breath test. However, all of these tests are associated with a high degree of interindividual variation, making them unrewarding for the diagnosis of SIBO. Therefore, these tests have very limited clinical utility for the routine evaluation of patients with suspected SIBO.[62]

A recent study has shown an increased serum D-lactate concentration in cats with various GI diseases. The D-enantiomer of lactic acid is not normally found in any appreciable quantities in serum from mammals. The increase in serum D-lactate in cats with GI disease is possibly a result of derangements of the intestinal microbiota and increased bacterial production of D-lactate. Further studies are needed to evaluate the use of D-lactate as a marker for intestinal dysbiosis.[66]

PANCREAS

Romy M. HeiLmann and Jörg M. Steiner

Exocrine pancreatic disorders are common in clinical practice and pancreatitis is the most common disorder of the exocrine pancreas in both dogs and cats. Clinical diagnosis of pancreatitis can be challenging and it has been proposed that most cases of canine and feline pancreatitis remain undiagnosed. This is supported by necropsy studies showing that histopathologic evidence of pancreatic inflammation is very common in both species, even in patients without clinical signs.[1-3] Pancreatitis may be accompanied by relatively uncommon pancreatic complications such as pancreatic abscesses and pancreatic pseudocysts.

Exocrine pancreatic insufficiency (EPI) is the next most common disease of the exocrine pancreas in small animals, and it occurs more commonly in dogs than in cats. In the past few years feline EPI has been diagnosed with increasing frequency, likely because of increased awareness and the availability of better diagnostic tests. The diagnosis of EPI is usually uncomplicated when appropriate tests are utilized.

Uncommon diseases of the exocrine pancreas include pancreatic neoplasia (metastatic or, less commonly, primary neoplasia), pancreatic pseudobladder, pancreatolithiasis, and pancreatic parasites. Nodular hyperplasia of the pancreas is a common histopathologic finding, especially in older dogs and cats. This lesion is rarely associated with clinical disease; however, it can potentially interfere with the diagnostic evaluation of the pancreas and display findings that are usually associated with other pancreatic diseases (e.g., pancreatitis, neoplasia) (Table 25-4).

Pancreatitis

Signalment, History, and Risk Factors

Although dogs of any age, breed, or sex can develop pancreatitis, certain groups might be predisposed. Most dogs presented with pancreatitis are middle-aged to old (usually older than 5 years).[4,5] Several breeds have been reported or suspected to be at increased risk (e.g., Miniature Schnauzer, Yorkshire Terrier, Cocker Spaniel, Cavalier King Charles Spaniel, Collie, and Boxer) but none of these predispositions are consistent among studies.[3-6] Also, no clear sex predisposition has been identified.

Several pathologic conditions have been identified as potential risk factors for pancreatitis in dogs and, although a cause and effect relationship has not been established for most of them, their presence along with compatible clinical signs may raise the concern for pancreatitis. Many dogs with pancreatitis are overweight or obese, and endocrinopathies (e.g., hyperadrenocorticism, hypothyroidism, and diabetes mellitus) may be risk factors.[5] A history of drug administration (e.g., potassium bromide, phenobarbital, azathioprine, L-asparaginase, meglumine antimonite, and others) in conjunction with compatible findings should also raise a concern for pancreatitis.[7] Hypertriglyceridemia, when severe (higher than approximately 850 mg/dL), is reported as a risk factor for pancreatitis in Miniature Schnauzers.[8] This might also be true for dogs of other breeds that exhibit severe hypertriglyceridemia, but this has not yet been proven. Dietary factors (e.g., dietary indiscretion, consuming table scraps, ingestion of "unusual" food) and surgery at any time prior to diagnosis of pancreatitis have also been suggested as risk factors for pancreatitis in dogs.[6]

Similarly to dogs, cats of any age, breed, or sex can develop pancreatitis. Older cats appear to be more likely to develop chronic pancreatitis.[2,9-11] Domestic short hair and Siamese breeds have been reported to be at an increased risk in some studies, but this has not been confirmed by others.[2,9-11]

Clinical Signs and Physical Examination Findings

Dogs with pancreatitis can present with a wide variety of clinical signs, which can range from mild partial anorexia with no apparent gastrointestinal signs to cardiovascular shock and disseminated intravascular coagulation (DIC). There is no single clinical sign or combination of clinical signs that is pathognomonic for canine pancreatitis. Recent evidence suggests that pancreatitis can be subclinical in some cases, or be associated with only mild and nonspecific clinical signs such as anorexia and weakness.[1] In more typical cases, in addition to anorexia and weakness, dogs are presented with vomiting, diarrhea, and/or abdominal pain.[5,12] In particular, the combination of vomiting and cranial abdominal pain is considered suggestive (but not pathognomonic) of pancreatitis in dogs. Dehydration, abdominal pain, icterus, fever or hypothermia, bleeding diathesis, or ascites may be seen on physical examination.[5] Severe systemic complications (e.g., cardiovascular shock, DIC, or multiorgan failure) might occur in patients with severe pancreatitis.[12,13] It is important to note that additional clinical signs might occur as a consequence of concurrent diseases (e.g., polyuria/polydipsia in animals with diabetes mellitus).[5]

The most common clinical signs in cats with pancreatitis do not specifically indicate gastrointestinal (GI) disease and include complete or partial anorexia and lethargy.[9-11,14] Less common clinical signs include vomiting, weight loss, and diarrhea.[9-11,14] Abdominal pain is likely to be present in most cats with acute pancreatitis, but is often missed during routine physical examination. The most common physical examination findings include dehydration, pallor, and icterus.[9-11,14] Tachypnea and/or dyspnea, hypothermia/fever, tachycardia, signs of abdominal pain, and a palpable abdominal mass may also be noted.[9-11,14] Severe systemic complications (e.g., DIC, pulmonary thromboembolism, cardiovascular shock, and multiorgan failure) may occasionally be seen in cats with severe pancreatitis.

Routine Clinical Pathology[5,9-12,14,15]

Results of complete blood count (CBC), serum biochemistry profile, and urinalysis are nonspecific and thus not useful for the diagnosis of pancreatitis in dogs and cats. However, these tests should always be performed in animals with suspected pancreatitis because they are useful for the diagnosis or exclusion of other diseases, and also give important information about the general condition of the patient.

Often, especially in mild cases, the CBC, serum biochemistry profile, and urinalysis are normal. Possible hematologic findings in dogs and cats with pancreatitis include anemia or hemoconcentration, leukocytosis or leukopenia, and thrombocytopenia. Coagulopathies and DIC might be seen in some cases. Increases in hepatic enzyme activities and hyperbilirubinemia are common in both dogs and cats, and might erroneously direct the clinician to suspect primary liver disease. Azotemia is variably present and is most often associated with dehydration as a consequence of vomiting and/or diarrhea. Other possible findings include hypoalbuminemia, hypertriglyceridemia, hypercholesterolemia, and hyperglycemia. Electrolyte abnormalities are often present and

Table 25-4 Sensitivities and Specificities for Selected Diagnostic Modalities for the Diagnosis of Pancreatitis in Dogs and Cats*

	Sensitivity (%)	Specificity (%)	Comment
Dogs			
Pancreatic enzymes			
Serum amylase activity	18 to 69	~50	Low sensitivity and specificity. Both positive and negative results require verification with other diagnostics.
Serum lipase activity	14 to 73	~50	Low sensitivity and specificity. Both positive and negative results require verification with other diagnostics.
Serum TLI concentration	36 to 47	Relatively high	Low sensitivity. Normal concentrations do not exclude pancreatitis. Renal failure and intestinal disease might give false-positive results. High concentrations in the absence of renal or intestinal disease are suggestive of pancreatitis.
Serum PLI concentration	64 to 93	78 to 97	Highly sensitive and specific. Most accurate serum test for pancreatitis currently available.
Imaging methods			
Abdominal radiography	24	Low	Not useful for the diagnosis or exclusion of pancreatitis. Useful for the evaluation of other diseases.
Abdominal ultrasonography	68	Can be high	Relatively high sensitivity and specificity if stringent criteria are applied. Usefulness is highly operator- and equipment-dependent. Negative results do not rule out pancreatitis.
Pancreatic cytology	N/A	N/A	Must be performed under ultrasonographic guidance. Specificity is believed to be high, but pancreatic lesions might be missed if they are localized.
Pancreatic histopathology	Can be high	High	The gold standard for confirmation of pancreatitis. It is invasive and cannot be performed in severely compromised patients. Lesions are often highly localized so ruleout of pancreatitis is difficult.
Cats			
Pancreatic enzymes			
Serum amylase activity	Very low	Low	Not useful for the diagnosis of pancreatitis.
Serum lipase activity	Very low	Low	Not useful for the diagnosis of pancreatitis.
Serum TLI concentration	28 to 64	82	Low sensitivity. Normal concentrations do not exclude pancreatitis. Renal failure and intestinal disease might give false positive results. High concentrations in the absence of renal or intestinal disease are suggestive of pancreatitis.
Serum PLI concentration	54 to 100	82 to 91	Highly sensitive and specific. Most accurate serum test for pancreatitis currently available.
Imaging methods			
Abdominal radiography	Low	Low	Not useful for the diagnosis or exclusion of pancreatitis. Useful for the evaluation of other diseases.
Abdominal ultrasonography	11 to 67	73	Relatively high sensitivity and specificity if stringent criteria are applied. Usefulness is highly operator- and equipment-dependent. Negative results do not rule out pancreatitis.
Pancreatic cytology	N/A	N/A	Must be performed under ultrasonographic guidance. Specificity is believed to be high, but pancreatic lesions might be missed if they are localized.
Pancreatic histopathology	Can be high	High	The gold standard for confirmation of pancreatitis. It is invasive and cannot be performed in severely compromised patients. Lesions are often highly localized so ruleout of pancreatitis is difficult.

PLI, pancreatic lipase immunoreactivity; TLI, trypsin-like immunoreactivity.
*Based on references 1,2,5,10,11,15,18,23,26-28-36,40,46-49,51-54.

variable, with hypokalemia, hypochloremia, and hyponatremia being the most common. Hypocalcemia is more commonly seen in cats than in dogs, and is one of the most clinically important electrolyte disturbances in this species. Some cats with pancreatitis have hypocobalaminemia, which likely reflects concurrent intestinal disease.

Clinical Enzymology

Serum Pancreatic Lipase Immunoreactivity

There are many different lipases of various cellular origins (e.g., pancreatic, hepatic, gastric, and others) and all of them share the same function (i.e., hydrolysis of triglycerides). Therefore, depending on the assay conditions, many of the different lipases may

contribute to the total serum lipase activity measured by traditional activity assays for lipase. However, lipases of different cellular origins are encoded by different genes and thus have distinct amino acid sequences. Pancreatic lipase is exclusively expressed by pancreatic acinar cells and is structurally different from other lipases. Thus, immunoassays for the specific measurement of pancreatic lipase have been developed and validated for dogs and cats.[16,17] During pancreatitis pancreatic lipase leaks from acinar cells and enters the circulation in larger than normal quantities and can be detected by specific immunoassays for pancreatic lipase.

The immunoassays developed originally for pancreatic lipase were in-house tests that used polyclonal antibodies and had limited availability. Widely available commercial immunoassays (Spec cPL for dogs and Spec fPL for cats) that use monoclonal antibodies and show the same clinical performance as the original pancreatic lipase immunoreactivity (PLI) assays have been developed and have now replaced the original PLI immunoassays.[18,19]

Canine pancreatic lipase is believed to be exclusively of pancreatic origin.[20-22] An immunolocalization study suggested that canine pancreatic lipase is exclusively expressed by pancreatic acinar cells.[20] Another study in dogs with EPI showed a nearly total absence of serum canine pancreatic lipase immunoreactivity (cPLI) concentration.[21] In another study of a group of 31 dogs with a normal pancreas on histopathology, the specificity of Spec cPL was very high (96.8%).[22] In a recent multicenter study, in which dogs with clinical evidence of pancreatitis but without histopathologic confirmation of the disease were studied, the specificity of this assay was estimated to be at least 78%, when very conservative assumptions were applied.[23] Experimentally induced chronic renal failure and prednisone administration were not found to have any clinically significant effect on serum cPLI concentration.[24,25]

Serum cPLI concentration is also sensitive for the diagnosis of pancreatitis in dogs.[18,23,26,27] The reported sensitivity of cPLI for the diagnosis of canine pancreatitis is between 64% and 93%, depending on the severity of the disease in the patients studied. This is considerably higher than the sensitivity reported for serum canine trypsin-like immunoreactivity (cTLI) concentration (36.4% to 46.7%), serum amylase activity (18.2% to 73.3%), or serum lipase activity (13.6% to 69%), and is similar to or higher than that of abdominal ultrasound (67% to 68%) performed by a board-certified radiologist.[5,18,23,26-28] In a recent preliminary report of a multicenter study the sensitivity of this assay was estimated at 93%.[23] Because of its high sensitivity, normal serum cPLI concentrations make a diagnosis of clinically relevant pancreatitis very unlikely. However, it remains to be determined if, because of its high sensitivity, cPLI detects pancreatic pathology that is not clinically relevant. Based on the previously mentioned studies, serum cPLI concentration is the most sensitive and specific test currently available for pancreatitis in dogs.

Recently, a rapid point-of-care test for the estimation of pancreatic lipase in serum (SNAP cPL) was released. Studies evaluating the performance of this test are currently lacking, but would be expected to show a similar clinical performance to the serum Spec cPL assay. A positive test result should be followed up by laboratory measurement of serum Spec cPL concentration to confirm a diagnosis of pancreatitis and to serve as a baseline for monitoring the disease progress. A negative result makes a diagnosis of pancreatitis unlikely.

Studies in cats with both experimental and spontaneous pancreatitis have shown that serum feline pancreatic lipase immunoreactivity (fPLI) concentration is very sensitive for pancreatitis.[29-31] In one of these studies, fPLI was found to be 100% sensitive for moderate to severe spontaneous feline pancreatitis, and was superior to the sensitivities of serum feline trypsin-like immunoreactivity (fTLI) concentration (28%) or abdominal ultrasound (80%).[29] A preliminary report of a multicenter study reported the sensitivity of serum fPLI concentration as 78%.[31] Considering the overall sensitivities for pancreatitis reported for serum fPLI concentration (67% to 78%), fTLI (28% to 64%), and abdominal ultrasonography (11% to 67%), serum fPLI concentration currently appears to be the most sensitive test for the diagnosis of feline pancreatitis.[29,31-35] The specificity of serum fPLI concentration (82% to 91%) is reported to be superior to that of fTLI (82%) or abdominal ultrasound (73%).[15,29,31] Although further studies are needed to confirm these findings, serum fPLI concentration currently appears to be the most useful test for the diagnosis of feline pancreatitis. A point-of-care test for the estimation of Spec fPL (SNAP fPL) is also available, but studies evaluating this test have not been reported to date.

Serum Amylase and Lipase Activity

Serum amylase and lipase activities have long been considered markers for pancreatitis in dogs.[36,37] Although serum activities of these two enzymes increase during experimental canine pancreatitis, several studies have shown that these markers are not useful for the diagnosis of spontaneous canine pancreatitis because of their low sensitivity and specificity.[18,36-41] Many tissues other than the pancreas (e.g., gastric mucosa, hepatic parenchyma, and others) synthesize amylases and lipases. This has been confirmed in studies of dogs that would have been expected to have no or minimal serum lipase and amylase activities, namely, pancreatectomized dogs and dogs with EPI. Dogs in these studies retained significant serum lipase and amylase activities (often within the reference intervals), clearly indicating that tissues other than the pancreas account for a large portion of serum activities of these enzymes.[21,41] Furthermore, traditional catalytic assays are not able to differentiate amylases and lipases according to the tissue of origin leading to a low specificity of measurement of these enzyme activities for pancreatitis in dogs.[28,36]

In one study, approximately 50% of dogs with an increased serum activity of either amylase or lipase had no histopathologic evidence of pancreatitis.[36] The main nonpancreatic conditions associated with increased activities of these enzymes include renal, hepatic, intestinal, and neoplastic diseases, as well as corticosteroid administration (only for lipase activity). It has also been suggested that only increases of amylase and lipase activities of more than three to five times the upper limit of the reference range should be considered suggestive of pancreatitis in dogs, in order to increase the specificity of these assays.[42,43] However, even increases of this magnitude can result from nonpancreatic disorders.[28,36,43,44]

The sensitivity of serum amylase and lipase activities for spontaneous canine pancreatitis is low (32% to 73% for lipase activity and 41% to 69% for amylase activity) and is even lower when a cutoff value of three or five times the upper limit of the respective reference interval is used (14% for lipase activity and 18% for amylase activity in one study that used a cutoff of three times the upper limit of the reference range).[5,18,27] Thus, many dogs with pancreatitis may have normal serum activities of these enzymes and, therefore, normal serum amylase and/or lipase activities cannot rule out pancreatitis.[5,36] The low sensitivity of serum amylase and lipase activity assays is at least partially associated with the broad reference intervals for these assays, which are the result of extrapancreatic amylase and lipase activities. A new lipase assay (using the substrate 1,2-o-dilauryl-rac-glycero glutaric acid-[6′ methyl resorufin]-ester

[DGGR]) was speculated to be more useful for the initial evaluation of dogs suspected of having pancreatitis because of its higher sensitivity (93%) compared with traditional assays.[45] However, the specificity of this assay was low (53%), limiting its clinical usefulness.[45]

Serum lipase activity increases and serum amylase activity decreases in cats with experimentally induced acute pancreatitis.[30,46,47] Although well-designed clinical studies are lacking, serum lipase and amylase activities do not appear to be of any clinical value in the diagnosis of spontaneous feline pancreatitis.[10,32,48]

Trypsin-Like Immunoreactivity

TLI assays are species-specific immunoassays that measure trypsinogen and trypsin in serum. Trypsinogen is the inactive preform (or zymogen) of trypsin, a proteolytic enzyme synthesized exclusively by pancreatic acinar cells and normally secreted into the duodenum where it is activated, with only minimal amounts reaching the circulation. During pancreatitis, trypsinogen and prematurely activated trypsin enter the circulation in large quantities, and can be measured with the TLI assay.

Serum cTLI concentrations increase after experimental induction of pancreatitis in dogs, but decrease to concentrations within the reference interval as soon as 3 days after induction of pancreatitis in some dogs.[40] The sensitivity of serum cTLI for the diagnosis of spontaneous pancreatitis is low (36% to 47%), probably as a consequence of its short half-life.[18,27,28] In addition, although there is strong evidence that trypsinogen is exclusively of pancreatic origin,[41] it is believed that it is cleared by glomerular filtration, and serum cTLI concentration can be increased in dogs with renal failure.[28,40] This clearly affects the specificity of the test and complicates the interpretation of increased serum cTLI concentrations in azotemic dogs.

In cats with experimentally induced pancreatitis, serum fTLI concentration increases sharply after induction of pancreatitis, but returns below the cutoff value for pancreatitis within 48 hours.[30] fTLI has been evaluated for the diagnosis of spontaneous pancreatitis in cats and several cutoff values have been suggested.[33-35] When cutoff values allowing adequate specificity of the assay are used (i.e., 100 µg/L), the sensitivity of fTLI for the diagnosis of pancreatitis in cats is generally low (28% to 33%), with the highest reported sensitivity for this cutoff value being 64%.[33-35] In addition, the specificity of fTLI has been questioned, because mildly increased serum fTLI concentrations have been reported in cats with no demonstrable pancreatic disease, but other gastrointestinal disorders (e.g., IBD or gastrointestinal lymphoma) or azotemia.[15,33,35]

In the face of availability of better serum markers (cPLI and fPLI), cTLI and fTLI are currently considered to be of limited usefulness for the diagnosis of canine and feline pancreatitis, respectively.

Other Diagnostic Markers

Other diagnostic markers for pancreatitis have been developed and studied, but none can currently be recommended for the diagnosis of canine and feline pancreatitis in clinical practice, either because their diagnostic performance has not been sufficiently evaluated, or because they have a low sensitivity and/or specificity. In addition, the availability of most of these diagnostic tests is currently limited. Such tests include the determination of serum concentrations of phospholipase A_2, trypsin–α_1-antitrypsin complexes, and α_2-macroglobulin, determination of plasma and urine concentrations of trypsinogen activation peptide (TAP), and determination of lipase activity in peritoneal fluid.

Diagnostic Imaging

Abdominal Radiography

Conclusive diagnosis or exclusion of pancreatitis is not possible based on abdominal radiography alone.[5,9-11,34,43] In the majority of cases of canine and feline pancreatitis, abdominal radiographs are normal or show only nonspecific findings. Despite this, radiography remains a logical initial approach for patients suspected of having pancreatitis because it is relatively inexpensive and useful for the diagnosis and/or ruleout of other differential diagnoses.

In a group of 70 dogs with fatal acute pancreatitis, the sensitivity of abdominal radiography was low (24%).[5] Radiographic findings reported for dogs with pancreatitis include increased soft-tissue opacity and decreased serosal detail in the cranial right abdomen, indicating localized peritonitis.[5] Other findings include displacement of the stomach and/or duodenum and gaseous dilation of bowel loops adjacent to the pancreas.[5] Abdominal effusion or the presence of an abdominal mass might also be detected. Radiographic findings in cats with pancreatitis are similar to those in dogs.[10,11,34,49] In any case, radiography should always be followed by use of more sensitive and specific tests for the definitive diagnosis or exclusion of pancreatitis.

Abdominal Ultrasound

Abdominal ultrasound is considered the imaging method of choice for the diagnosis of pancreatitis in dogs and cats. However, the performance of ultrasonography in the diagnosis of pancreatitis is dependent on the experience of the ultrasonographer and the quality of the equipment used.

Abdominal ultrasound has been reported to have a relatively high sensitivity (68%) for severe acute pancreatitis in dogs, although with increasing quality of equipment the sensitivity might now have increased.[5] Abdominal ultrasound has been assessed mainly in dogs with fatal acute pancreatitis, in which lesions are usually pronounced, but its sensitivity would be expected to be lower in cases with mild or moderate pancreatitis.[5] A normal pancreas on ultrasound examination does not rule out pancreatitis in dogs.

Ultrasonographic findings in dogs with pancreatitis include hypoechoic areas within the pancreas (possibly indicating necrosis or fluid accumulation), increased echogenicity of the surrounding mesentery (a result of necrosis of the peripancreatic fat), enlargement and/or irregularity of the pancreas, dilation of the pancreatic or biliary duct, and abdominal effusion (Fig. 25-9).[5,50] On occasion, hyperechoic areas of the pancreas can be identified, possibly indicating the presence of pancreatic fibrosis. Cavitary lesions, a thickened duodenum, and biliary obstruction might also be noted.[50] If stringent criteria are applied, the specificity of abdominal ultrasonography for canine pancreatitis is considered to be relatively high, although other diseases of the pancreas (e.g., neoplasia, hyperplastic nodules, edema caused by portal hypertension or hypoalbuminemia) may display similar ultrasonographic findings and cannot be differentiated from pancreatitis in many cases.[51,52] In a recent study where ultrasonography was performed in 26 animals (both dogs and cats) with suspected gastrointestinal disease, six (23.1%) of the animals had ultrasonographic evidence consistent with pancreatitis, while histopathology revealed either a normal pancreas or pancreatic hyperplasia.[53] In the same study, there was only a 22% agreement between the ultrasound report and pancreatic histopathology in dogs.[53] These data raise concerns regarding the accuracy of ultrasonography in evaluating the canine pancreas and underscore the importance of not overinterpreting ultrasonographic findings. However, findings of this particular study should be evaluated with

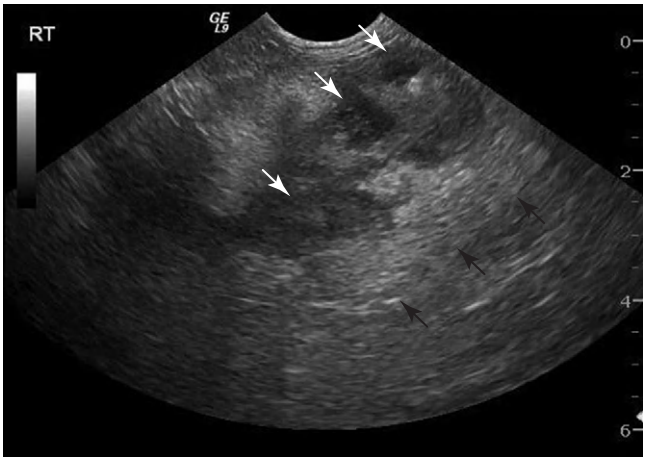


Figure 25-9 Ultrasonographic appearance of the pancreas of a dog with pancreatitis. The pancreas is enlarged and appears heterogeneous, with hypoechoic areas (*white arrows*) and hyperechoic surrounding fat (*black arrows*). These findings are highly suggestive of pancreatitis. (Courtesy of Dr. B. Young, Texas A&M University.)

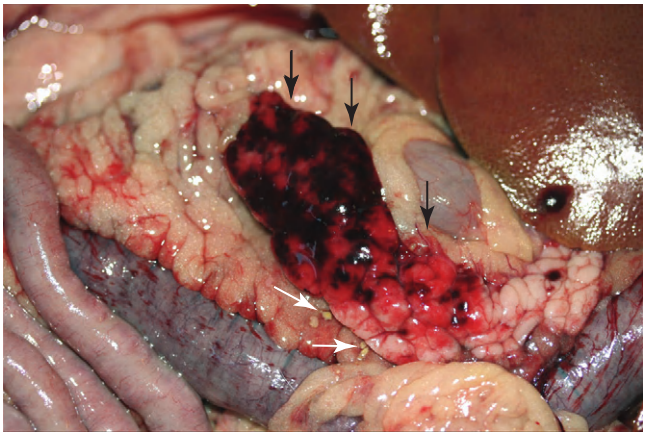


Figure 25-10 Gross appearance of the pancreas of a dog with acute pancreatitis. The pancreas appears severely hemorrhagic, necrotic, and edematous (*black arrows*). There is also peripancreatic fat necrosis (*white arrows*). Such appearance is highly suggestive of pancreatitis. (Courtesy of Dr. D. Ajithdoss, Texas A&M University.)

caution because localized pancreatic lesions suggestive of pancreatitis might have been missed on histopathology.

The reported sensitivity of abdominal ultrasonography for the diagnosis of feline pancreatitis is generally low (11% to 35%), with only one study reporting a sensitivity of 67%.[11,29,33,49] This high range of sensitivity likely reflects differences in the level of suspicion or the skills of the examiner, the equipment used, and the severity of lesions, and highlights the lack of standardized diagnostic criteria.[33,34,49] The generally low sensitivity of abdominal ultrasonography suggests that many cats with pancreatitis remain undiagnosed when the diagnosis is based solely on ultrasound examination.[11,33,49] The sensitivity of abdominal ultrasonography is believed to have increased since the reports cited previously because of advances in technology and an increasing level of awareness of the importance of feline pancreatitis, although this has not yet been confirmed. Abdominal ultrasonography has been thought to be relatively specific for the diagnosis of pancreatitis is cats but, similarly to dogs, other diseases (e.g., pancreatic neoplasia, edema) may be associated with similar findings.[54] In a recent study, there was an overall agreement of only 33% between the ultrasound report and pancreatic histopathology in cats, and some cats that had ultrasonographic evidence of pancreatitis had no evidence of pancreatitis on histopathology.[53] Ultrasonographic findings in cats with pancreatitis are similar to those described in dogs.[11,33,49,50,55] It is suggested that dilation of the pancreatic duct is suggestive of pancreatitis in cats, but recent studies have not confirmed this hypothesis.[56] In general, feline pancreatitis is often difficult to diagnose by abdominal ultrasound examination and it is important to note that a normal ultrasound examination does not rule out feline pancreatitis.[29,33]

Overall, abdominal ultrasonography is very useful for the diagnosis of pancreatitis in dogs and cats, especially when performed by an experienced ultrasonographer. Caution should be taken not to overinterpret ultrasonographic findings. Abdominal ultrasonography is also helpful in detecting possible concurrent abdominal disease in dogs and cats suspected of having pancreatitis. In addition, ultrasound-guided fine-needle aspiration is a useful tool for the confirmation of pancreatitis and some of its complications (e.g., pancreatic pseudocyst and pancreatic abscess), as well as the management of noninfectious fluid accumulations (e.g., pancreatic pseudocyst).[55]

Other Imaging Modalities

Contrast-enhanced computed tomography (CECT) is a valuable tool in the evaluation of human patients with suspected pancreatitis, but initial studies in dogs have not been promising.[57] The results of computed tomography (CT) performed in cats with histologically confirmed pancreatitis were also disappointing and this procedure currently cannot be recommended in diagnosis of feline pancreatitis.[29] Other imaging methods (e.g., endoscopic retrograde cholangiopancreatography [ERCP], endoscopic ultrasonography) have been used in healthy dogs and cats, in dogs with experimentally induced pancreatitis, and in dogs with gastrointestinal diseases, with varying results. However, as a consequence of the lack of standardized criteria for the diagnosis of pancreatitis, the complexity of these modalities, their limited availability, and the cost of the equipment, they cannot currently be recommended for the diagnosis of canine or feline pancreatitis.

Pathology

Direct visualization of the pancreas is possible during exploratory laparotomy or laparoscopy in live animals, or during necropsy. When certain gross lesions are present they are highly suggestive of pancreatitis and suggest preferred sites for biopsy.[10,18,49] Gross lesions suggestive of pancreatitis include peripancreatic fat necrosis, pancreatic hemorrhage and congestion, and a dull granular capsular surface (Fig. 25-10).[10,18,49] However, gross lesions may not always be apparent in dogs and cats with pancreatitis.[1,10,49]

At present, a definitive diagnosis of pancreatitis can only be made by histopathologic examination of the pancreas. Histopathology is also the only way to differentiate acute and chronic pancreatitis. Histopathologic scoring systems for the evaluation of severity of pancreatitis have been proposed for both dogs and cats.[1-3,58] However, histopathologic criteria for the classification of pancreatitis have not been universally standardized in veterinary medicine and substantial confusion exists regarding both classification and terminology of canine and feline pancreatitis, underlying the importance of developing a universally accepted multidisciplinary classification system as is available for human pancreatitis. Permanent histopathologic changes (e.g., fibrosis and acinar atrophy) are generally considered suggestive of chronic pancreatitis (Fig. 25-11).[1,43] The predominant cell type within an inflammatory infiltrate

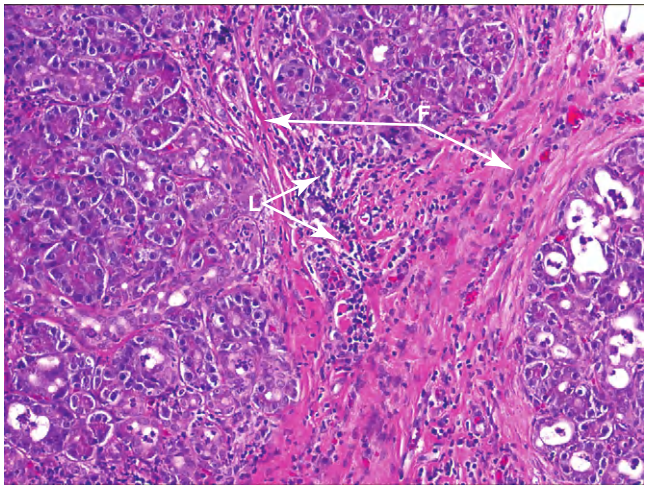


Figure 25-11 Histopathologic appearance of the pancreas of a cat with chronic pancreatitis. There is extensive fibrosis (*F*) and lymphocytic infiltration (*L*). Hematoxylin and eosin (H&E) stain; magnification ×200. (Courtesy of Dr. B. F. Porter, Texas A&M University.)

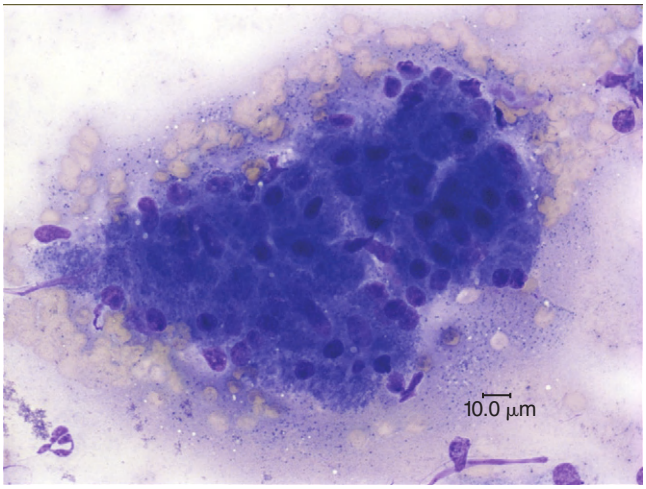


Figure 25-13 Cytologic appearance of a fine-needle aspirate from a normal canine pancreas. Acinar cells can be seen in the form of a multicellular cluster. Diff-Quik stain. (Courtesy of Dr. P. J. Armstrong, University of Minnesota.)

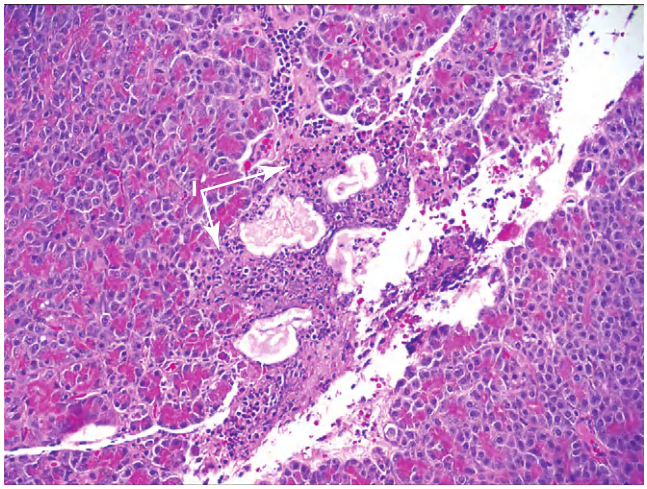


Figure 25-12 Histopathologic appearance of the pancreas of a cat with acute pancreatitis. There are areas of inflammatory infiltration (*I*) but there is no evidence of fibrosis or other permanent histopathologic changes. Hematoxylin and eosin stain; magnification ×200. (Courtesy of Dr. B. F. Porter, Texas A&M University.)

(neutrophils or lymphocytes) is often used to describe pancreatitis as suppurative or lymphocytic, and some authors consider that suppurative inflammation is compatible with acute disease and lymphocytic infiltration compatible with chronic disease (Fig. 25-12).[10,11] Some animals can show evidence of both suppurative and lymphocytic pancreatitis. Significant necrosis characterizes the pancreatitis as necrotizing.

Several limitations are associated with pancreatic histopathology as a definitive diagnostic tool for pancreatitis. First, determining the clinical significance of histopathologic findings may be challenging. In one study, 47 (64%) of 73 dogs that presented for necropsy for various reasons had microscopic evidence of pancreatitis.[1] Similarly, histopathologic lesions of pancreatitis were found in 67% of all cats examined, including 45% of healthy cats.[2] Currently, there are no standardized criteria that distinguish microscopic findings leading to clinical disease from those that do not, and it is possible that clinically insignificant pancreatic lesions could lead to a false diagnosis of pancreatitis. At the same time, exclusion of pancreatitis based on histopathology is difficult because inflammatory lesions of the pancreas are often highly localized and can easily be missed.[1,2,10,49] Consequently, multiple sections of the pancreas must be evaluated so as to increase the likelihood of finding microscopic lesions, although this is not always feasible in clinical practice. The absence of histopathologic features consistent with pancreatitis must be evaluated with caution, especially when only one section of the pancreas has been examined.[1,2] Finally, although pancreatic biopsy per se is considered safe, it requires invasive procedures that are expensive and potentially detrimental in patients with pancreatitis that are hemodynamically unstable.[53]

Because concurrent inflammation of the intestines and/or liver appears to be a common problem in cats and may also occur in dogs, intestinal and hepatic biopsies should be collected in patients (especially cats) suspected of having pancreatitis that are undergoing exploratory laparotomy. Likewise, cats with IBD and/or cholangitis that undergo laparotomy or laparoscopy should also have their pancreas evaluated.

Cytology

Fine-needle aspiration (FNA) of the pancreas and cytologic examination is minimally invasive, relatively safe, and can be used for the diagnosis of pancreatitis in both dogs and cats.[59] To date, no studies have evaluated the sensitivity and specificity of this diagnostic modality for the diagnosis of canine or feline pancreatitis, but the finding of inflammatory cells is considered specific for pancreatitis. Pancreatic acinar cells constitute the majority of the cells found in FNA smears from a normal pancreas (Fig. 25-13).[59] Acute pancreatitis is characterized by hypercellularity, and the presence of intact and degenerate neutrophils and degenerate pancreatic acinar cells (Fig. 25-14). In chronic pancreatitis, small numbers of lymphocytes and neutrophils are usually present, and the specimen is often characterized by low cellularity, possibly a result of replacement of the normal pancreatic tissue by fibrotic tissue.[59]

FNA cytology should be performed either under ultrasonographic guidance or during laparotomy.[59] It should be noted that, as for histopathology, highly localized lesions might be missed. Thus,

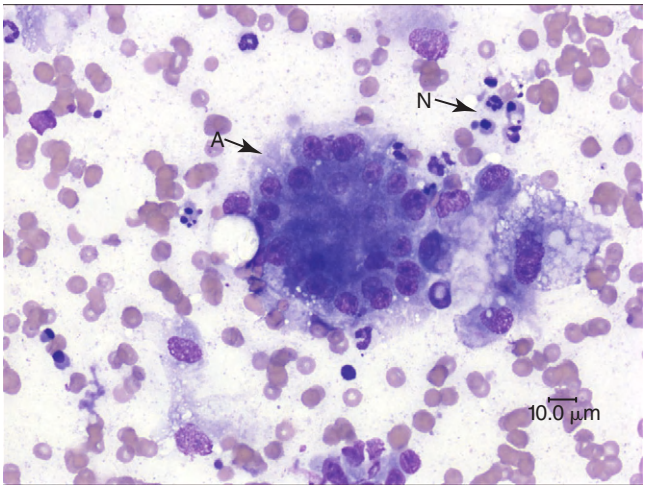


Figure 25-14 Cytologic appearance of a fine-needle aspirate from a canine pancreas with suspected pancreatitis. There is mild to moderate neutrophilic inflammation (*N*) with neutrophilic degeneration. A cluster of normal acinar cells (*A*) can also be seen. Diff-Quik stain. (Courtesy of Dr. P. J. Armstrong, University of Minnesota.)

negative results do not rule out pancreatitis. Although FNA cytology might also be useful in differentiating other conditions of the pancreas (e.g., neoplasia) from pancreatitis, it is not definitive.

Assessment and Prediction of the Severity of Pancreatitis

Assessment of the severity of human acute pancreatitis is based on the application of standardized severity scores.[60] Prediction of the severity of pancreatitis constitutes a very important component of the diagnosis of pancreatitis, because it allows prediction of the likelihood of complications and morbidity, and helps determine the optimal therapeutic plan before the patient enters a critical stage. It is based on a theory that states that the severity of an episode of pancreatitis is determined by events that occur within the first 24 to 48 hours of the episode.[61] These events are reflected through clinical, clinicopathologic, and imaging findings that can be used to predict the severity of the pancreatitis.[61]

In veterinary medicine, no well-established and universally accepted severity scoring systems for pancreatitis have been described. Serum PLI and TLI concentrations lack prognostic significance because they correlate poorly with histopathologic severity.[18] Currently, severity of canine and feline pancreatitis is determined based on clinical judgment, and typically a diagnosis of severe pancreatitis is made after the animal has entered a critical stage. In general, evidence of systemic complications (e.g., oliguria, azotemia, icterus, severely increased hepatic enzyme activities, hypocalcemia, hypoglycemia, severe hyperglycemia, leukocytosis, shock, or DIC) are considered as indicators of severe disease and a poor prognosis.[62-64] However, prediction of the severity of pancreatitis has not been studied sufficiently in dogs and cats. Markers that might prove useful in predicting the severity and/or outcome of an episode of pancreatitis are serum C-reactive protein concentrations, serum interleukin-6 concentrations, and plasma and urine TAP concentration, as well as the urine TAP-to-creatinine ratio.

Conclusions

No single diagnostic modality is 100% reliable for the diagnosis of canine or feline pancreatitis. Careful evaluation of the animal's history, physical examination, and routine clinical pathology findings, as well as the use of highly specific and sensitive tests (serum cPLI and fPLI concentration, abdominal ultrasonography, cytology, and/or histopathology), is crucial for an accurate diagnosis of pancreatitis. In clinical practice, a combination of serum cPLI or fPLI concentration, abdominal ultrasound, and in some cases FNA of the pancreas, currently constitutes the most practical and accurate approach for the diagnosis of both canine and feline pancreatitis.

Exocrine Pancreatic Insufficiency

Clinical Features

The classical presentation of dogs with EPI involves a chronic history of weight loss, a normal or increased appetite, and loose stools, usually characterized by passage of large volumes of semiformed feces. However, some dogs with EPI may present with a clinical history of periods of anorexia, absence of loose stools, occasional watery diarrhea, or vomiting. Other possible clinical signs include coprophagia, borborygmus, flatulence, abdominal discomfort, and a poor hair coat. In some cases, EPI may be subclinical and those cases can only be diagnosed with appropriate laboratory testing. Cats with EPI have a similar presentation to that of dogs. In cases where chronic pancreatitis is the cause of EPI, polyuria and polydipsia may be seen as a result of concurrent diabetes mellitus.

Trypsin-Like Immunoreactivity

Serum cTLI is the test of choice for the diagnosis of EPI in dogs. This test is highly sensitive and specific for the diagnosis of EPI, and a positive test (usually defined as <2.5 μg/L) in a dog with compatible clinical signs is sufficient to make a diagnosis.[65] A cTLI result well within the reference range is sufficient for excluding EPI, and a normal cTLI result should direct clinicians toward the investigation of other disorders as the cause of the observed clinical signs.[65] Single cTLI results within the equivocal range (usually between 2.5 and 5.7 μg/L) in dogs with clinical signs of gastrointestinal disease must be interpreted with caution.[66] In these patients, subsequent retesting of serum cTLI concentration shows either a normal concentration or progression to EPI.[66] Therefore, patients with cTLI results in the equivocal range should be investigated for chronic intestinal disease, with reevaluation of the cTLI a few weeks later. Some dogs with no clinical signs characteristic of EPI have repeatedly subnormal (<5.7 μg/L) cTLI concentrations.[66,67] These dogs have subclinical EPI and some are expected to develop clinical EPI in the future.[66,67] The time of progression from the subclinical to the clinical stage varies greatly, from a few months to years.[67] Thus, these patients should be closely monitored for the development of clinical signs of EPI, and cTLI testing should be repeated every 3 to 6 months.[66,67] Finally, because renal disease might increase serum cTLI concentrations and obscure a diagnosis of EPI, reevaluation of nondiagnostic serum cTLI concentrations in azotemic dogs suspected of having EPI is recommended. Similarly, concurrent inflammation might falsely increase the serum cTLI concentration.

EPI appears to be less common in cats than in dogs and the feline disease has been less-well investigated. Measurement of fTLI appears to be the most reliable test for the diagnosis of EPI in cats with a specificity of at least 85%.[68] The sensitivity of this assay for the diagnosis of feline EPI has not been evaluated. There are currently two assays that measure fTLI. A radioimmunoassay is available through the Gastrointestinal Laboratory at Texas A&M University, and an ELISA is available in Europe. Only the radioimmunoassay has been validated. Equivocal serum fTLI concentrations in azotemic cats suspected of having EPI should be reevaluated, because

renal disease might falsely increase serum fTLI concentration. The same is true for cats with concurrently increased serum fPLI concentrations indicating residual pancreatic inflammation.

Pancreatic Fecal Elastase

An ELISA for the measurement of pancreatic elastase in feces is commercially available and is marketed in Europe (Shebo Biotech, Germany) for the diagnosis of canine EPI.[69,70] A recent study reported false-positive results in 23.1% of cases,[71] and the sensitivity of this assay has not been sufficiently evaluated. Because of its poor positive predictive value, a positive test result must be verified by measurement of serum cTLI concentration. This test might also be useful for EPI cases that are caused by pancreatic duct obstruction; however, to date only one case has only been reported anecdotally.

Other Tests

Serum amylase and lipase activities have no value in the diagnosis of EPI in dogs or cats.[21,41,72] cPLI concentrations are low or undetectable in most dogs with EPI, but some overlap between healthy dogs and dogs with EPI exists, making this test inferior to cTLI for the diagnosis of EPI.[21] However, cPLI might be used to diagnose isolated pancreatic lipase deficiency, a rare form of EPI, where serum cTLI concentrations are expected to be normal.[73] Commercial assays for the measurement of serum PLI concentration (Spec cPL and Spec fPL) are not useful for the diagnosis of EPI in dogs and cats, respectively, because they have been optimized to detect changes in the higher ranges of their respective working ranges.

Measurement of fecal proteolytic activity has been used in the past for the diagnosis of EPI in dogs and cats, but is now only used for species for which a TLI assay is not available.[74,75] A plethora of other tests, including microscopic examination of feces and the bentiromide absorption (benzoyl-tyrosyl-paraaminobenzoic acid [BT-PABA]) test, have also been described for the diagnosis of EPI in the past. However, these tests often give false-positive and/or false-negative results and many of them are impractical, expensive, or of limited availability; thus none is recommended for the diagnosis of canine or feline EPI.

Histopathology

EPI is a functional and not a histopathologic diagnosis; thus histopathology is not indicated for the diagnosis of EPI. More than 90% of the pancreatic parenchyma must be destroyed before clinical signs of EPI develop, so it is almost impossible to make an accurate gross or histopathologic estimate of the extent of pancreatic atrophy. The only value in histopathology is determination of the underlying cause of EPI (pancreatic acinar atrophy or pancreatitis). However, in breeds of dog that are predisposed to EPI as a consequence of acinar atrophy (i.e., German Shepherd, rough-coated Collies, and Eurasian) histopathology is redundant.[76] Therefore, histopathology should only be used in atypical cases where the cause of EPI needs to be definitively determined.

LIVER

Dennis J. Meyer

The liver is mainly comprised of hepatocytes, sinusoidal cells, and biliary epithelium. Hepatocytes make up approximately 60% of the hepatic parenchyma with sinusoidal endothelial cells, hepatic stellate cells (formerly referred to as Ito cells), liver-associated lymphocytes, and Kupffer cells comprising the remainder (Fig. 25-15). The approximation of the gutter-like hemicanals on adjacent surfaces of neighboring hepatocytes form the intercellular space called the *canaliculus*, which is the beginning of the hepatobiliary system. The liver has two blood supplies. The hepatic artery and the portal vein comprise approximately 20% and 80%, respectively, of the total blood flow, which mixes as it enters the sinusoids. Multiple tests have been developed to assess liver function because of this cellular, biliary, and vascular complexity. In general, these tests aim to

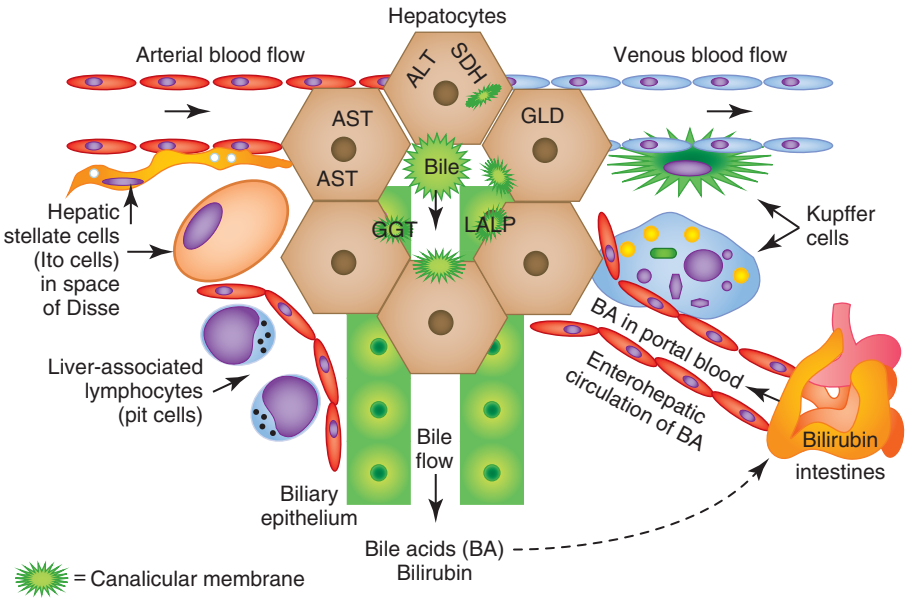


Figure 25-15 Hepatic function. This figure shows the complex cell constituency comprising the liver and the microanatomic relationships of these cells, the cellular location of liver enzymes, and the enterohepatic circulation of bile acids. (Modified with permission from Meyer DJ, Harvey JW: *Veterinary Laboratory Medicine—Interpretation and Diagnosis*, 3rd ed. Philadelphia: Saunders, 2004.)

Box 25-2 Breed Predilection for Progressive Liver Disease

Inflammatory Liver Disease[71-78]
Labrador Retriever
English and American Cocker Spaniels
Bedlington Terrier (copper-related)
West Highland White Terrier (± copper-related?)
Dalmatian (copper-related?)
Doberman Pinscher
Skye Terrier
Siamese Cat (copper-related?)

Amyloidosis[79-82]
Chinese Shar Pei
Abyssinian cat
Oriental cat
Siamese cat

Box 25-3 Breed Predilection for Congenital Portosystemic Vascular Anomalies Including Primary Portal Vein Hypoplasia (Microvascular Dysplasia)

Congenital Portosystemic Vascular Anomalies[62,68-70]
Yorkshire Terrier
Maltese
Havanese
Dandie Dinmont Terrier
Pug
Miniature and Standard Schnauzer
Shih Tzu
Bernese Mountain Dog
Bichon Frise
Cairn Terrier
Irish Wolfhound
Longhaired Dachshund
Jack Russell Terrier
Pekingese
Miniature Pinscher
West Highland White Terrier
Pomeranian
Lhasa Apso
Old English Sheepdog
Shetland Sheepdog
Chihuahua
Scottish Terrier
Miniature Dachshund
Australian Cattle Dog
Mixed breed cats
Himalayan cat
Persian cat

evaluate hepatocyte membrane integrity and function, hepatobiliary function, the portal circulation, and the enterohepatic circulation. Because of the intimate anatomic and intertwining functional relationships of hepatic components, there is frequent overlap of findings with varied pathology of the liver, the portal circulation, or even extrahepatic disease.

When evaluating a patient with suspected hepatobiliary disease signalment, clinical history, and physical examination can help to formulate a list of reasonable differential diagnoses. Several hepatobiliary diseases have been reported to show breed predilections (Boxes 25-2 and 25-3).

Serum Hepatic Enzyme Activities

Alanine aminotransferase (EC 2.6.1.2; also known as alanine transferase, ALT), aspartate aminotransferase (EC 2.6.1.1; also known as aspartate transaminase, AST), glutamate dehydrogenase (EC 1.4.1.3; GLD, GLDH), alkaline phosphatase (EC 3.1.3.1; ALP), and γ-glutamyltransferase (EC 2.3.2.2; γ-glutamyl-peptide:amino acid, γ-glutamyl transferase, GGT) are the predominant hepatic enzyme activities that are relatively sensitive indicators of primary hepatic pathology. The interpretation of tests for liver disease is confounded by the effect of extrahepatic inflammatory diseases, especially those involving the pancreas or the intestines, on the liver, notably Kupffer cells, leading to abnormal results of liver tests and histopathologic changes sometimes referred to as nonspecific or reactive hepatitis. Endocrinopathies and induction of hepatic enzyme activities by medications can cause abnormal serum liver enzyme activities that mimic primary hepatic pathology (Box 25-4). Thus, the finding of abnormal serum hepatic enzyme activities should always prompt consideration of extrahepatic disorders in addition to primary liver pathology. In the aged dog (i.e., older than approximately 8 years of age), nodular regenerative hyperplasia of the liver is a common benign liver pathology that is associated with increases in liver enzyme activities, often with an ALP prominence, abnormal ultrasound findings, and varied histopathologic findings that may suggest vacuolar hepatopathy and/or chronic hepatitis.[1,2]

ALT is predominately located within the hepatocyte cytosol with minimal skeletal muscle activity. Following release from hepatocytes, it has a half-life of approximately 45 to 60 hours in the dog and 3.5 hours in the cat (Fig. 25-16 and Table 25-5).[3,4] AST has high activity in hepatic tissue and skeletal muscle. It has a half-life

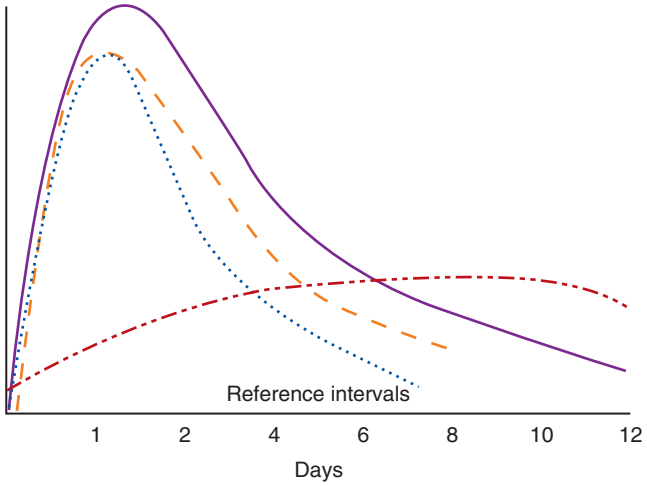
Box 25-4 Selected Extrahepatic Disorders and Drugs that May Be Associated with Increased Serum Bilirubin and/or Liver Enzyme Activities in the Absence of Primary Liver Disease

Inflammation/Infection[44,45,67]
Pancreatitis
Enteritis
Bacterial infections
Septicemia, pneumonia, bite wounds, endocarditis, pyothorax, peritonitis, pyometra

Endocrinopathies
Hyperthyroidism–cat
Hypothyroidism–dog
Diabetes mellitus
Hyperadrenocorticism–dog

Drugs
Corticosteroids–dog
Anticonvulsants
Phenobarbital
Primidone
Phenytoin

Bone Disease
Osteosarcoma
Osteomyelitis



Approximate half-life of liver enzymes (hours)		
Enzyme	Dog	Cat
ALT	60	3.5
GLD	18	–
AST	12	1.5
LALP	66	6

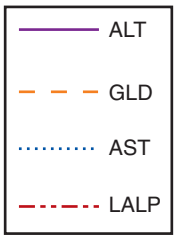


Figure 25-16 Time course of serum hepatic enzyme activities. This figure shows the approximate time course for serum enzyme activities following acute, severe hepatocellular injury with resolution in the dog. (Modified with permission from Meyer DJ, Harvey JW: *Veterinary Laboratory Medicine—Interpretation and Diagnosis*, 3rd ed. Philadelphia: Saunders, 2004.)

of approximately 12 hours in the dog and 1.5 hours in the cat.[4,5,6] Pathology involving hepatocytes in the dog results in the release of ALT and, if the insult is sufficiently severe, AST will also increase, but with a rise in AST activity that is less than that of ALT (see Fig. 25-16 and Table 25-5). In the cat, AST frequently increases concomitant with a rise in ALT activity. Resolution of hepatocellular pathology is indicated by normalization of serum AST activity, followed by normalization of ALT activity as determined by repeated sampling (see Fig. 25-16). A persistent increase in serum ALT activity for several weeks, especially if accompanied by a rise in AST, is one indication for a liver biopsy (Fig. 25-17). GLD is located within the mitochondria of hepatocytes. It has a half-life of approximately 18 hours in the dog.[7] A rise in GLD is interpreted in similar fashion to that of ALT and has a sensitivity that is similar to or better than ALT for the detection of liver pathology in the dog.[8,9] A variety of drugs cause mild increases in the serum ALT activity, presumably as a result of enzyme induction without causing liver pathology.[10,11]

A rise in ALP is generally caused by increased osteoblast activity, impaired bile flow, and/or drug induction. In the growing animal, ALP activities are higher than in adults as a result of increased bone

Table 25-5 Approximate Half-life of Serum Hepatic Enzyme Activities (Hours) for the Dog and Cat

Enzyme	Dog	Cat
ALT (alanine aminotransferase)	60	3.5
GLD (glutamate dehydrogenase)	18	Not determined
AST (aspartate aminotransferase)	12	1.5
LALP (liver alkaline phosphatase)	66	6

Modified with permission from Meyer DJ, Harvey JW: *Veterinary Laboratory Medicine–Interpretation and Diagnosis*, 3rd ed. Philadelphia: Saunders, 2004.

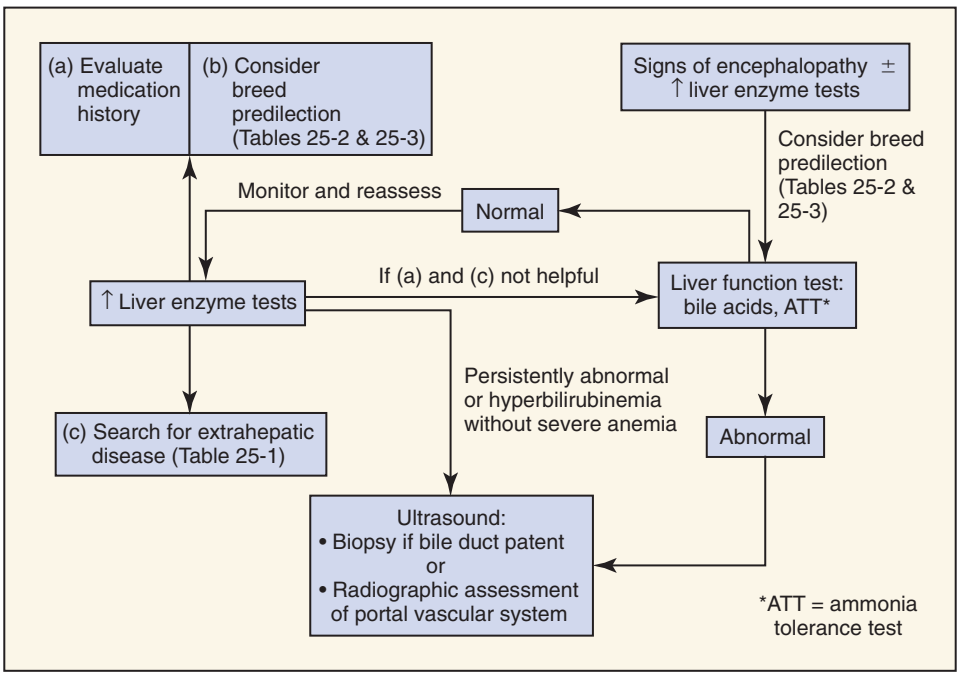


Figure 25-17 Diagnostic approach for abnormal liver tests. This figure outlines a diagnostic approach for the evaluation of abnormal liver tests and/or hepatic encephalopathy.

turnover, but they do decline with bone maturation. An increase in the total ALP activity because of an increase of bone ALP in the adult can be associated with osteomyelitis and osteosarcoma.[12] Bone ALP can be measured specifically to make that determination and follow the effect of treatment. Impaired bile flow caused by intrahepatic pathology or obstruction of the common bile duct stimulates the liver to increase ALP production and release into the circulation. Liver ALP has a half-life of approximately 66 hours in the dog and 6 hours in the cat.[4,13] A rise in ALP precedes a rise in bilirubin subsequent to impaired bile flow in the dog.

Drugs that stimulate the production of ALP include corticosteroids and anticonvulsants (e.g., phenobarbital, phenytoin, or primidone).[11,14] Endogenous or exogenous corticosteroids induce production of an ALP isoenzyme in the dog that is unique for this species. It has a half-life of approximately 74 hours.[4,13] Individual variation occurs as to the magnitude of increase, which can be dramatic in some dogs and is associated with severe microscopic hepatocellular ballooning degeneration (vacuolar change) and foci of neutrophilic inflammation.[15] The finding of an increased serum ALP activity with hepatocellular ballooning degeneration on biopsy, without a history of exogenous corticosteroid administration or laboratory findings of hyperadrenocorticism, should prompt consideration of nodular regenerative hyperplasia or chronic extrahepatic disease.[2,16] Hepatic ALP activity and the corticosteroid-induced ALP isoenzymes can be measured separately. However, the diagnostic reliability of these isoenzyme-specific assays is poor because of overlap in increases of these isoenzymes with primary liver pathology and increases secondary to corticosteroid and phenobarbital induction.[14,17-19] Phenobarbital causes an increase in predominantly liver and corticosteroid-induced ALP isoenzymes, but there is no unique phenobarbital-associated isoenzyme.[14]

The Scottish Terrier has a markedly higher serum alkaline phosphatase activity than other breeds, which rises further with age. However, the cause and clinical importance of this finding is unknown.[20,21]

Serum GGT activity is of hepatic origin; there is no bone GGT. Increased production of GGT by the liver and release into the circulation is stimulated by impaired bile flow or drug induction.[22,23] Drugs that cause a rise in serum GGT activity in the dog include phenobarbital and corticosteroids.[11,23,24]

Despite similar hepatobiliary tissue localization and a rise subsequent to increased enzyme production and release from the liver, there is not necessarily a concomitant rise in ALP and GGT activities subsequent to liver pathology or drugs that stimulate their hepatic production for reasons that are poorly understood. ALP, but not GGT, is increased following the administration of primidone or phenytoin to dogs.[11] In dogs with liver pathology, the frequency and magnitude of increase is generally greater for ALP than for GGT, and ALP has higher sensitivity but lower specificity than GGT as an indicator of liver disease.[25] In contrast, in cats the frequency and magnitude of increase is generally greater for GGT than for ALP and GGT has higher sensitivity but lower specificity than ALP for liver pathology.[26] However, a generally marked increase in ALP compared with GGT in feline hepatic lipidosis is notable.[27]

Tests Dependent on Liver Function

Albumin is produced by hepatocytes and has a half-life of approximately 8 days in the dog and probably slightly shorter in the cat.[28] Liver-related hypoalbuminemia is associated with portosystemic vascular anomalies and hepatic cirrhosis. Hypoalbuminemia because of protein-losing nephropathy or protein-losing enteropathy should be considered before ascribing hypoalbuminemia to decreased hepatic production. Albumin is a negative acute-phase protein and mild reductions (values remain within the reference interval) as a result of reduced synthesis are associated with chronic extrahepatic inflammation. There is often a concomitant mild rise in globulin concentration as a consequence of increased production of acute-phase proteins by the liver.[29]

The majority of coagulation factors are synthesized in the liver. The liver also plays a key role in the production of anticoagulant factors and the removal of activated clotting factors and products of fibrinolysis. Prothrombin time (PT) and activated partial thromboplastin time (aPTT) should be evaluated prior to procedures that compromise vessel integrity, notably liver biopsy, when hepatic pathology is suspected. aPTT and PT are both likely to be prolonged in severe, acute hepatic necrosis,[30] whereas only aPTT tends to be prolonged in dogs with congenital portosystemic vascular anomalies.[31,32] Also, in a model of chronic hepatic pathology, aPTT becomes abnormal earlier than PT.[33] Coagulation factors II, VII, IX, and X are dependent on vitamin K for activity. Vitamin K deficiency and the likelihood of hemorrhage are associated with bile duct obstruction and prolonged anorexia (e.g., in cats with hepatic lipidosis). Measurement of PIVKAs (protein induced by vitamin K absence or antagonists) appears to be more sensitive for the detection of vitamin K deficiency than the PT and aPTT assays.[34] When vitamin K deficiency is the cause of the abnormal coagulation tests, these return to reference values within 24 to 36 hours following the parenteral administration of vitamin K, but remain abnormal if the activity of other coagulation factors is reduced because of liver pathology.

Ammonia is produced in the intestinal tract and transported by the portal circulation to the liver where it is metabolized. One by-product is urea nitrogen, which enters the circulation and is excreted by the kidneys. Hyperammonemia is associated with portosystemic shunting because of portosystemic vascular anomalies that are either congenital or acquired secondary to cirrhosis. The finding of hyperammonemia supports the clinical suspicion of hepatic encephalopathy. Hyperammonemia also facilitates the development of ammonium biurate crystalluria, which is commonly associated with congenital portosystemic vascular anomalies. In one hospital setting, the measurement of the fasting plasma ammonia concentration was more sensitive and specific for the detection of portosystemic shunts in dogs than fasting plasma bile acid concentration.[35] Ammonia can be measured before and after the administration of ammonium chloride per os or per rectum. Ammonium chloride at 100 mg/kg and up to a maximum dose of 3 g is mixed in 20 to 100 mL of warm tap water to a concentration not to exceed 30 mg/mL and is administered orally or by orogastric intubation. Blood is collected into ammonia-free heparinized tubes and blood ammonia measured.[36] For the rectal route, a warm-water enema is given 12 hours prior to the administration of 2 mL/kg of a 5% ammonium chloride solution by a rectally placed catheter, and the blood ammonia is measured 20 and 40 minutes later.[37] A more than a two- to threefold increase in blood ammonia at any time point is considered abnormal.

Rare cases of hyperammonemia caused by an enzyme deficiency in the urea enzyme cycle in the dog have been reported.[38] Clinical signs of hepatic encephalopathy in these cases are associated with an abnormal ammonia tolerance test but a normal serum concentration of total bile acids. Measurement of the urea cycle enzymes in

liver tissue obtained by biopsy is needed for confirmation of the diagnosis.

As mentioned previously, blood urea nitrogen (BUN) is a by-product of ammonia metabolism. BUN is below the reference interval or inappropriately low compared with creatinine in most dogs and cats with congenital portosystemic vascular anomalies as a consequence of shunting of ammonia-rich portal blood directly into the systemic circulation.[39]

Bilirubin is derived from the metabolism of aged erythrocytes by macrophages and transported to the liver. This metabolite is referred to as unconjugated (indirect-reacting) bilirubin. Hepatocytes efficiently remove it from the sinusoidal blood and conjugate it with glucuronic acid; a process that is catalyzed by UGT1A1, an enzyme in the uridine diphosphate glucuronosyltransferase (UGT) family.[40,41] Some drugs impair the function of UGT1A1, resulting in an increase in unconjugated bilirubin in the circulation (unconjugated hyperbilirubinemia) without concomitant anemia or hepatic pathology.[42,43] Conjugated bilirubin is excreted by the canalicular membrane into the bile and carried to the intestinal tract where bacteria convert it to urobilinogens and stercobilin, the latter imparts the brown color to feces (see Fig. 25-15). Some of the colorless urobilinogen is passively reabsorbed and renally excreted. Measurement of urinary urobilinogen is an archaic test that was developed to determine patency of the bile duct and is now considered clinically useless. A variety of extrahepatic bacterial infections can release substances that impair canalicular membrane function, resulting in retention of conjugated bilirubin in the circulation (conjugated hyperbilirubinemia) (see Box 25-4). Because there is no physical biliary obstruction, it is considered a functional impairment of bile flow. Often there is only minimal concomitant change in liver enzyme activities or findings observed histologically.[44,45] Hyperbilirubinemia resolves with successful management of the extrahepatic infection.

Hyperbilirubinemia, an increase in the circulating total bilirubin concentration, leads to icterus (jaundice). The kinetics of bilirubin metabolism differ between the dog and man.[46] Conjugated, but not unconjugated bilirubin can appear in the urine (bilirubinuria) and a small amount of conjugated bilirubin can be detected in healthy dogs. Measurement of the unconjugated and conjugated fractions of serum bilirubin is generally not necessary or even helpful in determining the cause of hyperbilirubinemia. A rapid acceleration of erythrocyte destruction because of severe hemolytic disease resulting in hyperbilirubinemia (prehepatic icterus) is associated with anemia. Liver enzyme activities may also be abnormal in these patients because of the anemia-related, hypoxia-induced degeneration of hepatocytes, notably in the centrilobular region (zone 3) of the liver. Differentiation of hyperbilirubinemia because of intrahepatic pathology (hepatic icterus) versus obstruction of the bile duct (posthepatic icterus) is challenging. Ultrasound is used to assess bile duct patency and, if abnormalities are not detected, examination of a liver biopsy is often necessary.

Variable amounts of a second type of conjugated bilirubin can form with prolonged cholestasis.[47] Conjugated bilirubin can become irreversibly bound to albumin through a poorly understood mechanism. This type of bilirubin is referred to as biliprotein or δ-bilirubin. Instead of being rapidly eliminated (hours) in bile like the first form of conjugated bilirubin once the cholestatic process is resolved, δ-bilirubin is removed from the circulation at the rate of albumin degradation, which is approximately 6 to 8 days. If the majority of conjugated hyperbilirubinemia is in the form of biliprotein, icterus will be protracted (days to weeks) following successful management of the cholestatic process. Some chemistry analyzers can directly measure biliprotein.

Hepatocytes synthesize two primary bile acids from cholesterol, cholic acid and chenodeoxycholic acid, and conjugate them to glycine or taurine. Bile acids are secreted by the canalicular membrane into canaliculi for transport to the intestinal tract by the biliary system. Conjugated bile acids are efficiently absorbed (~95%) by the ileum into the portal circulation and transported back to the liver for efficient first-pass uptake (~60% to 80%) by hepatocytes primarily located in periportal region (see Fig. 25-15).[48,49] Conjugated bile acids are reexcreted into the biliary system for another enterohepatic journey during which they contribute the osmotic force that impels bile flow and provide surface-active detergent properties that facilitate intestinal absorption of lipids. This recycling of bile acids is referred to as an *enterohepatic circulation*. Small quantities of primary bile acids that are not reabsorbed in the ileum are dehydroxylated by anaerobic bacteria in the colon to form secondary bile acids. Some of these are absorbed into the portal venous circulation and recycled as well. Conjugated primary and secondary bile acids comprise the majority of the bile acid pool in the portal circulation. Uptake of bile acids by hepatocytes from the sinusoidal blood involves the sodium taurocholate cotransporting protein (NTCP) and the organic anion transporting protein (OATP), and bile acid transport into the bile at the canalicular domain is driven by the bile salt export pump (BSEP).[50-53]

Circulating total bile acid concentrations are usually measured after withholding food for 8 to 12 hours and again approximately 2 hours after a small meal of canned pet food in an attempt to stimulate contraction of the gallbladder and challenge the liver. To avoid lipemia, approximately 2 to 3 teaspoons are given to animals weighing less than 10 to 15 pounds and up to 2 to 3 tablespoons are given to larger animals. Postprandial gallbladder contraction is inconsistent or may occur during the fasting period, resulting in a fasted value that exceeds the postprandial value. However, both values are usually within the reference interval. Total bile acid concentrations increase in the circulation when pathology alters the enterohepatic circulation. Fasting and/or postprandial serum bile acid concentrations approximately greater than 15 μmol/L for the cat and 25 μmol/L for the dog are supportive of liver pathology or portosystemic vascular abnormality.[54-57] Bile acids can also be measured in the urine of dogs and cats.[58,59] Microscopic examination of a liver biopsy is required to characterize the liver pathology and determine its severity. Some of the highest values are found in congenital portosystemic vascular anomalies and cirrhosis. Maltese dogs can have high total bile acids without liver pathology for unknown reasons; the ammonia tolerance test in these dogs is normal. If the ammonia tolerance test is abnormal, a congenital portosystemic vascular anomaly is indicated. Small intestinal bacterial overgrowth (SIBO) can enhance the deconjugation of bile acids, which are less efficiently removed from the portal circulation resulting in an increase in the circulating total bile acid pool. An increase of a specific unconjugated bile acid, unconjugated cholic acid, has been associated with SIBO in dogs in one study, but the diagnostic value of this test was not verified in another study.[60,61]

Hypoglycemia caused by liver disease is often associated with congenital portosystemic vascular anomalies, especially in small breeds and in patients with acute severe hepatocellular necrosis.[30,62] Hypoglycemia is also associated with glycogen storage disease and primary hepatic neoplasia.[63,64,65,66]

Liver-related hypocholesterolemia is often associated with congenital portosystemic vascular anomalies.[62]

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STOMACH AND SMALL INTESTINE

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CHAPTER 26

Diagnostic Imaging of the Gastrointestinal Tract

RADIOGRAPHY

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Indications

With the exception of the esophagus, digestive tract organs share many common characteristics, including their location (peritoneal cavity), their afferent blood supply (i.e., celiac and cranial mesenteric arteries), portions of their efferent blood drainage (i.e., portal and hepatic veins) and a number of functions (e.g., motility, digestion, secretion, absorption, and excretion). These common characteristics must be considered in the approach to diagnosis. Clinical signs of gastrointestinal disease include vomiting, diarrhea, anorexia, abdominal pain, and weight loss. However it must be remembered that diseases of other organs, such as the pancreas, liver, kidneys, or adrenal glands can cause similar clinical signs. The diagnostic process is thus aimed at expeditiously including or excluding differential diagnoses using cost-effective diagnostics, including serum biochemical analysis and survey radiographs. In addition, these cost-effective diagnostics are generally available in primary care small animal practices, making them practical and applicable. Once initial diagnostic tests have been concluded, a more focused, but often more costly, diagnostic test, such as abdominal ultrasonography, endoscopy, or cytology, can be used to further localize the disease or make a specific diagnosis. This chapter describes an organized approach to the radiographic assessment of the gastrointestinal tract.

Technical Considerations

There are several reviews on specific radiographic techniques published elsewhere.[1-6] Several decisions need to be made before considering any imaging procedure, particularly those that are invasive or more costly. Specifically, what is the aim of the radiographic study? Is it to investigate organ geometry (i.e., size, shape, location, surface character, number or degree of organ involvement), organ opacity (i.e., gas, fluid, soft-tissue parenchyma, mineral, or metal), organ function (i.e., motility, breakdown, secretion, absorption, or excretion), organ leakage, organ obstruction, organ wall anatomy, organ wall thickness or pliability, etiology of dilation (segmental or diffuse), gas patterns, or effect of a diseased adjacent organ? Once the intent of the imaging procedure is established, it should then be determined whether survey radiographs alone are adequate to make the diagnosis or whether additional imaging procedures will be necessary. Horizontal beam or contrast procedures could be a necessary part of the additional medical workup. If a contrast procedure is indicated, the type of contrast medium should also be considered. Considerations for a contrast radiographic procedure should include the goal of the study (e.g., assessment of organ distention, motility, leakage, or foreign bodies), potential for body cavity or pulmonary contamination, options for contrast medium administration (i.e., oral, gastric, nasoesophageal, or nasogastric intubation), potential for air embolism from negative contrast medium, and the best choice for the contrast agent. Micropulverized barium sulfate suspensions are utilized in the assessment of motility and mucosal morphology, but can cause inflammation if the suspensions gain entry into the lungs or body cavities. Ionic iodinated oral preparations are associated with rapid propulsion, but are less useful for evaluating mucosal morphology, and side effects because of airway aspiration may be significant. Nonionic iodinated media are useful for the assessment of motility but not mucosal morphology, and fewer side effects have been reported if the media gains entry into lungs or body cavities. Another consideration is whether the positive contrast medium should be used as constituted or administered with food. In general, contrast agents should be administered without food for evaluation of mucosal morphology, detection of leakage, and timing of organ transit (e.g., stomach and small bowel) unless the goal is to assess the solid phase of gastrointestinal transit. Once these questions have been answered, other considerations related to the patient may be addressed.

Preprocedural Considerations

Patients with alimentary disease can be nauseous, weak, or dehydrated as well as having complications of alimentary tract disease, including aspiration pneumonia, sepsis, electrolyte and acid–base abnormalities, and abdominal distention. A balance between what is optimal for the patient and what is optimal for the imaging procedure should take these complications into account. Dyspnea and acute pain, for example, could be significant factors to consider in delaying the decision to perform an imaging procedure. Patient attitude and preparation are equally important patient parameters to take into account. Fractious patients may harm staff or themselves and must be adequately restrained or sedated. The authors prefer light phenothiazine sedation if sedation is needed.[7,8] Generally, no specific preparation is necessary for survey radiographs. In fact, unnecessary preparations or patient alterations may interfere with

image quality. For example, sedation may lead to slight accumulation of air in the esophagus that may be confused with megaesophagus. No specific preparation is required for an esophagram, but both the upper gastrointestinal (GI) series and the barium enema require cleansing enemas and/or cathartics, and, unless imaging is considered an emergency, food should be withheld for at least 18 to 24 hours.

Consideration should also be given to personnel safety. Appropriate radiation safety precautions must be taken for any radiographic procedure, including use of personnel shielding devices (e.g., aprons, gloves, eye shields, and/or thyroid shields). Appropriately placed personal body monitors must be used. Radiographic procedures should be planned such that manual restraint of the patient is minimized. Potential radiation exposure, including scatter and primary beam radiation, should also be minimized.

Positioning and Views

Standard Views

Standard, vertical–beam radiography (i.e., recumbent views taken with the patient on the x-ray table) with variable positioning can be used to characterize gas and fluid distribution within organs. The authors recommend right lateral and ventrodorsal (VD) recumbent views as a starting point for routine survey radiographs. The pylorus can appear like a ball-shaped foreign body in these views (Fig. 26-1).

Horizontal-Beam Views

The objective of horizontal-beam radiography (i.e., the x-ray beam is directed parallel to the x-ray table) is to use the influence of gravity on gastrointestinal fluid distribution to clarify findings suspected on routine survey radiographs. The most common uses of horizontal-beam radiography are (a) to position the patient such that any freely movable (free) fluid can be shifted away from the area of interest; (b) to position the patient such that free fluid can be serially quantified; (c) to position the patient to permit differentiation of free and trapped fluid, which is often associated with inflammatory and neoplastic conditions; and (d) to position the patient such that air observed in the abdominal cavity is freely movable or trapped within normal viscera. A horizontal fluid line indicates the presence of both air and fluid in the abdominal cavity (Fig. 26-2).

Esophagram

Contrast Media, Dose, and Route of Administration

If a perforation that potentially communicates with the lung or airways (e.g., bronchoesophageal or esophagopulmonary fistula) is suspected, a nonionic iodinated contrast agent (e.g., iohexol or iopamidol) or barium should be used. Alternatively, a half-strength water-soluble ionic iodinated contrast agent (e.g., oral Hypaque, or any angiographic or urographic iodinated contrast agent) can be used. If the study using an iodinated agent is negative, a study using liquid barium should follow, as some perforations cannot be identified using iodinated agents. Either type of contrast agent should be administered via buccal pouch infusion of 5 to 15 mL. If the goal of

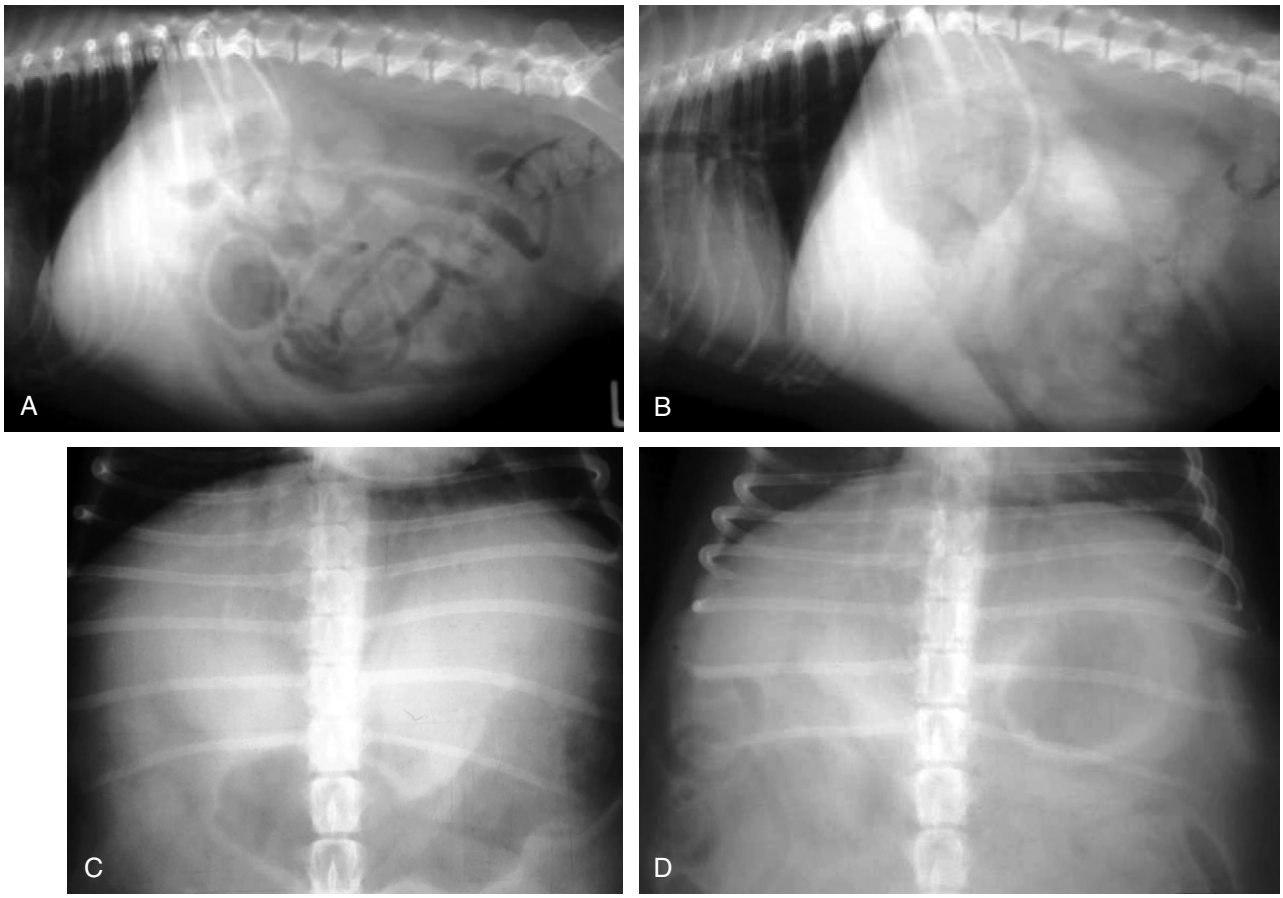


Figure 26-1 Abdominal radiograph, normal dog. (A) Left lateral recumbent, **(B)** right lateral recumbent, **(C)** dorsally recumbent, and **(D)** sternally recumbent. Note the shifting of gastric gas and fluid between the four different views.

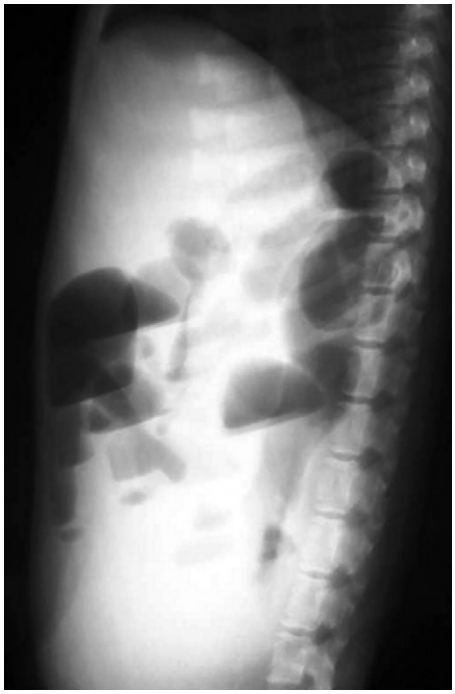


Figure 26-2 **Horizontal-beam radiography.** This lateral abdominal radiograph was taken with a horizontal beam. The radiograph shows small intestinal loops dilated with fluid and gas. Note the flat air–fluid interface in each of the loops.

the study is to outline the esophageal mucosa, liquid barium (i.e., >30% weight per volume [w/v] or a >25% wet weight [w/w] suspension) should be used. If the intent of the study is to instead assess esophageal peristalsis, a mixture of barium and canned food should be used. The barium/food mixture is best offered voluntarily, but could be force-fed if necessary. Contrast studies may not be needed if the esophagus is grossly dilated on survey radiographs.

Radiographic Views

All alimentary contrast procedures must be preceded by survey radiographs of the area of interest. The contrast agent should be given with the patient in the position that is intended to be obtained (i.e., usually lateral recumbency). The radiograph should be taken within 10 to 15 seconds of administration of the food, but is best taken 5 to 10 seconds after the first swallowing attempt to assess esophageal mucosal integrity. If trying to assess esophageal motility, the views should be taken within 15 to 30 seconds of the first swallowing episode. Solid food will normally be evacuated from the cervical and intrathoracic esophagus in less than 1 minute and any food remaining in the esophagus for more than 2 minutes is considered grossly abnormal. Radiographs may need to be repeated depending upon the effectiveness of esophageal clearance. Repeating the sequence with different types of food may be necessary as some patients may have adequate motility for liquids, but may not have adequate motility for solid food.

Upper Gastrointestinal Series

Contrast Media, Dose, and Route of Administration

There are several variations of the traditional upper gastrointestinal contrast series, including the air gastrogram and the double-contrast gastrogram. However a standard single-contrast study is recommended in most cases. For a routine upper GI study, approximately 6 mL/kg body weight (BW) of a 30% to 60% w/v (approximately 25% to 40% w/w) preparation of micropulverized barium sulfate suspension is administered via stomach tube. The concentration of the material can be readily adjusted by adding water. The only indication for ionic iodinated compounds is if a perforation of the GI tract is suspected. In those cases, the barium sulfate should be substituted with half-strength ionic iodinated or a more costly nonionic iodinated agent, which are given at an equal volume as for the barium. Nonionic agents are better if large volumes are needed, but are also more expensive.

Radiographic Views

Survey radiographs of the area of interest should be taken first. If the stomach is the site of a suspected abnormality, an image should be taken immediately after the administration of the contrast agent. The bulk of the liquid barium should be used to distend all aspects of the gastric lumen, and right and left lateral images as well as VD and dorsoventral (DV) views should be taken. If the small bowel is the site of an abnormality, only a right lateral and either a DV or a VD views are taken immediately after contrast administration. After these initial images, followup images are taken at least every 30 minutes until the contrast agent has reached the colon and the stomach is evacuated. In patients with a rapid onset of gastric emptying, as indicated by an almost immediate duodenal opacification, images should be taken every 15 minutes during small intestinal transit.

Barium Enema

Contrast Media, Dose, and Route of Administration

Approximately 20 mL/kg of a 30% w/v (approximately 25% w/w) preparation of micropulverized barium sulfate suspension is administered via hanging bucket and delivery tube. The barium product used may be packaged either as a liquid or a powder as flocculation in the colon is nonspecific.

Radiographic Views

Survey radiographs are taken of the area of interest. VD and left and right lateral views are taken immediately after complete filling is achieved. However if a patient shows signs of discomfort, it may be necessary to take an occasional lateral view before the entire dose has been given. In addition, it may be necessary to administer more than the initial dose to achieve complete filling. Therefore, one lateral view should be taken after the initial dose has been administered to determine if all parts of the rectum, colon, and cecum have been distended. Distention should be continued until questionable areas are either distended or reveal a specific defect.

Interpretation

Alimentary disease should be classified as luminal, mural, extramural, or transmural (e.g., perforation [Fig. 26-3]). The intent of this classification is to define the general likelihood of various differential diagnoses. An understanding of basic principles of pathology makes this less complicated. For example, extramural lesions affect alimentary organ position and dimensions (e.g., compression of the colorectal junction by an enlarged prostate gland), but do not originate in the alimentary organ itself. Intraluminal lesions, on the other hand, are generally completely surrounded by the administered contrast medium. Finally, mural lesions, such as tumors or strictures, are generally only partially surrounded by the administered contrast medium. When considering mural lesions, wall thickness measurements play an important role. The normal wall

thickness is 2 to 4 mm for the esophagus, 4 to 5 mm for the stomach (interrugal), and 3 to 4 mm for the small bowel and the colon.[1,3-6] Any deviation from these measurements is usually a result of local or regional infiltrates causing wall thickening that can range from diffuse infiltrative bowel disease to focal/multifocal mural infiltrates such as tumors and strictures. Annular lesions are a unique subset of mural lesions and resemble either a napkin ring or an apple core because of their circumferential distribution and concentric luminal narrowing. Although possibly seen with strictures, this pattern is most commonly seen with intestinal neoplasia.

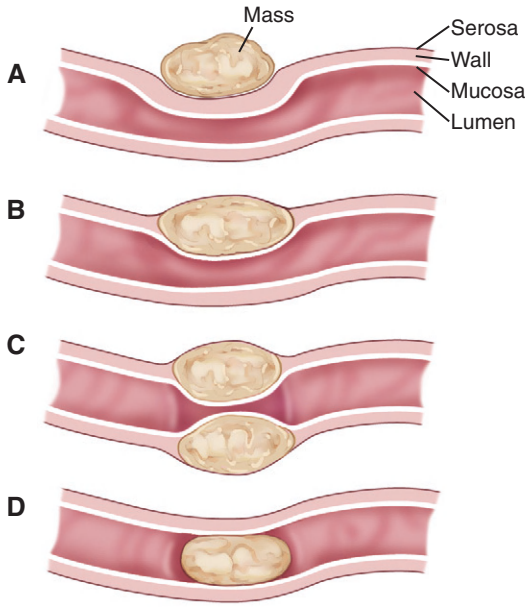


Figure 26-3 Types of intestinal lesions. This figure shows a diagrammatic representation of (**A**) extraluminal, (**B**) intramural, (**C**) annular intramural, and (**D**) intraluminal gut lesions.

Considerations for Alimentary Tract Imaging

The use of a few common sense rules can greatly simplify the imaging of the alimentary tract. Survey radiographs are crucial for the diagnostic process as they allow assessment of the GI tract without being affected by procedure-related stress and aerophagia, peristaltic effects of drugs or tube passage, and the soothing (barium) or irritating (ionic iodine) effects of contrast agents. It is also important to have a perspective on the relative roles of imaging procedures and endoscopic procedures. In general, endoscopic procedures are superior to imaging procedures for mucosal characterization, although this may change as imaging-based virtual endoscopic procedures are further investigated and refined. By comparison, radiographic procedures, particularly positive contrast procedures, are superior for characterization of intramural, transmural, and extramural diseases.

Of particular value is an assessment of the fluid and gas volumes along the gastrointestinal tract. First, any reproducible distention of the esophagus is abnormal. As a general rule, approximately 30% to 60% of the small bowel in dogs contains air, which is spread evenly throughout the bowel and relates in some reasonable proportion to the gas and fluid in the stomach. By comparison, most of the feline alimentary tract is devoid of gas, except in aged cats. This is a consequence of both anatomy and physiology (Fig. 26-4). The

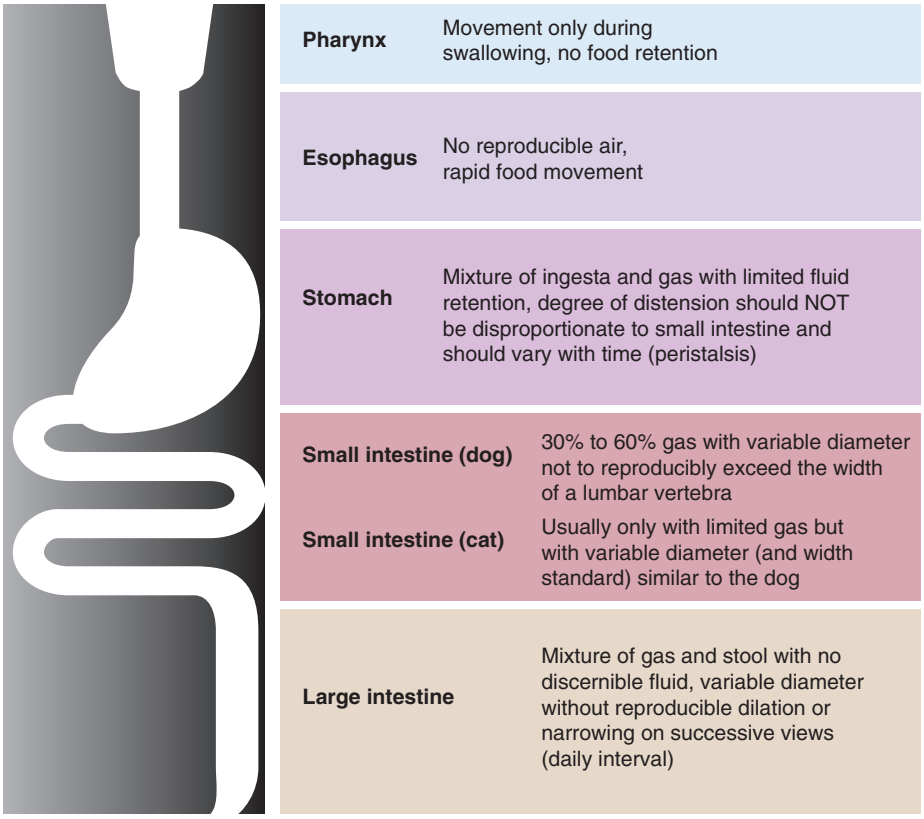


Figure 26-4 Radiographic parameters along the alimentary tract. This figure shows an illustration of the expected alimentary content, motility, and proportionality along the alimentary tract in small animals.

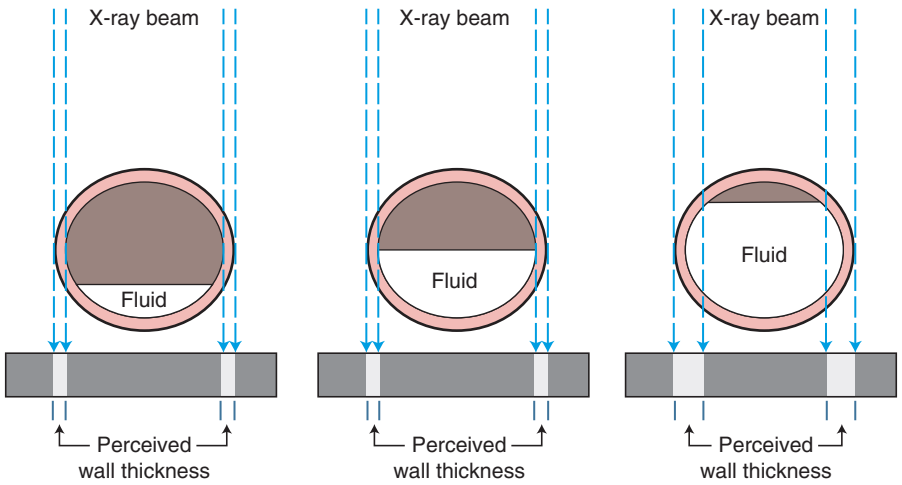


Figure 26-5 Perception of wall thickness. Illustration of perception of bowel wall thickness caused by fluid content of the stomach.

gastrointestinal tract is one continuous tubular lumen and there should be an orderly flow of ingesta from proximal to distal. There should be no disproportionate accumulation of fluid or solute or lack of any of these contents along the course of the GI tract. If such changes are identified on survey radiographs, this is an indication for further imaging investigation. The alimentary organs can be affected by regional and systemic influences as well as the local effects of the ingesta. The fluid/gas balance coupled with the organ size or diameter and distribution of a perceived abnormality can provide clinically useful insights into the pathophysiology of the disease. For example, a focal or multifocal distribution is associated with foreign bodies, tumors, strictures, and small incarcerations. In comparison, a diffuse distribution is associated with widespread intramural disease (e.g., infiltrative bowel disease), as well as widely differing luminal osmolarities related to bacterial proliferation, digestion, or absorption. A diffuse distribution can also result from disease involving other components of the digestive system, especially the liver (e.g., portal hypertension causing fluid buildup in the small bowel). Regional effects can be the result of intraluminal, intramural, or serosal irritation or inflammation (e.g., caused by peritonitis, pancreatitis, or a migrating foreign body).

The size of an alimentary organ as well as its contents can provide an insight concerning the underlying abnormality. Organ size is governed by several factors, including peristaltic capacity (i.e., neuromuscular disease, ischemia, inflammation, wall trauma, or altered electrolyte status), downstream or outflow resistance (i.e., sphincter dysfunction, strictures, or any obstruction), the digestibility and bulk of intraluminal contents (e.g., foreign material or engorgement), wall pliability (e.g., fibrosis or cellular infiltrates), wall thickness (e.g., tumor), upstream delivery of materials, and the volume and viscosity of ingested or administered material (e.g., aerophagia, psychogenic polydipsia, or polyphagia). Impedance to flow is characterized by buildup of fluid, ingesta, and air proximal to the impedance, and a lack of these contents distal to the impedance. Partial obstructions are characterized by buildup of fluid and ingesta with only small amounts of gas. Near complete obstruction is characterized by a mixture of gas and fluid, but with little accumulation of ingesta. Dysmotility may mimic any of the previously mentioned conditions.

Gas volume and its distribution can be key components in the interpretation of alimentary tract disorders. In omnivores, most alimentary gas derives from swallowed air. From low-grade impedance of gastrointestinal flow to complete obstruction, the likelihood of intraluminal buildup is air, fluid, digestible solids, and nondigestible solids (e.g., small bone fragments or small foreign objects). Unless an obstruction is nearly complete, only limited amounts of air will accumulate proximal to it because air can move past a partial obstruction more readily than fluid, food, or mobile fragments suspended in the partially digested chyme. The relationship of relative air versus fluid in a tubular organ segment and the influence of gravity are relevant variables to the assessment of gut wall thickness using survey radiography. As illustrated in Figure 26-5, the appearance of the wall of a hollow alimentary organ is based on the optical perception of the serosal and mucosal surfaces with the distance between them presumed to represent the wall thickness on routine vertical-beam radiographs. Overestimation occurs when the lumen is more than half full, which is common on alimentary survey radiography and must be factored into every attempt to assess wall thickness and may prompt a decision to perform additional imaging, including contrast or ultrasonographic procedures.

For interpretation of any survey radiograph, the well-accepted "Roentgen sign" approach (e.g., size, shape, location, surface characteristics, opacity, and function) provides useful basic information. Several questions should be considered to avoid over- or underinterpretation of these findings. Radiographs should be reviewed for any unexpected or disproportionate regions of organ distention, and whether any distention is caused by fluid, gas, solids, or some combination of all three phases. Radiographs should also be reviewed for signs suggestive of mechanical disruption or dysmotility. Gas-to-fluid ratios should be determined and whether luminal gas is randomly distributed. Another question that needs to be addressed is whether the distribution of fluid, gas, and ingesta is diffuse or segmental. Areas of segmental distribution, regional peristaltic abnormalities, and wall rigidity should be identified. The mixture of fluid and gas in the bowel should be assessed for evidence of obstruction and to differentiate it from ischemia, the latter of which is mostly associated with intraluminal air. Radiographic review should also include identification of unexplained localized intraluminal opacities or persistent material. Serosal contrast should especially be evaluated in areas of gut abnormalities. Masses should be identified and assessed for visceral displacements, invasion, or origination from the gut. Another very important question to pose is whether there is any free air or fluid in the peritoneal or retroperitoneal cavity. The etiology of the alimentary problem may not be obvious on survey

radiographs alone, and if that is the case, the radiographic interpretation may still help focus selection of more appropriate imaging techniques for further clarification or definitive diagnosis.

There are some useful clinical clues to the underlying etiology of an alimentary tract disease.[1,3-6] The buildup of a grainy opacity can indicate a chronic partial obstruction in either the stomach or the small intestine. A "thumbprinted" bowel, which describes a segment of the bowel that looks similar to a tubular piece of clay into which a thumb has been pressed, is suggestive of segmental or diffuse intramural infiltration because of neoplasia or pyogranulomatous infiltration. The thumb-printing effect comes from loss of wall pliability and variability in wall thickness. Another finding that can be observed is the so-called onion-skin or coil-spring appearance caused by contrast medium spreading between contiguous intestinal loops involved in an intussusception. The so-called washboard effect can be caused by regional mesenteric ischemia. The appearance of mural or wall layering may also be noted during radiography, which can be a result of infiltration of the wall with gas or minerals. Layering of luminal content may also be seen on horizontal-beam views, as different types of bowel content occupy different "layers" relative to gravity. Finally, the appearance of tubular plication, which appears as an eccentric accumulation of air, is caused by intestinal bunching occasioned by ingestion of linear foreign bodies (e.g., cloth, string).

The authors advocate two approaches to interpreting radiographs. The first is the gamut approach[9] in which the radiographic signs are listed and the pathophysiologic or pathoanatomic causes are considered. The findings are then ranked in descending order of likelihood based on risk modifiers including clinical history, age, gender, breed, and species. Another helpful approach is the use of the so-called DAMNIT system, which adopts a pathogenesis approach to diagnosing radiographic findings. The disease processes considered in the DAMNIT system are degenerative, drug-induced, and developmental (D); anatomic, allergic, autoimmune, and anomalous (A); metabolic and mechanical (M); nutritional and neoplastic (N); infectious (bacterial, fungal, viral, parasitic), inflammatory, and immune-mediated (I); and, toxic, traumatic, and teratogenic (T). Judicious use of the DAMNIT approach limits the likelihood of a diagnosis being missed because it was not included in the gamut approach.

Specific Considerations for Different Organs of the Gastrointestinal Tract

Oral Cavity and Pharynx

Anatomic considerations

Coordinated prehension, mastication, bolus formation, and swallowing are all necessary to facilitate coordinated aborad propulsion of food and water into the esophagus and beyond. Any morphologic or functional abnormality can be detrimental to the process of ingestion (see Chapter 54). The anatomic structures important for ingestion include the tongue, teeth, supporting bones of the maxilla and mandible, oropharynx, hyoid apparatus, and larynx. The tongue is important for complex movements that allow for prehension, mastication, and swallowing. The teeth and the supporting bones of the maxilla and the mandible are needed for mastication, and the oropharynx, pharynx, and larynx are needed for propulsion, swallowing, and protecting the airway during swallowing, respectively. The hyoid apparatus acts as a suspensory mechanism for tongue and larynx during swallowing. Positioning is crucial for radiographs of the aforementioned structures to avoid erroneous interpretation. A lateral view provides the most information, but orthogonal views should always be obtained.[10] The size and shape of the air-filled oropharynx varies with the position of the tongue, but the rectangular air-filled pharynx should maintain its size and shape independent of tongue position and phase of respiration (Fig. 26-6).

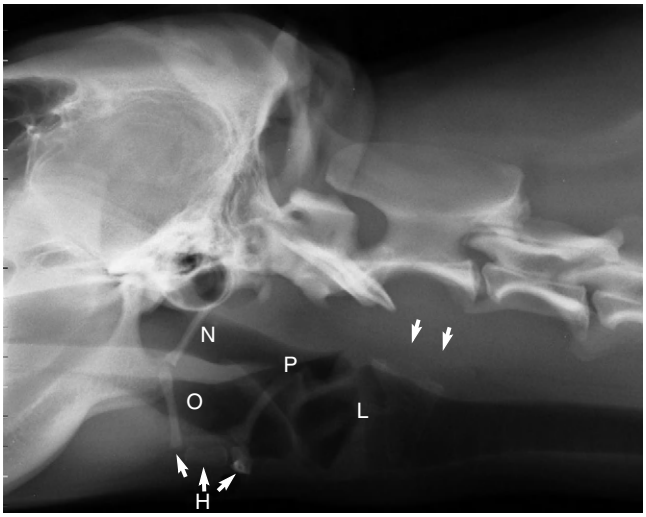


Figure 26-6 Normal canine pharynx. This radiograph shows a lateral view of the normal canine pharynx. Note the soft palate separating the air-filled nasopharynx (*N*) from the air-filled oropharynx (*O*), the air-filled pharynx (*P*), the hyoid apparatus (*H*), and the larynx (*L*; i.e., epiglottic, arytenoid, thyroid, and cricoid cartilages). Note the position of the structures relative to the cervical spine. Care must be taken not to mistake the normal cricopharyngeus muscle as a mass or foreign body (*white arrows*).

Functional Considerations

The primary functions of the oral cavity and pharynx are to prehend, masticate, and propel food into the esophagus. Prehension, mastication, and propulsion all require an intact innervation and coordinated relaxation response of the cricopharyngeus to permit passage of the bolus into the esophageal body. During these coordinated movements of swallowing, the soft palate closes the nasopharynx to prevent reflux of food into the nasal passage, and laryngeal closure protects the trachea from aspiration of food. A lesion associated with any of the involved structures can lead to an incomplete swallowing response.

Abnormal Radiographic Signs

Close inspection of lateral and DV or VD views will elucidate some of the diseases of the pharynx, but most will require further investigation by visual inspection, special procedures (e.g., contrast studies), and alternate imaging studies (e.g., fluoroscopy, ultrasound, computed tomography [CT], or magnetic resonance imaging [MRI]). It is important to closely evaluate the surrounding soft tissues for air, which can be caused by penetrating foreign bodies, lacerations, or abscessation. Poor pharyngeal tone, pharyngeal collapse, mural infiltrates, edema, and mural or extrinsic masses may lead to an abnormal size and shape of the pharynx (Fig. 26-7). Extrinsic masses often lead to displacement of the pharynx, larynx, and/or the trachea and are also often associated with accompanying compressions of these structures (Fig. 26-7C). The hyoid apparatus may become displaced or may contain fractures in association with dysfunction (Fig. 26-7A and B).

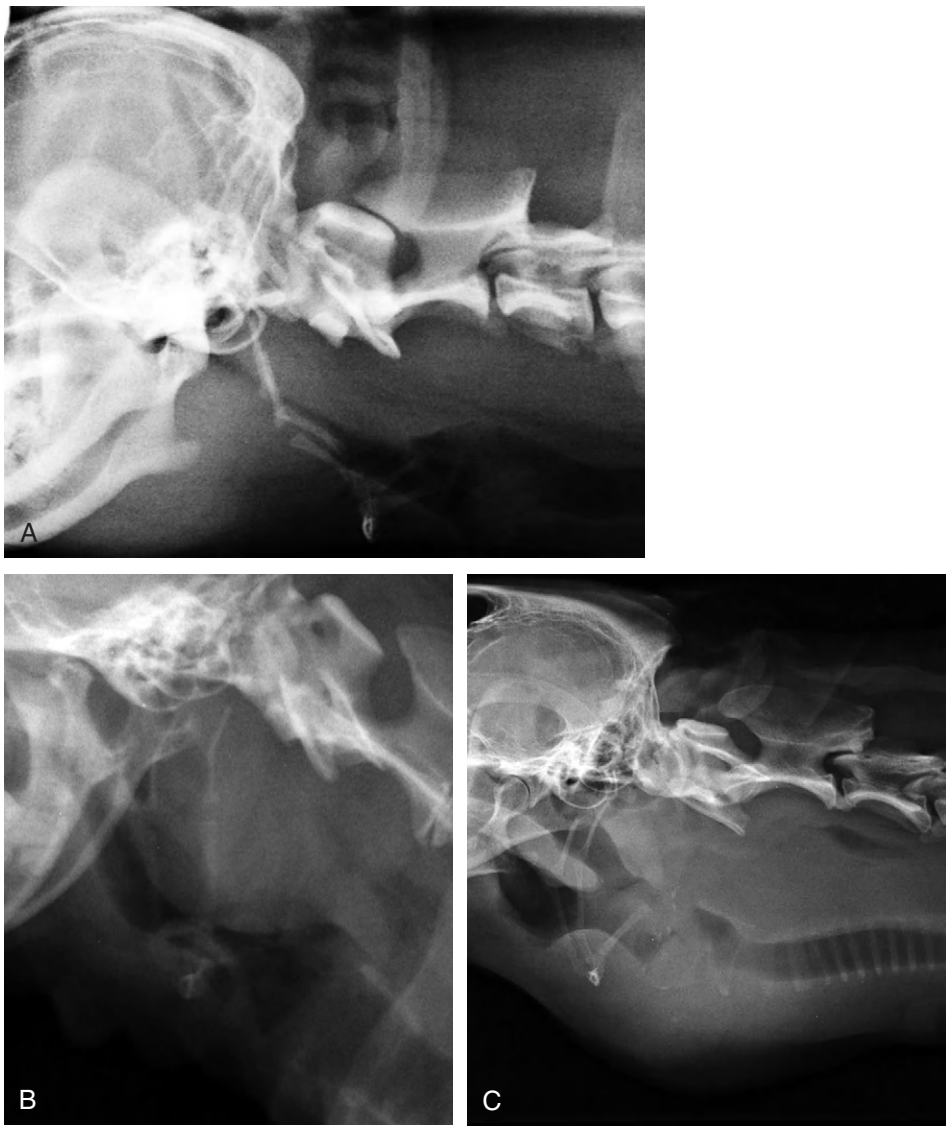


Figure 26-7 Pharyngeal disorders. This figure shows a variety of pharyngeal disorders. **A,** Lateral view of a dog with pharyngeal collapse. Note the lack of gas in the pharynx and the caudal migration of the hyoid apparatus as the dog inspires. No mass is present. **B,** Lateral view of a dog with a pharyngeal/retropharyngeal mass. Note the rounded mass causing compression leading to narrowing of the pharynx and to ventral displacement of the hyoid apparatus. **C,** Lateral view of a dog with a large circumferential neck mass causing compression and displacement of the pharynx, larynx, and trachea.

A contrast procedure utilizing a nonionic iodinated contrast agent can be helpful when evaluating the pharyngeal region for draining tracts. It is important to determine the extent of tissue involvement, especially as it is not uncommon for foreign bodies to penetrate the oropharynx or pharynx. Interpretation of the study involves determining the direction and extent of the tract, communication of the tract with the oropharynx, pharynx, esophagus, or other regional structures, and the cause of the draining tract (Fig. 26-8).

Dysfunction. Pharyngeal function is best observed fluoroscopically using liquid barium and barium-coated material (dynamic fluoroscopy).[11] Sometimes an impression regarding pharyngeal function can be gained using static survey radiographs obtained during inspiration and expiration. Survey radiographic findings suggesting pharyngeal dysfunction include caudal migration of the hyoid apparatus during inspiration, hyperinflation of the pharynx during expiration, collapse of the pharynx during inspiration (see Fig. 26-7A), and persistent gaseous distention of the proximal esophagus. These findings should be further evaluated with the use of pharyngeal fluoroscopy. Diseases associated with pharyngeal dysfunction include myasthenia gravis and other muscular disorders; cricopharyngeal achalasia, which is characterized by cricopharyngeal hypertension and inability of the sphincter to relax; and cricopharyngeal dyssynchrony, which is characterized by an incoordination of pharyngeal contraction and cranial esophageal sphincter relaxation.[11,12]

Pharyngeal Diseases

Disease processes resulting in abnormal size and shape of the pharynx will be governed by multiple factors. Downstream resistance leading to hyperinflation can be caused by laryngeal paralysis, laryngeal neoplasia, laryngeal pyogranulomatous inflammation, and tracheal obstruction as may occur due to a foreign body. Abnormal pharyngeal tone may be caused by neuromuscular disorders such as

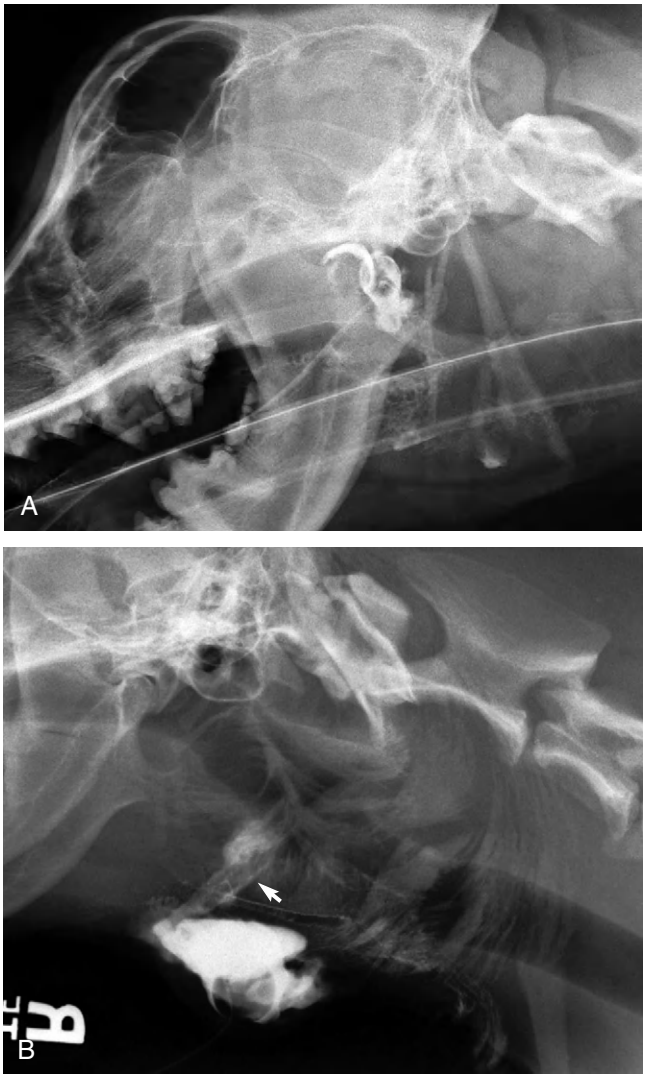


Figure 26-8 **Fistulograms. A,** Lateral view of a fistulogram. A balloon catheter was placed into a draining tract in the oral cavity of a dog and a nonionic iodinated contrast agent was injected. Note the contrast outlining the right temporomandibular joint. **B,** Lateral view of a fistulogram. Note the rectangular filling defect in the contrast area (*white arrow*), which was later identified as a piece of wood.

myasthenia gravis. Upstream resistance may be a result of stenotic nares, severe obstructive rhinitis, nasal neoplasia, or an inflammatory polyp. Pharyngeal collapse or mural lesions may be caused by redundant pharyngeal tissue, pharyngeal edema, inflammation, polyp, granuloma, or neoplasia. Extrapharyngeal lesions, such as retropharyngeal lymphadenopathy, neoplasia, abscess, granuloma, or foreign body, may also lead to pharyngeal compression.

The location and shape of the larynx may be governed by similar and additional factors. As with pharyngeal disease, downstream resistance may be a result of laryngeal paralysis, laryngeal neoplasia, laryngeal pyogranulomatous inflammation, or various causes of tracheal obstruction, including foreign bodies. Extralaryngeal lesions, such as retropharyngeal lymphadenopathy, neoplasia, abscess, granuloma, foreign body, or failure of the supporting structures such as hyoid luxation or hyoid fracture can all lead to radiographic changes of the larynx. An additional important consideration is that of regional opacity. Radiographic signs noted may include extrapharyngeal or laryngeal radiolucency caused by regional emphysema from pharyngeal or laryngeal perforation. Regional mineralization due to neoplasia, chronic hematoma, abscess, pyogranulomatous inflammation, or foreign body may also be observed. Penetrating pharyngeal foreign bodies can be potentially serious events in the dog and cat.[13] Metal foreign bodies are usually easily identified, but less-dense objects may be easily missed. The most frequent radiographic abnormality identified in patients with a pharyngeal foreign body is subcutaneous gas accumulation or gas in fascial planes or gas accumulating subcutaneously.[13] In some cases, a foreign body may be misinterpreted as a soft-tissue mass caused by regional inflammation or edema.[10]

Esophagus

Anatomic Considerations

The canine and feline esophagus is usually not visible on survey radiographs. There are occasional exceptions to this rule, including the increased likelihood of gastroesophageal reflux in left lateral recumbency and stress-induced or spontaneous reflux. These instances usually only involve the distal half of the esophagus and are transient. When visible, particularly when coated with barium, the normal esophagus exhibits bolus propulsion with interbolus linear stranding of the collapsed portion of the esophagus (Fig. 26-9A). There are some important species differences. The distal one-half to two-thirds of the feline esophagus normally has a "herringbone" appearance in the mucosal surface due to the presence of smooth muscle (Fig. 26-9B).

Functional Considerations

The primary function of the esophagus is the propulsion of food boluses. There is some fluid, mucus, and cation secretion, but the primary function is one of motility. If the propulsive functional capacity is sufficiently poor the esophagus will dilate. In most cases there is little need for contrast studies unless there is a suspicion of an obstruction causing the dilation. However the degree of esophageal dysfunction can be variable, ranging from diffuse dilation and complete flaccidity to a seemingly normal esophagus that fails to propel dry kibble but will move fluids and most soft foods without difficulty. The latter point illustrates the importance of esophageal imaging studies.

Abnormal Radiographic Signs

The normal esophagus is not visible on survey radiographs and needs to be rendered visible by contrast agents. The esophagus originates dorsal to the larynx and the proximal cervical trachea, courses gradually to the left of the trachea at the thoracic inlet to again become dorsal to the trachea in the cranial mediastinum, and track caudally dorsal to the heart to the esophageal hiatus of the diaphragm (Fig. 26-10). When rendered visible by positive contrast media, the location, morphology, and distribution of esophageal dysfunction can be identified (Figs. 26-11 and 26-12).[6,14] In addition, when surface-coating agents such as barium are being used, the mucosal surface can be assessed. In normal patients the esophageal mucosal surface should be smooth and regular. The most common cause of ventrally displaced trachea is esophageal dilation.

Esophageal Diseases

As with other parts of the digestive system, a systematic approach should be used to arrive at a list of differential diagnoses based on radiographic findings. The peristaltic capacity of the esophagus can be altered by idiopathic megaesophagus, dysautonomia, esophagitis, overt electrolyte imbalance, heavy metal toxicity, congenital or

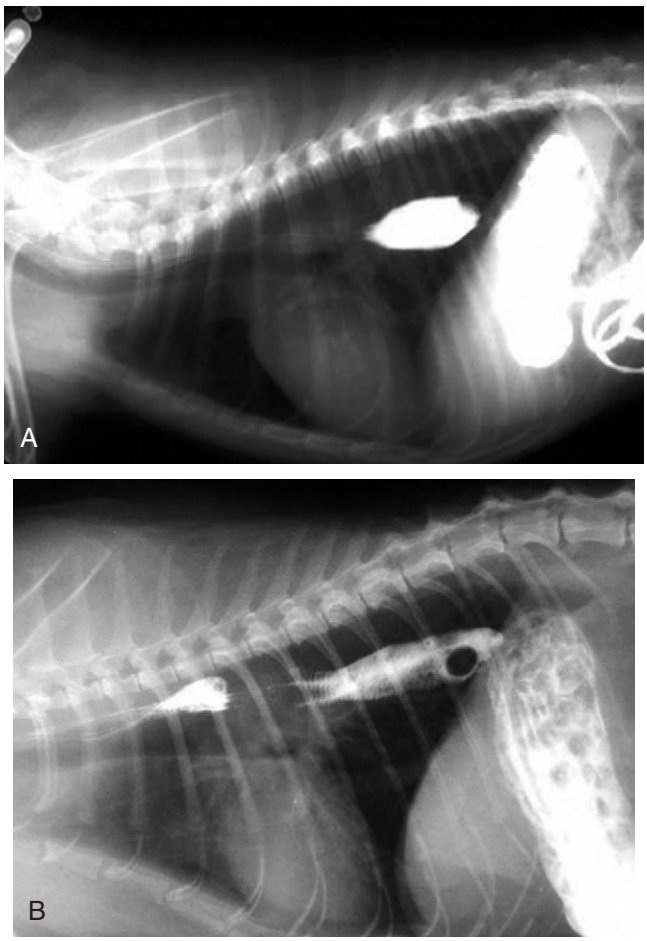


Figure 26-9 Normal esophagus. A, Lateral view of an esophageal bolus that is driven by peristalsis in a normal dog. Note the barium-coated linear folds in the collapsed esophagus cranial to the bolus. **B,** Lateral view of an esophageal bolus that is driven by peristalsis in a normal cat. Note the herringbone mucosal pattern in the esophagus between the heart and the diaphragm.

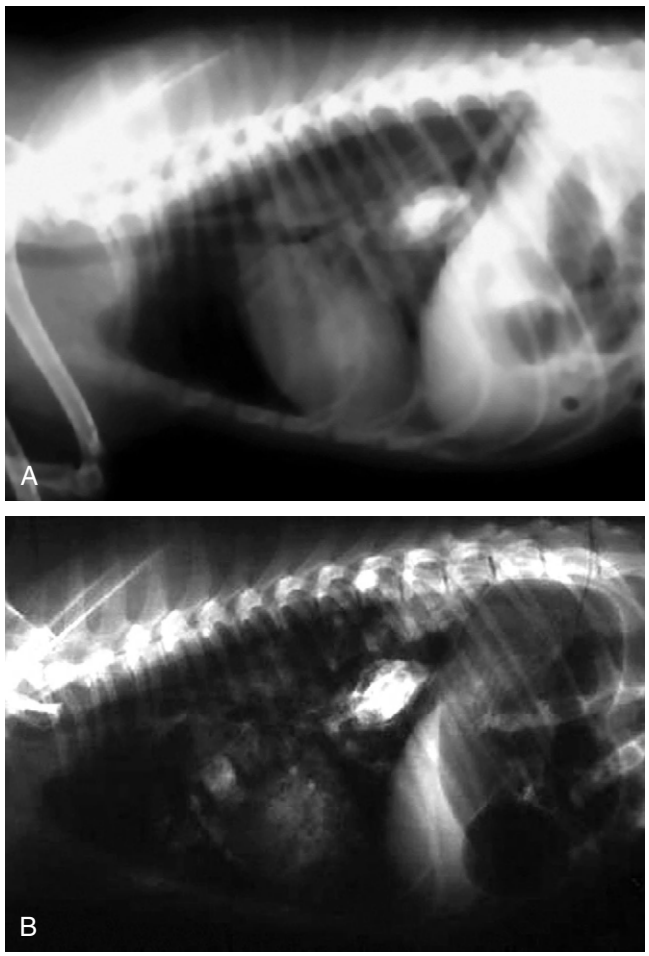


Figure 26-10 Survey radiograph and esophagram. (A) Left lateral recumbent survey radiograph and **(B)** left lateral recumbent contrast radiograph made after dilute iodine was administered to determine if there was leakage caused by the bony foreign body. Note the patchy opacity of the lung that occurred because of a caudal lobar bronchoesophageal fistula.

acquired diverticula, and thyroid status (see Chapter 55). Downstream resistance can be the result of a stricture, tumor, anomalous constrictions such as vascular ring anomalies, or any intraluminal obstruction, such as a foreign body. Wall thickness and pliability can also be altered because of fibrosis, inflammatory reactions, or neoplastic infiltrates. The upstream delivery of ingested materials is governed by a primary esophageal peristaltic wave that takes less than 10 seconds to move from the pharynx to the stomach. Luminal distention triggers a secondary peristaltic wave that originates at the site of the distention and proceeds toward the stomach in less than 5 to 10 seconds. Esophageal abnormalities should be further classified as intraluminal, intramural, transmural, or extramural. Examples of intraluminal abnormalities are foreign material or retained ingesta because of ineffective peristalsis or increased downstream resistance. Intramural abnormalities can be a consequence of strictures or tumors. Transmural abnormalities can be caused by penetrating objects or by bronchoesophageal fistulae. Extramural abnormalities can be caused by compression, distortion, or displacement by a regional organ or mass. Finally, the esophageal mucosa should be evaluated. Mucosal ulceration can be caused by erosion from gastric or gastrointestinal reflux, trauma from lodged or migrating foreign bodies, tumors that disrupt the mucosal surface, or the ingestion of corrosive chemicals such as sodium hydroxide. Esophageal leakage because of traumatic or ulcerative lesions can lead to septic mediastinitis and should be carefully considered. In the authors' experience, pneumomediastinum is a rare finding with esophageal penetrating lesions. The material that leaks into the mediastinum is usually of insufficient volume to noticeably distend the mediastinum. This makes the positive contrast esophagram all the more important in the assessment of a suspected esophageal perforation. This is usually initially performed with an iodine-based contrast agent, as these agents are isotonic and do not cause irritation if there is a tract involving the airway or lung. If the initial study is negative, it is followed by a barium study, which is more useful for detecting and localizing small leaks. Any barium contamination of the mediastinum should be surgically irrigated as soon as is practicable, but definitely in less than 12 hours.

Stomach

Anatomic Considerations

The canine and feline stomach usually contains modest amounts of fluid, but generally not enough to cause the appearance of distention on any radiographic view or recumbency. If the stomach begins to appear rounded rather than elongated in the transverse plane in a

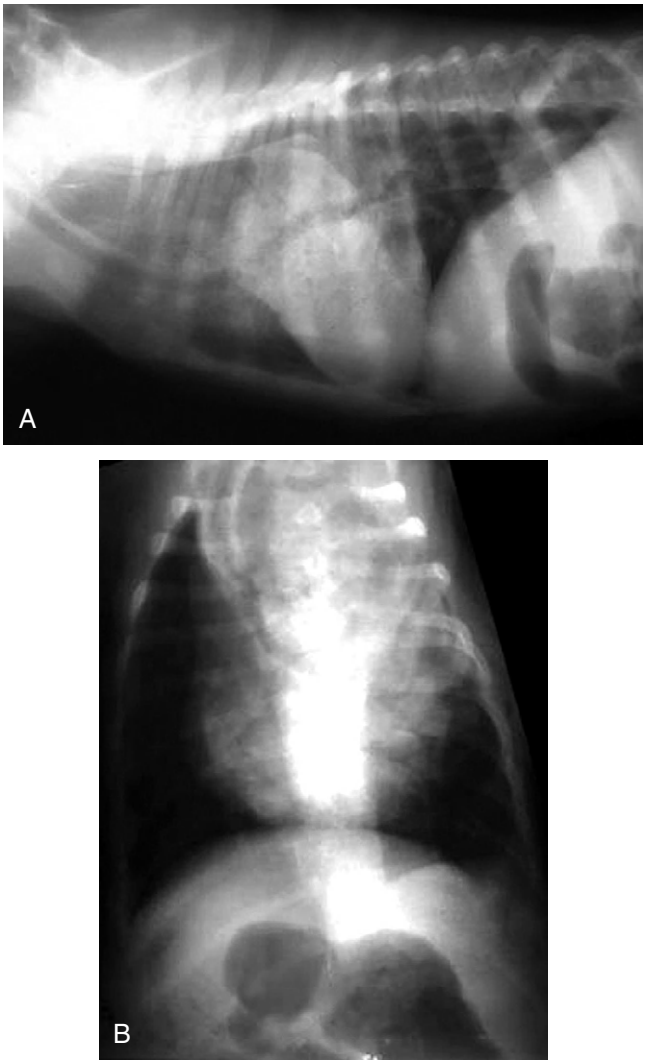


Figure 26-11 Vascular ring anomaly. (**A**) Left lateral recumbent and (**B**) dorsally recumbent survey radiographs of a dog. A gas-containing structure can be seen deviating the cranial mediastinal part of the trachea ventrally caused by a vascular ring anomaly. Note the alveolar disease in the left cranial lobe caused by aspiration pneumonia.

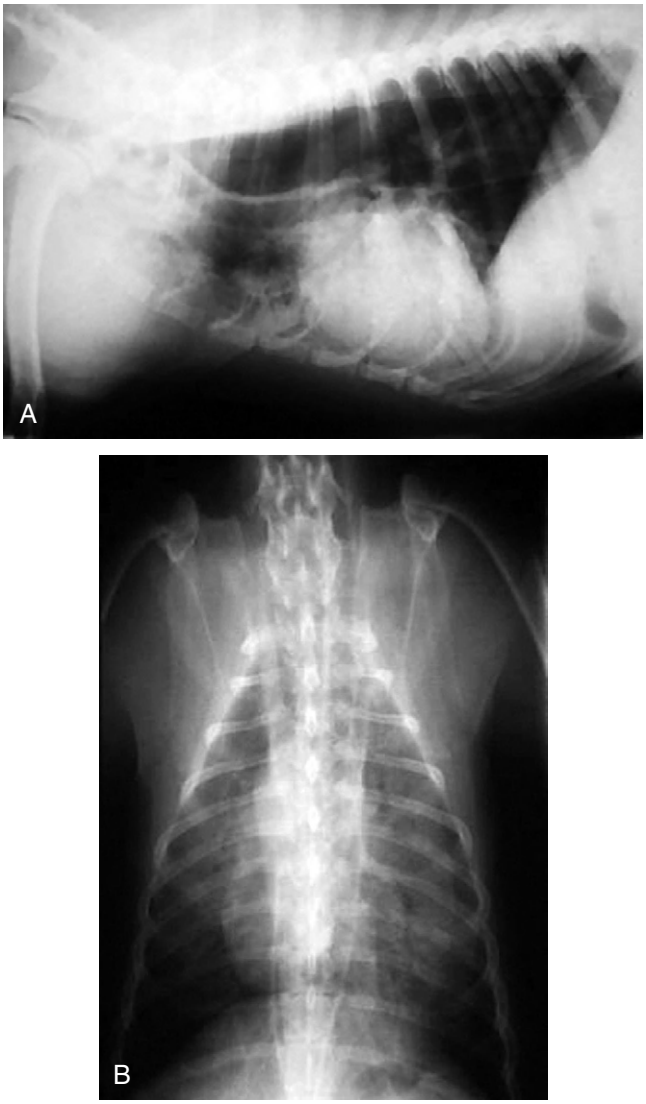


Figure 26-12 Megaesophagus. (**A**) Left lateral recumbent and (**B**) dorsally recumbent survey radiographs from a dog. A gas-containing structure is deviating the intrathoracic trachea ventrally. This structure can be identified as a diffusely dilated esophagus. Note the alveolar disease in the cranial and middle lobes, which are a result of aspiration pneumonia.

fasted animal, it should probably be considered to be abnormal. The cardiac region is more or less anchored behind the left diaphragmatic crus as a result of the distal esophagus passing through the esophageal hiatus. The stomach position is influenced by the liver, and to a lesser degree by the spleen, regional masses, the morphologic and functional integrity of the diaphragm, as well as the degree of luminal distention. In general, the long axis (i.e., fundus to pylorus) of the stomach is parallel to the last few ribs in lateral recumbency and perpendicular to the spine in sternal or dorsal recumbency. The cardiofundic region of the stomach is in the left craniodorsal abdomen behind the left diaphragmatic crus and the gastroesophageal junction is located on the right medial aspect of the cardia. The pylorus is in the right cranioventral abdomen behind the liver near the right lateral abdominal wall in the dog, and just to the right of the midline in the cat. Cats usually have little gastric gas, whereas dogs often have equal amounts of fluid and gas in the stomach. The position of the fluid and gas as a function of gravity and recumbency can influence the appearance of the stomach, giving the illusion of a thickened wall (see Fig. 26-5) or a ball-shaped foreign body, which can be a result of fluid accumulating in the pylorus in right lateral recumbency. Depending on whether the patient is fed or unfed, the stomach may contain varying amounts of food. Unfortunately, many ingested foreign materials cannot be distinguished from food except by recheck radiographs after 18 to 24 hours. Digestible solid food will exit the stomach by 14 to 18 hours after eating, unless there is an outflow problem (see Chapter 26). In contrast, nondigestible foreign material will persist for many hours. Gaseous distention of the stomach has many causes including aerophagia and atony, which can be pathologic, but can also be caused by sedative or anesthetic drug effects. By comparison, gastric distention caused by an outflow obstruction is usually associated with a mixture of fluid and gas and is often accompanied by the retention of grainy material. This tends to accumulate proximal to the outlet obstruction and may gravitate within the lumen depending on patient recumbency. These opacities may be an indication

for a foreign body or they may simply indicate the buildup of materials normally dispersed in food (e.g., bone fragments).

Functional Considerations

The stomach has many functions, including storage, digestion, propulsion of solids and liquids, and secretion of gastric acid, pepsins, and mucus (see Chapters 1 and 56). A disease process involving any one of these functions can result in gastrointestinal signs ranging from anorexia to vomiting and can affect the size of the stomach as well as the makeup of the luminal contents. Because of pyloric resistance, fluid may remain in the stomach for up to 2 to 3 hours after ingestion, whereas solid food requiring greater breakdown can remain in the stomach for up to 18 hours. From a practical standpoint, the least invasive and most cost-effective radiographic procedure to determine whether gastric outflow is decreased is to repeat survey radiographs the following day or to obtain an alternate radiographic view. However retention of material in the stomach can be secondary because of reflex inhibition of gastric emptying by various intestinal (see Chapter 1) and/or peritoneal conditions. However retention can also be pathologic as a result of pyloric stenosis, foreign body, or tumor. Considerations of the various causes of gastric retention may help to facilitate the decision to use endoscopy, upper GI, laparoscopy, or exploratory laparotomy to further investigate the problem. To further characterize stomach wall conditions, including those of the pyloric sphincter, contrast gastric radiographic studies should be considered. The most practical and useful is a barium-based upper GI study.

Abnormal Radiographic Signs

The normal and abnormal stomach are both visible on survey radiographs. Consequently, it is important to differentiate transient physiologic conditions, such as postprandial gastric distention from disorders that may cause alterations of gastric size, shape, and position. The localization of gas and fluid in the stomach depend on the position of the patient during radiography. Before arriving at a definitive diagnosis based on one radiographic view, additional views may provide helpful clues and limit the likelihood of premature or inaccurate diagnosis. Identification of discrete cardiofundic, gastroesophageal, and pyloric regions is clinically important and is usually accomplished by shifting the gas–fluid interface with changes in patient positioning (Fig. 26-13). Once an assessment of physiologic versus pathologic distention has been made, an assessment of gastric contents and presence or absence of segmental mural variations can be carried out. Other important parameters such as mucosal integrity, which may be altered because of ulceration, luminal status that may indicate the presence of a foreign body (Fig. 26-14), and wall thickness, which may be altered as a consequence of hypertrophy or tumor (Fig. 26-15), are best assessed by use of contrast studies.[15-19] Similarly, the position of the gastroesophageal junction, and integrity of the gastric wall can be best assessed by contrast studies. Finally, the initiation and continuity of the peristaltic wave (normally there are two to five peristaltic waves per minute) are best assessed by gastric contrast studies. The choice between barium and an iodinated contrast medium should be made based on the goals of the study, such as mucosal coating, assessment of peristaltic capacity and pyloric function, or the identification of a leak.

Gastric Diseases

The overall size and position of the stomach should be evaluated, particularly as it relates to regional changes, such as a diaphragmatic hernia or microhepatica. The position of each of the gastric compartments (i.e., cardia, fundus, corpus, antrum, and pylorus) should be assessed at the same time. The size of the stomach or any of its compartments is governed by multiple factors including peristaltic capacity, dysautonomia, inflammation, chemical corrosion, overt electrolyte imbalance, and smooth muscle disorders. Downstream resistance caused by pyloric spasm, stricture, or tumor, for example, can affect gastric size and position. Intraluminal obstruction and alterations in gastric wall pliability have predictable effects on gastric size, position, and function. In case of a gastric outflow problem, reflex inhibition of gastric emptying may be contributing to the overall pathology. As with other components of the gastrointestinal tract, a useful classification of gastric abnormalities is to consider them as intraluminal, intramural, transmural, or extramural. Gastric mucosal abnormalities, including ulceration, can be caused by acid or peptic erosion, trauma from stationary or migrating foreign bodies, surface disruption caused by tumors, and ingestion of corrosive substances. Although the assessment of gastric erosions is possible by radiographic and ultrasonographic techniques, it is best assessed by endoscopy. Gastric perforation should always be ruled out as leakage from traumatic, neoplastic, and ulcerative lesions may lead to septic peritonitis. In the authors' experience, horizontal-beam radiography is a clinically useful tool for the initial assessment of free peritoneal air and suspected gastric perforation. If free peritoneal air is found and cannot be attributed to a recent surgical intervention, the next step should be a positive-contrast gastrogram. That said, the identification of unexplained free intraperitoneal air is always sufficient justification for an exploratory laparotomy. If a contrast procedure is deemed necessary to further investigate potential gastric leakage, this is usually performed initially using iodine-based contrast agents and, if negative, followed by barium, which is more useful for detecting and localizing small leaks. Any barium contamination of the peritoneum or retroperitoneum should be surgically irrigated as soon as is practicable, but definitely in less than 12 hours.

Small Intestine

Anatomic Considerations

The amount of gas normally contained in the small intestine differs between dogs and cats. In dogs, typically 30% to 60% of the small bowel volume is gas unless the space is occupied by ingesta. In contrast, the normal adult cat usually has almost no gas in the small bowel unless ingesta are moving through it. In aged cats, there may be some stress-induced excess small intestinal gas, which must be taken into account during interpretation. Excessive, but evenly distributed, gas in the small bowel has been reported in association with mesenteric volvulus. The small intestine is usually evenly distributed along the ventral abdominal wall caudal to the stomach and liver and cranial to the urinary bladder. On VD views of obese cats, the left perirenal fat may give the illusion of right displacement of the small intestine. Both species have some degree of diffuse mucosal surface irregularity as can be identified using positive contrast materials. These irregularities in normal patients are a result of the normal mucosal villi.[20,21] In both species small intestinal loops should appear homogeneous throughout. That said, active peristalsis will influence the perceived external diameter of small bowel loops and some variation of bowel loop diameter may be observed. The best approach to assess effects of peristalsis is to repeat survey radiographic views. This assures that patterns are not reproducible and that changes of loop content do occur.

To facilitate assessment of small intestinal size, the authors suggest a subjective comparison of the diameter of the small intestinal lumen to the size of a midlumbar vertebral endplate. Canine and feline small bowel diameter is usually less than the DV diameter

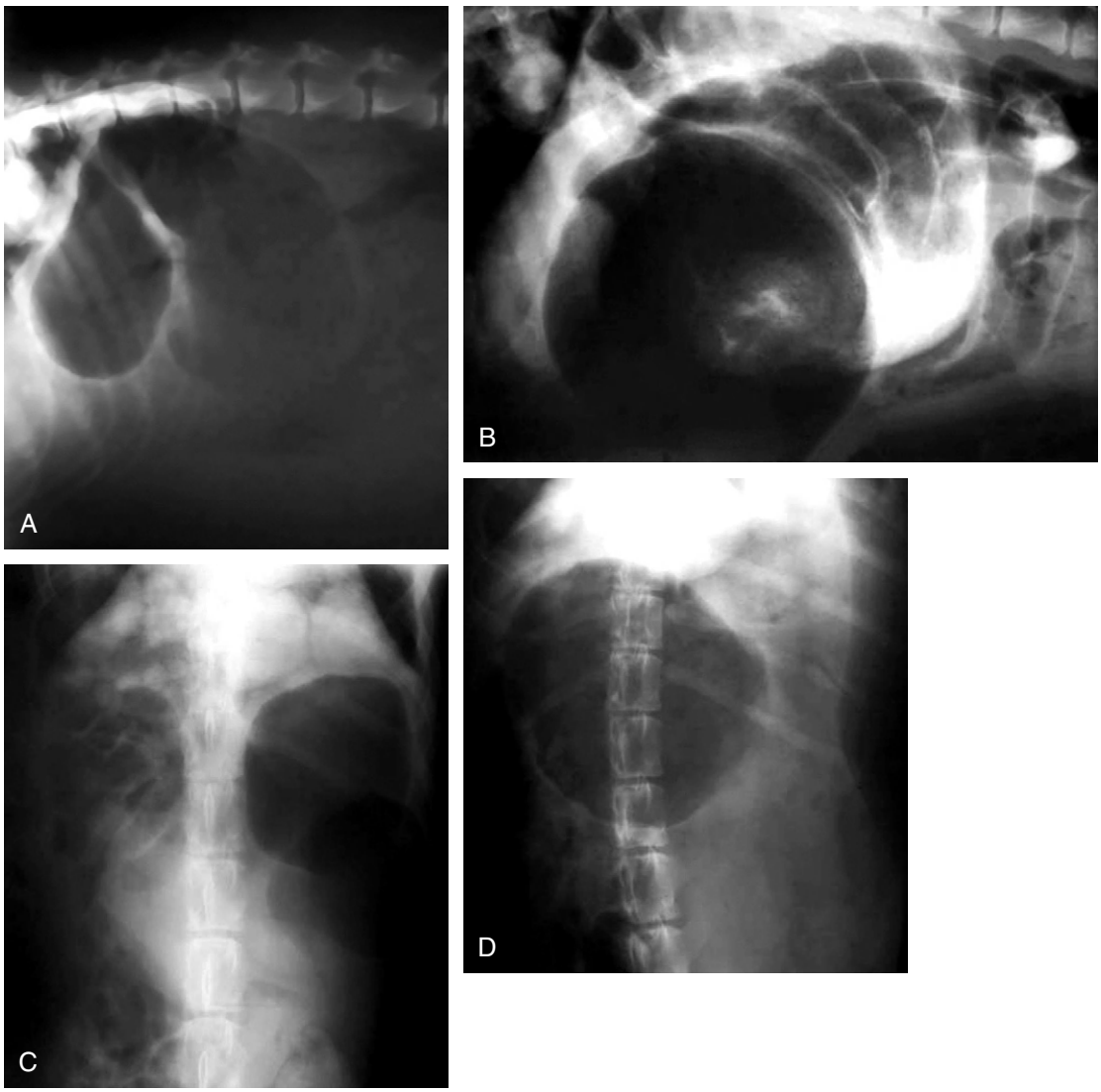


Figure 26-13 Gastric volvulus. Radiographs of a (**A**) Right lateral recumbent, (**B**) left lateral recumbent, (**C**) sternally recumbent, and (**D**) dorsally recumbent dog with gastric volvulus. Note the positional effects on the pyloric gas and fluid, which is why the right lateral and DV views are the preferred images for the diagnosis of this condition. The right lateral view should be an inverted "U" with the pylorus cranially while the DV view shows the so-called double-bubble with the pylorus cranially.

of a vertebral endplate. Further assessment and/or observation by repeat radiographic views should be considered if the small bowel diameter exceeds the transverse diameter of a vertebral endplate. If the small bowel diameter approaches or exceeds the length of a vertebral body, pathologic dilation is likely present. Small bowel dilation can be a result of obstruction, inflammation (e.g., luminal, mural, or serosal), trauma, irritation (e.g., by a migrating foreign body), or ischemia (incarceration or thromboembolism). Ingesta have a grainy appearance and, if present, should be evenly distributed throughout the length of the small bowel. Well-organized contents, particularly when seen in only one section of small bowel, should be noted. Such organized contents are a common indicator of a soft-tissue opacity foreign body. Reproducibly dilated small bowel segments can be associated with foreign bodies, annular lesions (i.e., tumor or stricture), intestinal incarceration, and infiltrative bowel disease–induced bowel wall rigidity. In addition, gas in the bowel lumen should be centrally distributed. Peripherally distributed gas may indicate a diverticulum or plication because of a linear foreign body. Finally, gas in the gut wall, which is termed *pneumatosis intestinalis*, can be associated with ulceration, ischemic necrosis, or bacterial translocation.

Functional Considerations

The small intestine has many functions, including propulsion and segmentation, secretion, digestion, and absorption. These functions are achieved through the interaction of peristalsis, small intestinal microbiota, and the nutritional or volume effects of the chyme. A problem with any one of these can result in signs of gastrointestinal disease, ranging from anorexia to vomiting and diarrhea, and can affect the size of the small bowel as well as its luminal contents. Fluids normally move through the bowel in 2 to 3 hours, whereas solid food is slower and quite dependent upon the rate of gastric emptying. As with gastric studies, the least-invasive and most cost-effective special radiographic procedure may be repeated or alternate radiographic views may be obtained within 24 hours. Retention of material in small bowel segments can be a result of inadequate

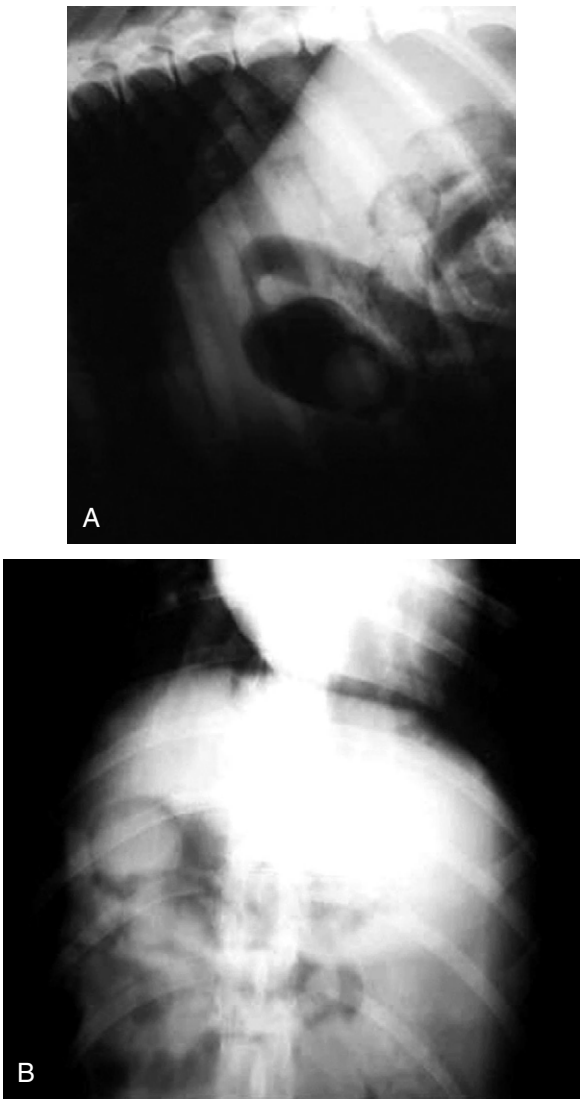


Figure 26-14 Gastric foreign body. Survey radiographs of a (**A**) Left lateral recumbent and (**B**) dorsally recumbent dog showing a soft tissue, dense, round object (foreign body) in the stomach that contains excess gas and fluid. Varying the position of the gas and fluid using gravity effects facilitated the identification of the foreign body in this case without the need for administration of a positive contrast material.

short-segment peristalsis; downstream intraluminal mechanical impedance to fluid, gas, or ingesta; or local disruptions in bowel homeostasis as a consequence of mucosal, mural, or perimural inflammation. Other intestinal pathologies, like ischemia, fibrosis, neoplasia, malabsorption, maldigestion, and bacterial overgrowth, can contribute to chyme retention. The decision to commit to small bowel endoscopy requires consideration of disease type and distribution as well as potential morbidity associated with anesthesia. Other imaging procedures, particularly upper GI contrast studies and abdominal ultrasound, may provide useful, cost-effective information with less patient stress.

Abnormal Radiographic Signs

In most patients, the normal or abnormal small bowel is readily visible on survey radiographs. The key to interpretation of survey radiographs is to be sure to differentiate transient physiologic

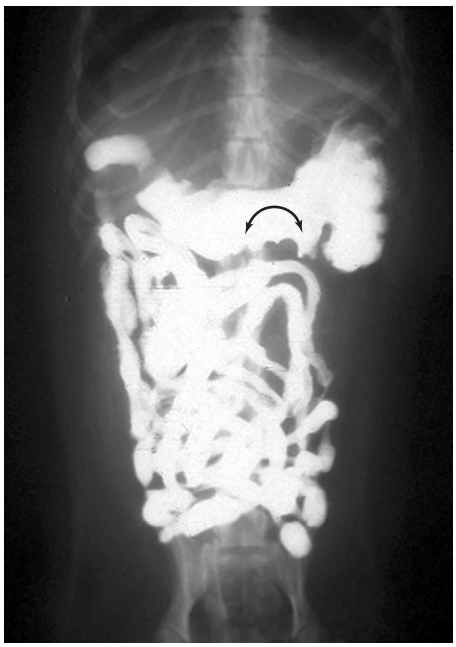


Figure 26-15 Gastric mass. Radiograph of a dorsally recumbent dog following barium administration. An irregularity of the greater curvature can be seen and is indicative of an infiltrative mass (*curved arrow*) impeding pyloric peristalsis.

changes such as postprandial luminal distention from pathologic changes in small bowel size, shape, and position. The localization of gas and fluid in the small bowel depends on the position of the patient during radiography. Several survey radiographic views may help to differentiate pathologic from physiologic findings. As discussed previously, the type and distribution of luminal contents may provide clues to the duration and severity of a disease process. In general, large-diameter intestinal loops are associated with greater duration, and high gas-to-fluid ratios are associated with greater severity. It should be kept in mind that bowel dilation has four specific causes: obstruction, inflammation, trauma or irritation, and ischemia. Large quantities of gas involving many or all small bowel segments may be a result of ischemia or severe serosal inflammation (Fig. 26-16), and not necessarily distal small bowel obstruction. There is also a continuum of bowel luminal compromise ranging from partial to complete obstruction. The recognition of these differences is paramount to the diagnostic process. Partial obstructions are usually segmental (i.e., two distinct populations of bowel can be recognized) and are characterized by greater fluid accumulation (than gas) whereas a complete or high-grade obstruction is characterized by equal amounts of gas and fluid or a clear predominance of gas. Partial obstructions can be due to mural lesions, such as tumors, strictures, or other intraluminal abnormalities like foreign bodies. The relative likelihood of these vary with age, behavior, and medical history (Figs. 26-17 and 26-18). As a general rule, conditions associated with large gas accumulations in the small intestine tend to be surgical diseases. Those conditions with proportionally more fluid than gas are more of a diagnostic and prognostic dilemma.[22-25] Assessment of small bowel mucosal changes (e.g., ulcerations), luminal abnormalities (e.g., foreign bodies), wall thickness, peristaltic capacity and continuity, as well as wall integrity is best achieved by positive contrast studies. However the choice of barium versus an iodinated contrast medium should be made based on the goal of the study, including mucosal coating, assessment of peristaltic

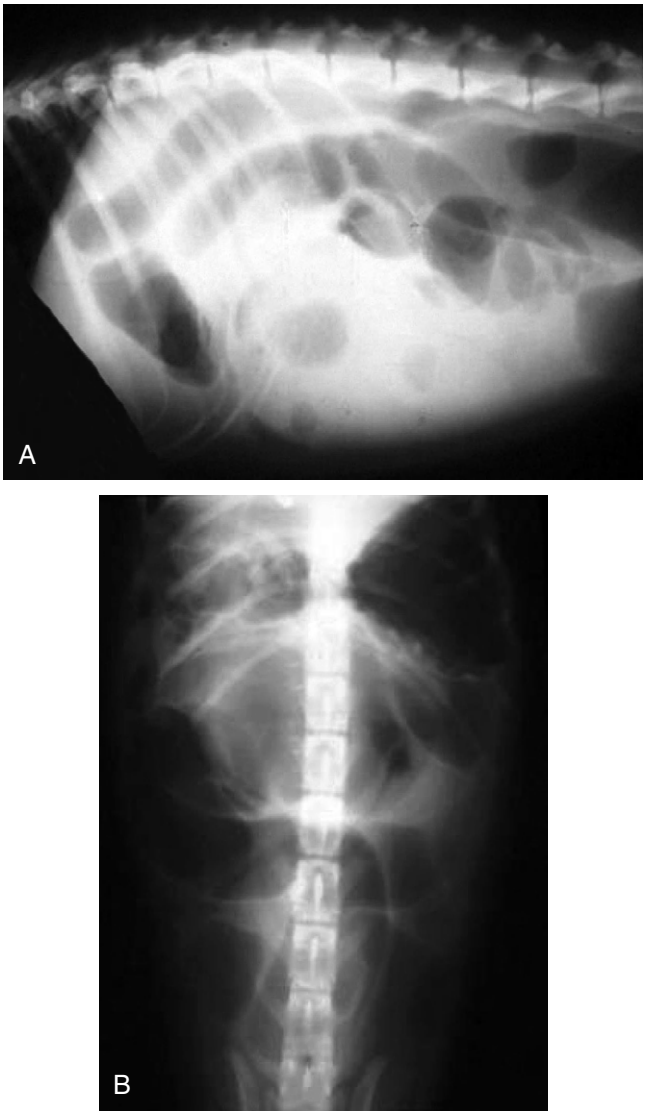


Figure 26-16 Septic peritonitis. Radiographs of a (**A**) left laterally recumbent and (**B**) dorsally recumbent dog. The radiographs show numerous tubular gas-containing structures. The peritoneal contrast is poor because of confirmed septic peritonitis. The small bowel loops are distended with fluid and gas to a degree consistent with intraluminal obstruction due to severe intestinal inflammation.

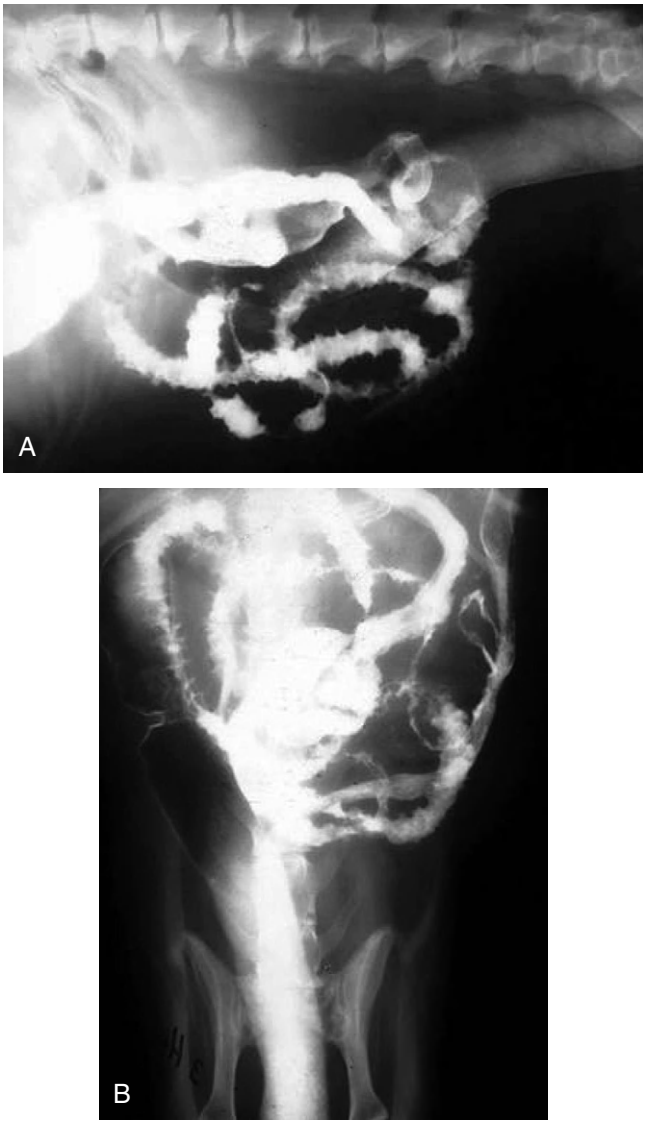


Figure 26-17 Lymphoma. Survey radiographs of a (**A**) Right laterally recumbent and (**B**) dorsally recumbent dog showing a corrugated ("thumbprinted") appearance of the small intestine caused by intramural infiltrative disease, which was later histologically confirmed as a Lymphoma.

capacity, or the identification of a leak. The role of abdominal ultrasonography in relation to contrast radiography has not been systematically studied and needs to be determined in large prospective studies. Concerns persist regarding the predictability of the sonographic diagnosis in the hands of inexperienced individuals and problems associated with user-dependent techniques such as ultrasound.[23-25]

Small Bowel Diseases

Differentiation of small intestinal abnormalities into intraluminal, intramural, transmural, or extramural lesions is useful not only for narrowing the list of differential diagnoses, but also for determining what diagnostic or therapeutic procedures may be useful in the further management of the patient.

Small intestinal mucosal ulceration is uncommon, except when associated with neoplasia. Smoothly marginated rectangular outpouchings of the duodenal lumen are occasionally seen in normal dogs, and have been termed *pseudoulcers* (Fig. 26-19). Although identification of small bowel surface erosion is possible by radiographic and ultrasonographic techniques, these lesions are best assessed by endoscopic techniques bearing in mind that only the descending duodenum and the ileum are accessible using this technique. Moreover, visual assessment of the mucosal brush-border to diagnose small intestinal disease or to differentiate between different disease processes has not been shown to be clinically useful.[21] As with gastric pathology, the unexplained presence of free peritoneal air is usually associated with alimentary tract perforation. If there is any question about the presence or absence of free air, horizontal-beam radiography is a very useful technique (Fig. 26-20). The assessment of free peritoneal air as discussed for gastric disease is equally applicable for diseases of the small bowel.

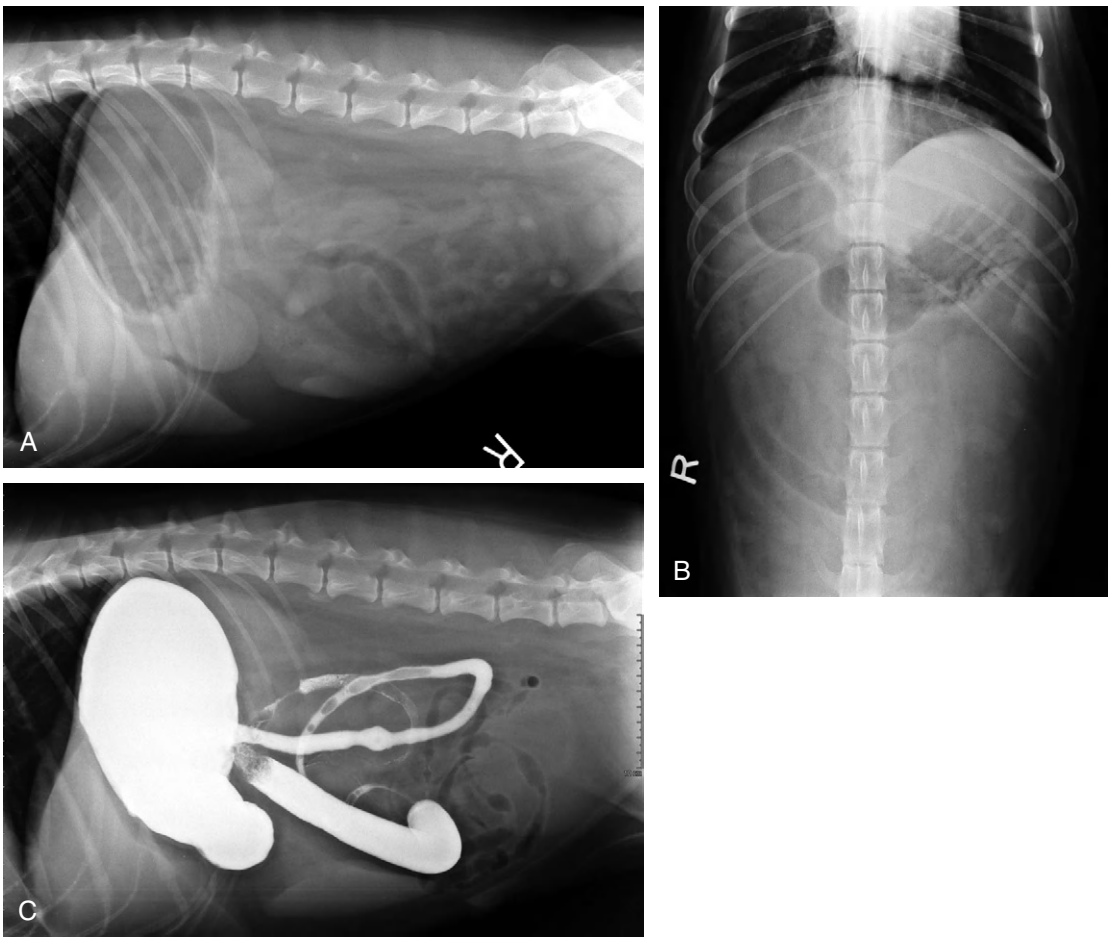


Figure 26-18 Intraluminal obstruction. Survey radiographs of a (**A**) Right laterally recumbent and (**B**) dorsally recumbent dog. Excess gastric gas and some fluid are visible. Also, there are two different diameters of the small bowel loops. (**C**) View in right lateral recumbency made 30 minutes after barium administration from the same patient. An intraluminal obstruction is visible in the ascending duodenum causing the disproportionate duodenal dilation.

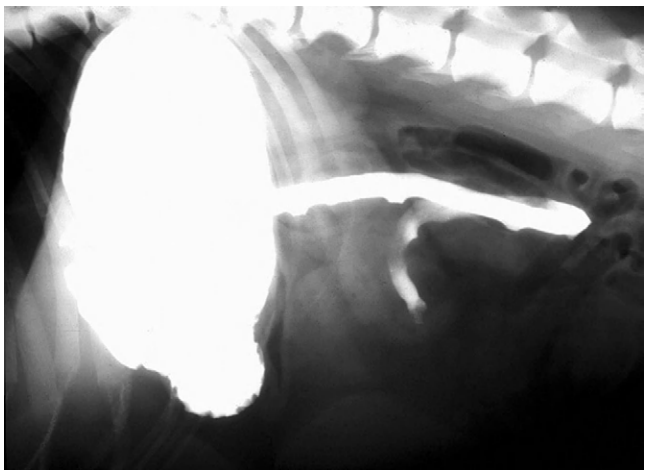


Figure 26-19 Pseudoulcers. Radiograph of a right laterally recumbent dog following barium administration. Three smooth, nearly rectangular, areas of widening of the descending duodenum are visible. These represent pseudoulcers and are a normal observation in the canine duodenum caused by foci of normal lymphoid tissue.

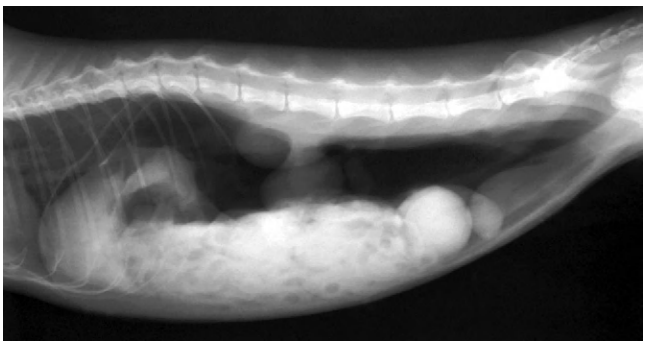


Figure 26-20 Intestinal rupture. A radiograph from a laterally recumbent dog with visible air outside the bowel loops in the peritoneal space, which is caused by an intestinal rupture. The kidneys are visible because they protrude into the peritoneal space.

Large Intestine

Anatomic Considerations

The large intestine is organized anatomically into the cecum, colon (ascending, transverse, and descending portions), rectum, and anal canal. The large intestine is most readily thought of as a distensible, thin-walled (2- to 4-mm) tube (see Chapters 1 and 58). The cecum is located to the right of the midline at approximately the level of L3 and is a gas-filled sigmoid or corkscrew-shaped structure in the dog, and a conically shaped end of the ascending colon in the cat. In most cases the ascending colon is to the right of midline. The transverse colon passes from right to left cranial to the root of the mesentery. The descending colon is located to the left of the midline and then courses toward the midline when entering the pelvic canal, where it may be displaced toward the right by a distended urinary bladder. The colon is held relatively loosely by the mesocolon and its position in the dorsal- or mid-abdomen can therefore be variable. In the normal canine and feline patient, the colon contains a variable amount of gas and formed fecal material and is generally visible and traceable on survey radiographs. The rectum is located midway between the ventral surface of the sacrum and the floor of the pelvis on the lateral view, and on the midline on the VD view. The colonic and rectal diameters can be quite variable, including regional areas of narrowing and dilation, depending upon the amount of feces. However the colon is approximately twice the diameter of the small intestine. The upper limit of normal colonic diameter should be considered to be less than 1.5 times the length of the body of L7. Reproducible focal narrowing or dilation should always be noted, particularly when fecal material accumulates proximal to the narrowing. This finding would be suspicious for a tumor or stricture and should be further evaluated, especially if persistent over time.

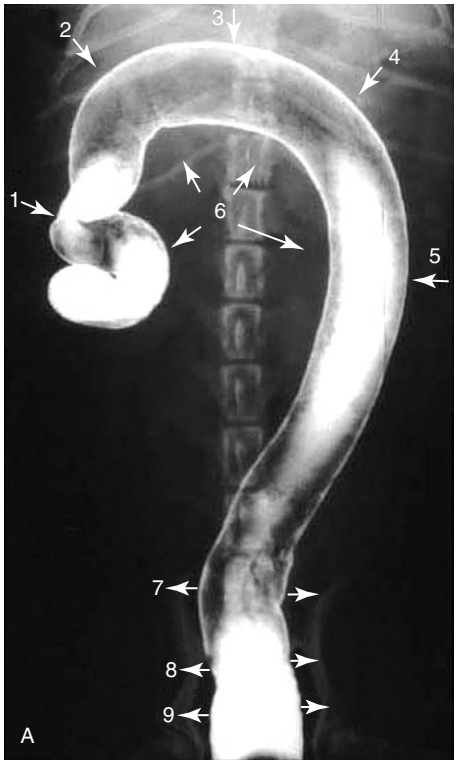
Functional Considerations

The colon has several functional properties. One of the most important functions is the absorption of water, electrolytes, ammonia, and short-chain fatty acids in the cecum and proximal ascending colon (see Chapters 1 and 58).[26] The colon also serves as a storage site for fecal material prior to propulsion.[26] In the normal patient, these peristaltic waves, which are infrequent, are generally not appreciated radiographically. Final evacuation from the large bowel is controlled by the defecation reflex (Chapters 1 and 59).

Abnormal Radiographic Signs

Because of the variable radiographic appearance of the normal colon, it can be difficult to detect early or mild abnormalities. Colonic position is often best determined by tracing the large bowel proximally from the rectum. Interpretation of malpositioning of the colon is based upon knowing the normal position of the colon as well as the regional effects of extracolonic structures (Fig. 26-21). Excessive gas and fluid could be consistent with colitis. Excessive gas alone might also be indicative of ischemia, which if seen with abnormal colonic positioning could suggest the presence of colonic torsion (Fig. 26-22). Diffuse distention with highly opaque fecal material is consistent with constipation (i.e., difficult, infrequent, or painful defecation) or obstipation (i.e., intractable constipation). Anorexic patients may have no feces in the colon as a consequence of a completely empty GI tract, but may also show evidence of fecal accumulation because the colon has not been stimulated to empty by a full stomach.

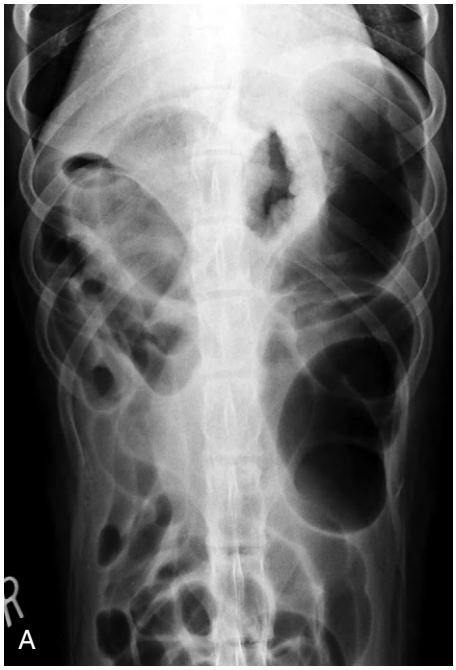
Dysfunction. Dysfunction of the colon is generally recognized as a dilated colon filled with feces. Constipation should always be treated as a primary diagnosis of abnormal motility unless a cause,



1. Duodenum, pancreas, liver
2. Liver (rt)
3. Pancreas, stomach, liver (caudate)
4. Liver (lt), spleen
5. Spleen
6. Mesentery, lymph nodes, small bowel
7. Bladder, iliac lymph nodes
8. Prostate, uterus, iliac, and sacral lymph nodes
9. Vagina

1. Lymph nodes
2. Lymph nodes
3. Uterus, bladder, prostate
4. Prostate, vagina, urethra

Figure 26-21 Barium enema. (**A**) Ventrodorsal view of a double-contrast and (**B**) lateral view of a positive-contrast barium enema depicting influences of regional structures on the position of the large intestine.



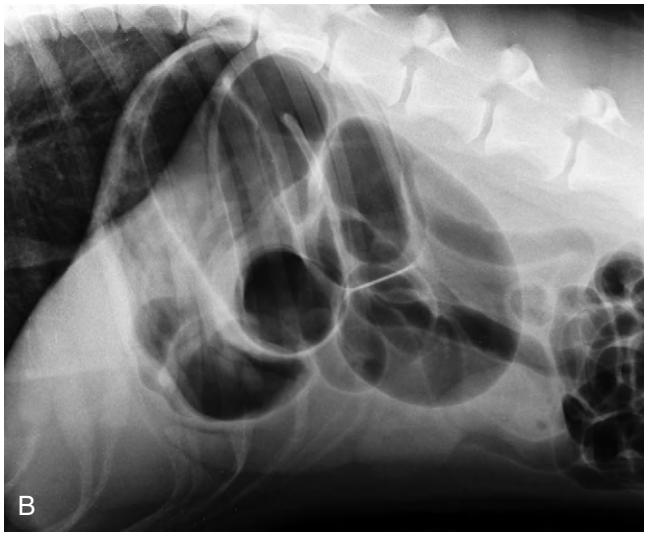


Figure 26-22 Colonic torsion. (**A**) Ventrodorsal and (**B**) lateral views of the cranial abdomen of a Great Dane with a colonic torsion. Note the marked gas distention and abnormal position of the colon in the cranial abdomen.

such as a pelvic fracture, mural infiltrate or tumor, or stricture can be identified (Figs. 26-23 and 26-24). There are no proven imaging procedures for studying colonic motility in animals. It should also be noted that anorexic or dehydrated patients may show evidence of fecal build up.

Large Bowel Diseases

The clinical presentation of the case aids in the inclusion and exclusion of differential diagnoses. Initial review should include assessment of the position of the large bowel, which is generally determined by the anchoring tissues of the mesorectum and mesocolon as well as regional organ enlargement or malpositioning. Displacements of the large bowel are generally caused by extramural lesions, which can also cause compression or distortion, or less often may lead to colonic torsion. The size of the colon can be governed by a

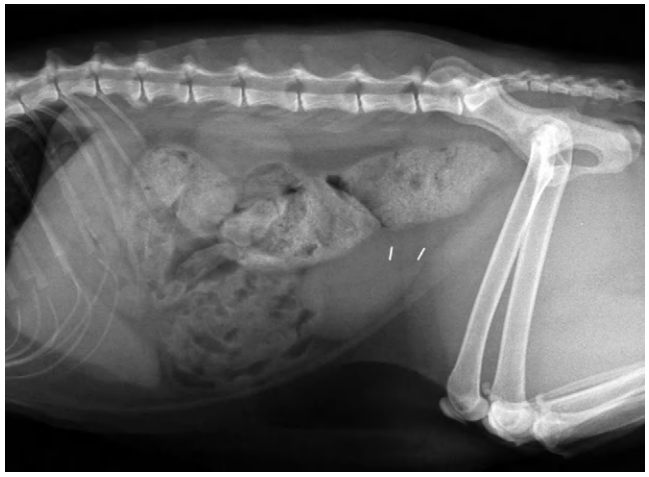
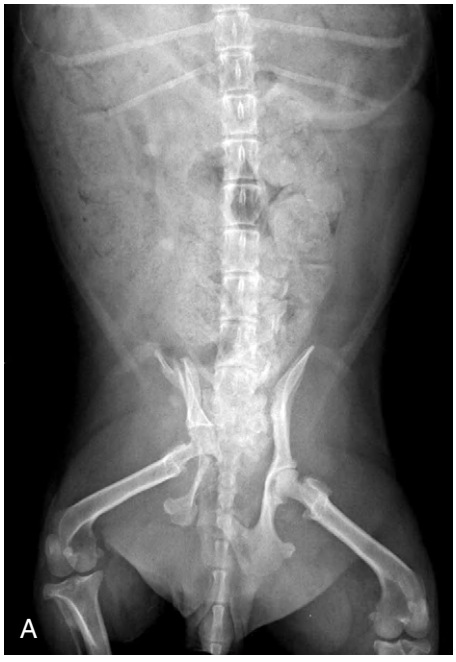


Figure 26-23 Megacolon. Lateral view of a cat with primary megacolon and obstipation.



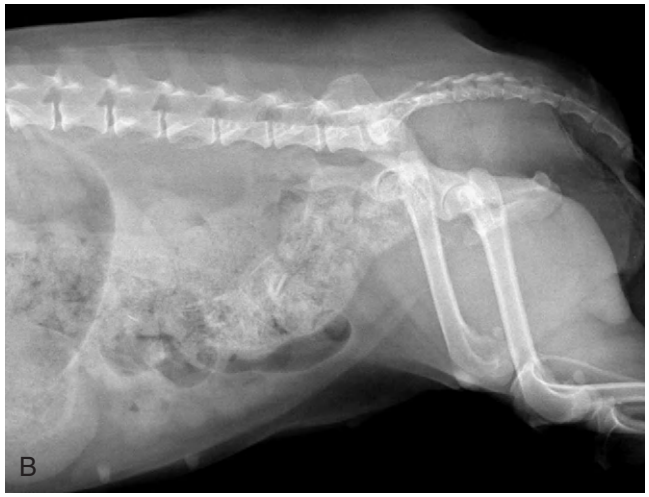


Figure 26-24 Constipation. (**A**) Ventrodorsal and (**B**) lateral views of a dog with constipation secondary to chronic pelvic fractures leading to pelvic canal impingement of the colon.

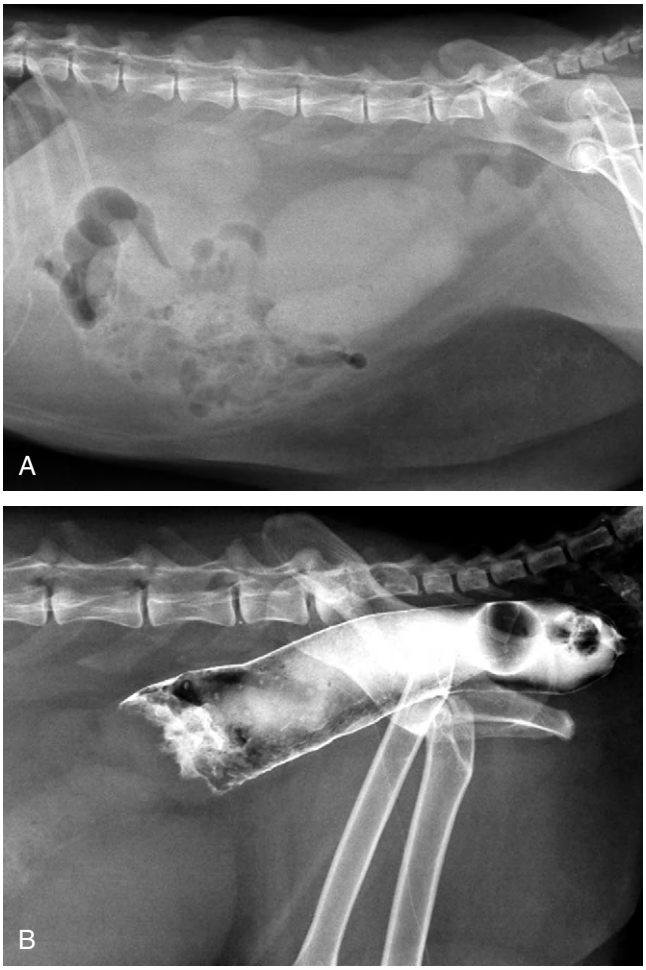


Figure 26-25 Colonic adenocarcinoma. A, Lateral view of the abdomen of a cat with a colonic adenocarcinoma. A mural mass is apparent as a soft-tissue mass in the distal descending colon caudal to the bladder neck. An abnormal gas pattern is visible within the lumen at this level and fluid is accumulating in the colon proximal to the mass. **B,** Lateral view of a double-contrast barium enema from the same patient. Note that a mural mass with an irregular mucosa is causing complete luminal obstruction.

multitude of factors including the evacuation frequency of the patient, anorexia, dehydration, peristaltic capability, inflammation, smooth muscle disorders, downstream resistance, wall pliability, and wall thickness. As for other gastrointestinal segments, differentiation into intraluminal, mural (Fig. 26-25), transmural, or extramural lesions is useful not only for narrowing the list of possible/likely diagnoses, but also for determining additional diagnostic and therapeutic approaches.

As with gastric and intestinal disease, the unexplained presence of free peritoneal air is usually associated with alimentary tract perforation. Colonic perforations generally occur secondary to foreign-body penetration, or are secondary to deep ulceration of a tumor or granuloma. It is important to determine that the air is free within the peritoneal cavity and not dissecting within the wall of the colon (i.e., pneumatosis coli). To determine if the air is free within the peritoneal cavity, the authors recommend horizontal-beam techniques (see Fig. 26-20). The consequences of and approaches to free peritoneal air are similar to those discussed for the upper gastrointestinal tract.

Liver and Biliary System

Survey radiography is an inexpensive and noninvasive diagnostic test for the workup of hepatobiliary disorders in small animals. Patients often have a nonspecific history and clinical signs in conjunction with specific laboratory parameters suggesting hepatic or biliary pathology (see Chapter 25). Survey radiographs are indicated in these patients to assess liver size, shape, and margination, as well as opacity of the liver and biliary tract. Survey radiographs are also useful to assess patients for changes associated with hepatobiliary disorders, such as ascites, which may consist of a transudate because of portal hypertension, hemorrhage caused by coagulopathy or bleeding masses, peritonitis caused by gallbladder rupture, or neoplasia from carcinomatosis. Another radiographic finding secondary to hepatobiliary disease may be nodules in the lungs on the edge of the radiograph, which may indicate metastasis of hepatic neoplasia. Unfortunately, survey radiography is limited in its ability to assess the internal architecture of the liver and the appearance of the biliary tract.

Anatomic Considerations

In general, the normal canine and feline liver are easily evaluated for size, shape, margination, position, and opacity on the survey right lateral and VD radiographs. The liver is bordered cranially by the diaphragm, on the left and right hand side by the body wall, and caudally by the stomach on the left and the duodenum and right kidney on the right. The liver of the dog and cat is divided into several lobes (i.e., left lateral and medial lobe, quadrate lobe, right medial and lateral lobe, and caudate lobe with its caudate and papillary process), the divisions of which are not typically seen on survey radiographs. If the patient is overweight, fat may dissect between some of the lobes. The left lobe of the liver is the largest and makes up the majority of the ventral shadow on the lateral view. In the dog, the right kidney silhouette joins with that of the caudate lobe as it is nestled in the renal fossa. Liver size is assessed by identification of the gastric axis (i.e., a line drawn from the mid portion of the fundus through the pylorus), which parallels the last few ribs on the lateral view and is perpendicular to the spine on the VD view in normal patients. The liver generally shouldn't extend beyond the costal arch and the margins should be sharp and well-defined. In the cat the liver often appears smaller on lateral radiographic views because of right-sided positioning and the large falciform fat pad that leads to dorsal elevation of the liver (Figs. 26-26 and 26-27). The normal liver is of uniform and soft-tissue opacity.

The components of the biliary tract include the gallbladder, the cystic duct, the intrahepatic ducts, the extrahepatic ducts, and the common bile duct. The normal biliary tract is not seen on survey radiographs. One exception is a distended gallbladder in anorexic cats, which may appear as a round, soft-tissue shadow at the ventral hepatic margin in the lateral view (Fig. 26-28). The gallbladder is situated between the quadrate and right liver lobe just to the right of midline.

Functional Considerations

Although liver function cannot be determined radiographically, certain radiographic signs may infer abnormal function. Peritoneal effusion in a patient with liver disease may be a result of ascites because of hypoalbuminemia, portal hypertension, portal thrombosis, or portosystemic shunting or a result of hemorrhage as a consequence of coagulopathy or disseminated intravascular coagulation (DIC).

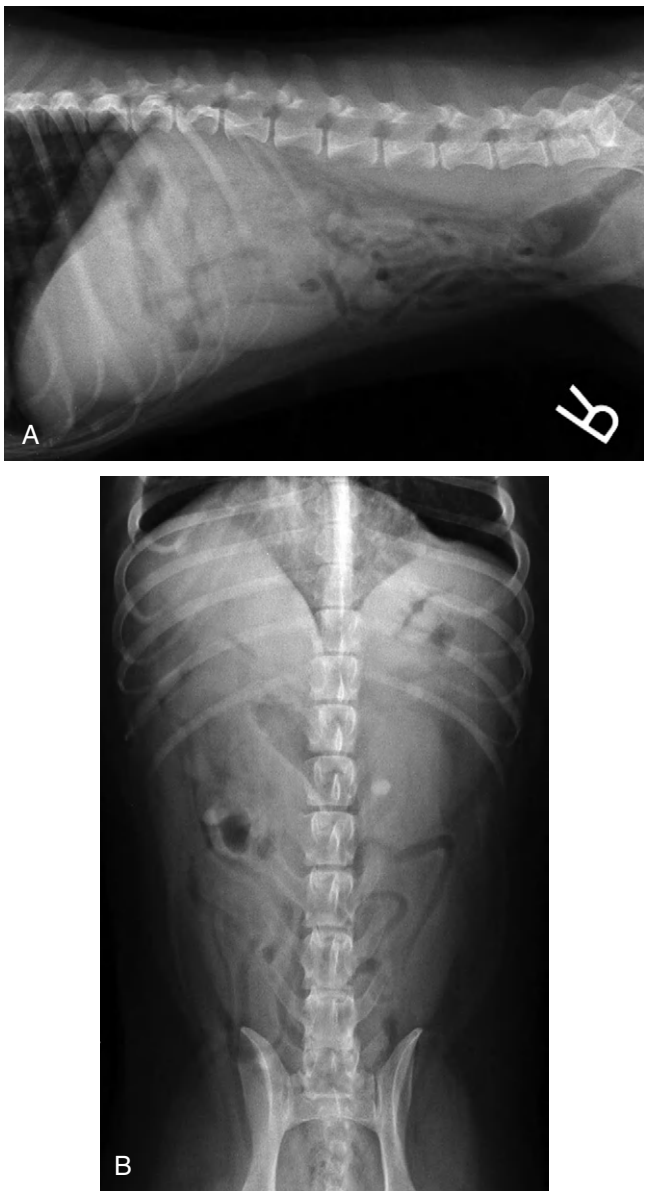


Figure 26-26 Normal liver in a dog. (**A**) Lateral and (**B**) VD views of a normal liver in a dog. Note that the gastric axis essentially parallels the last few ribs on the lateral view and is perpendicular to the spine on the ventrodorsal view. The ventral hepatic margin appears sharp.

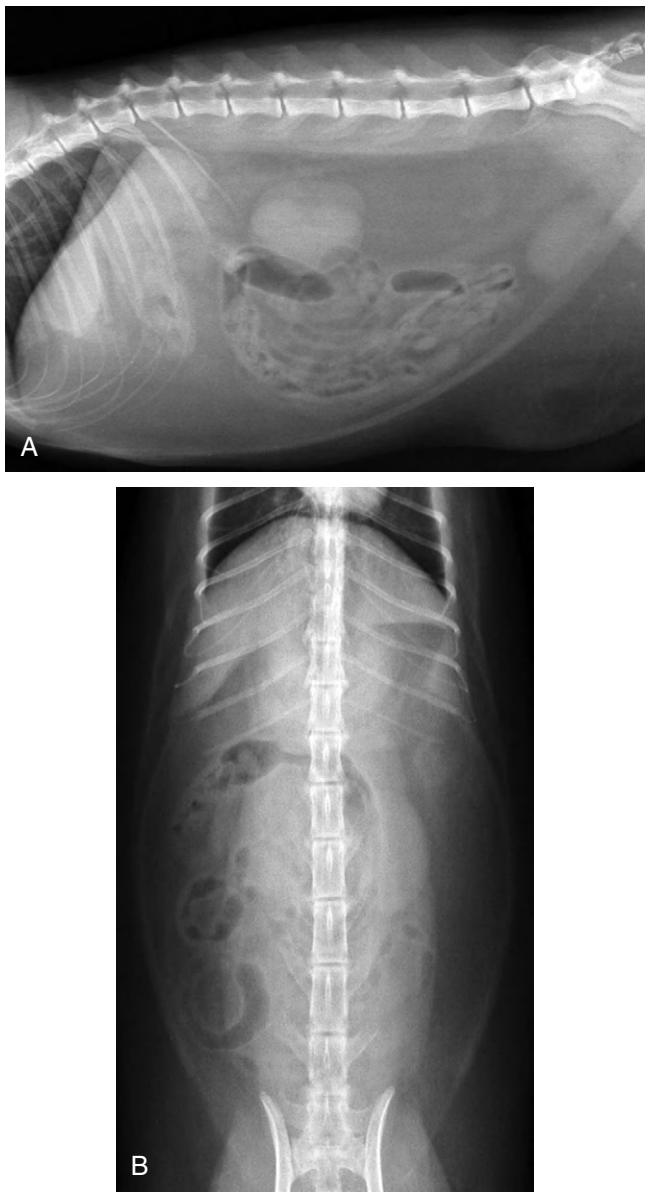


Figure 26-27 Normal liver in a cat. (**A**) Lateral and (**B**) VD views of a normal feline liver. Note that the large falciform fat pad causes the liver to artifactually appear small.

Abnormal Radiographic Signs

A change in liver size is one of the most common abnormal radiographic signs. Microhepatia, or a small liver, is recognized by the gastric axis being shifted cranially and/or a decrease in distance between the stomach and diaphragm (Fig. 26-29). It should be noted that this appearance could also be caused by a congenital or traumatic diaphragmatic hernia and thus the thorax should be assessed concurrently. Additionally, hepatic size should be assessed cautiously in obese cats (see Fig. 26-27) and deep-chested dogs. Hepatomegaly, or an enlarged liver, should be characterized as being either due to a generalized or focal enlargement. In patients with generalized hepatomegaly, the entire shadow of the liver is enlarged causing the stomach to be uniformly displaced caudally on both the lateral and the VD views (Fig. 26-30). Focal hepatomegaly is recognized when only a portion of the liver is enlarged. Regional organ displacement will often aid in the localization of a focal hepatic mass. A left-sided hepatic mass is seen ventrally on the lateral view displacing the pylorus caudally or dorsally, and is seen to the left of the stomach on the VD view, displacing the fundus towards the midline. A central hepatic mass in the midportion of the liver may displace and distort the stomach caudally on the lateral view, may displace the pylorus caudally on the lateral view, or may displace the pylorus towards the midline on the VD view (Fig. 26-31). A right-sided hepatic mass can be seen dorsally and possibly caudal to the fundus of the stomach on the lateral view, and can be seen to the right of the stomach on the VD view, displacing the pylorus toward the midline. A right-sided hepatic mass may also displace the right kidney caudally and toward the midline. Changes in hepatic shape

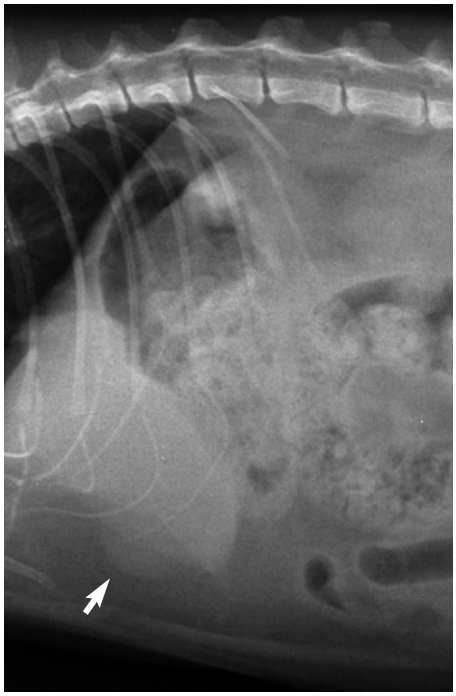


Figure 26-28 **Distended gallbladder.** Lateral view of a cat with a distended gall bladder. Note the round, soft-tissue shadow (*white arrow*) ventral to the ventral liver margin.

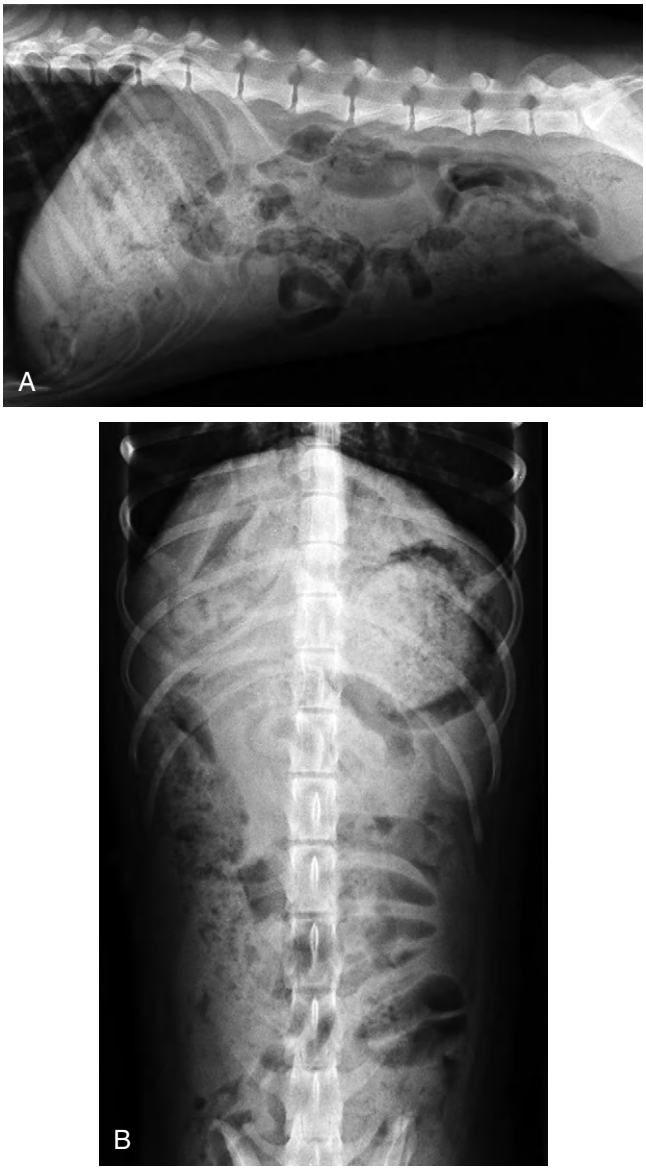


Figure 26-29 **Microhepatia.** (**A**) Lateral and (**B**) VD views of a dog with microhepatia. Note the displacement of the gastric axis cranially and the small liver shadow. The stomach is very close to the diaphragm on both views.

may alter the normal triangular shape of the liver on the lateral view and the dome shape of the liver on the VD view. Most masses will present as bulges or as alterations in the margin of the normal hepatic shadow. However a ventral round soft-tissue structure may indicate a distended gallbladder in an anorexic patient, especially in cats (see Fig. 26-28).

The edges of the normal liver are sharp and well defined. Careful evaluation of the hepatic margins aids in detection of hepatic disease on survey radiographs. In patients with generalized hepatomegaly, the margins are often rounded. Focal masses (i.e., those due to neoplasia, granuloma, large regenerative nodule, abscess, cyst, or hematoma) generally have round margins, but may also be nodular or irregular. Nodular margins may indicate nodular regeneration seen with cirrhosis, multifocal diseases, or neoplastic disorders (Fig. 26-32).

The normal liver and biliary tract are of a uniform soft-tissue opacity. Gas radiolucencies within the liver shadow may be focal, such as those due to hepatic abscessation or emphysematous cholecystitis. They may also be diffusely distributed throughout the branching biliary tract. Figure 26-33 illustrates a radiograph of a dog with a hepatic abscess. Mineralized opacities may be seen within the hepatic parenchyma (i.e., dystrophic mineralization associated with granuloma, hematoma, or hepatic tumor) or may be seen within the biliary tract (i.e., due to choleliths or choledocholiths; Fig. 26-34).

Any abnormal radiographic findings should be further investigated. Transabdominal ultrasound permits excellent evaluation of the internal architecture and parenchymal changes of the liver.

Dysfunction and Special Procedures. No special radiographic procedures for evaluation of the liver itself are currently performed. An upper GI study may allow for better delineation of hepatic size and shape by evaluating the position of the GI tract, especially if detail is diminished because of ascites. Portography, most commonly an operative mesenteric study, but in some cases splenoportography, can be useful for the diagnosis and characterization of congenital or acquired portosystemic shunts[27] and portal vein thrombosis. Caval venography can be used to diagnose Budd-Chiari syndrome. However it should be noted that vascular ultrasound can be both sensitive and specific for these conditions. Special radiographic procedures for assessment of the biliary tract include oral and intravenous cholangiocystography,[27,28] but these studies are not routinely performed in veterinary medicine. Percutaneous transhepatic ultrasound-guided cholangiocystography with followup radiographs has been described for assessment of patency of the biliary tract.[27,28] Another uncommonly performed special procedure for assessment of the hepatobiliary system is retrograde cholangiography utilizing endoscopy and fluoroscopy.[29,30] Patients must be under general

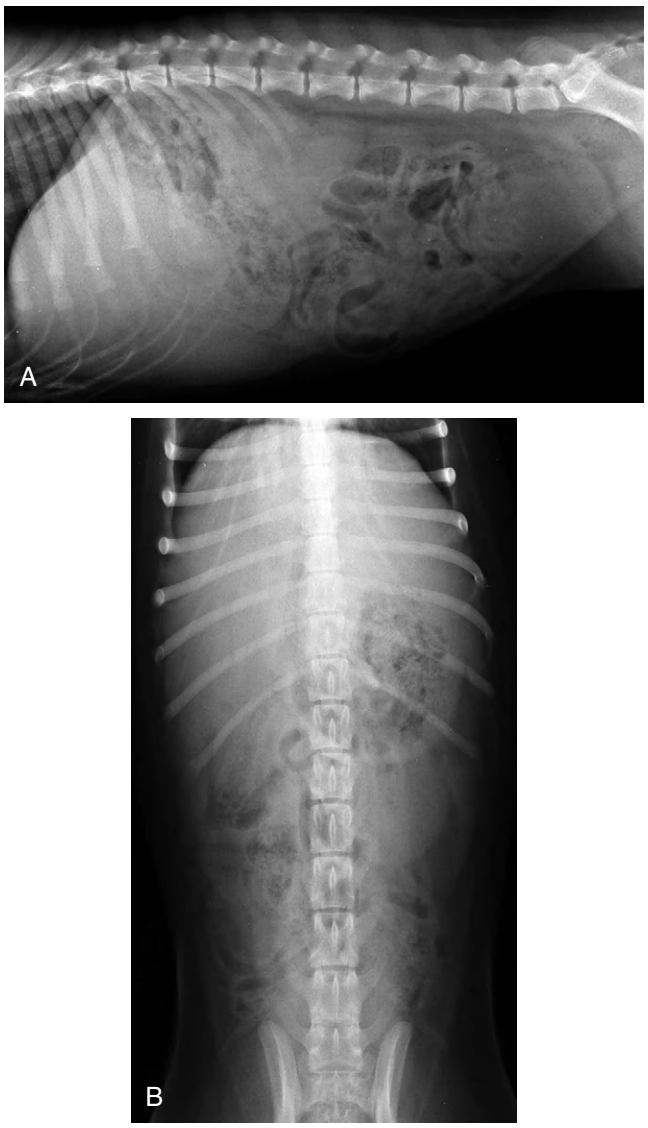


Figure 26-30 **Hepatomegaly.** (**A**) Lateral and (**B**) VD views of a dog with generalized hepatomegaly. Note the caudal displacement of the gastric axis on both views. The liver extends beyond the costal arch and the margin is rounded.

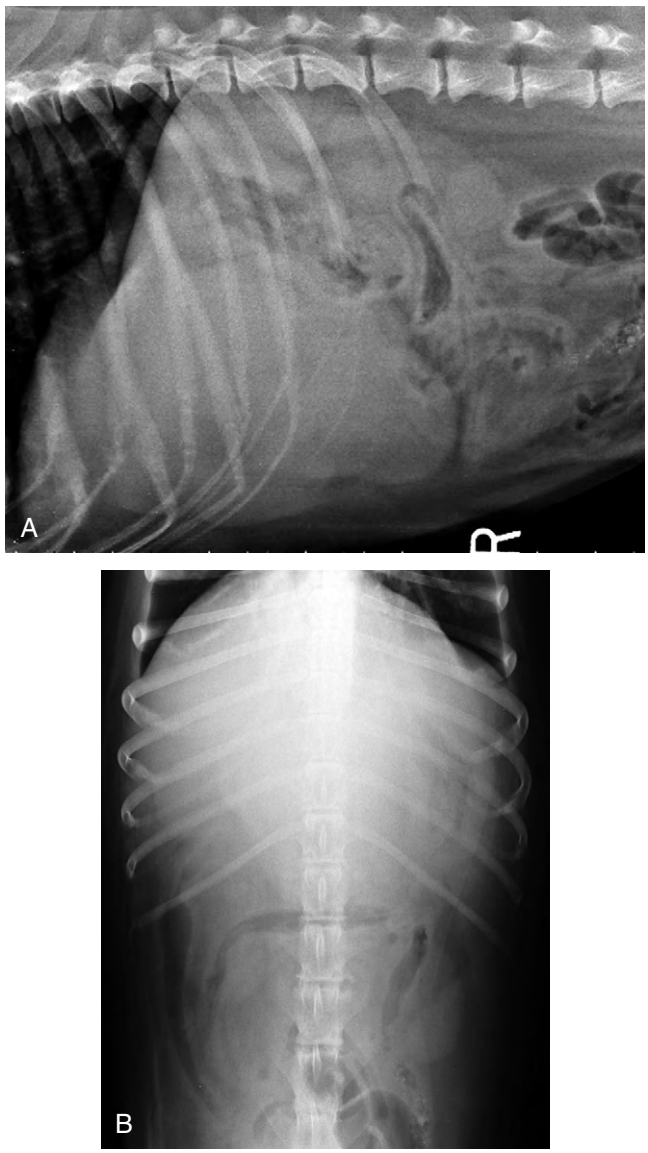


Figure 26-31 **Hepatic mass.** (**A**) Lateral and (**B**) VD views of a dog with a large central hepatic mass. Note the large, round mass displacing the stomach caudodorsally and to the left.

anesthesia for this procedure. Advanced imaging procedures (i.e., ultrasound [US], CT, magnetic resonance [MR], and nuclear scintigraphy) are generally necessary to further characterize hepatic disorders.

Hepatobiliary Disorders

Careful evaluation of survey radiographs in combination with signalment, history, and laboratory data should allow for the development of an appropriate list of differential diagnoses. In most cases, the patient will need to be further characterized with transabdominal ultrasound and fine-needle aspiration or biopsy for definitive diagnosis.

Initial evaluation of the liver should include determination of hepatic size and shape. Microhepatia can be caused by vascular abnormalities, such as a portosystemic shunt, portal atresia, or microvascular dysplasia or by cirrhosis, secondary to chronic inflammatory or fibrotic disorders. Generalized hepatomegaly may be associated with smooth margins and may be a result of hepatic congestion; steroid hepatopathy; fatty infiltration of the liver associated with diabetes mellitus; hepatic lipidosis; toxic, inflammatory, or infectious hepatitis; round cell neoplasia; or amyloidosis or other storage disorders. Hepatomegaly and nodular margins can be associated with nodular regeneration, metastatic disease, or multifocal primary neoplasia. Focal hepatomegaly is generally caused by a primary hepatic tumor, such as a hepatocellular carcinoma, bile duct carcinoma, hemangiosarcoma, hepatoma, or biliary cystadenoma, but may also be caused by metastatic neoplasia, a large regenerative nodule, hematoma, cyst, granuloma, or abscess. The radiographic sensitivity for hepatic metastasis is low. However one should carefully evaluate hepatic margins for nodularity. Nodular margins can also be seen with hepatic cirrhosis with nodular regeneration. In conjunction with evaluation of the liver shadow, other radiographic

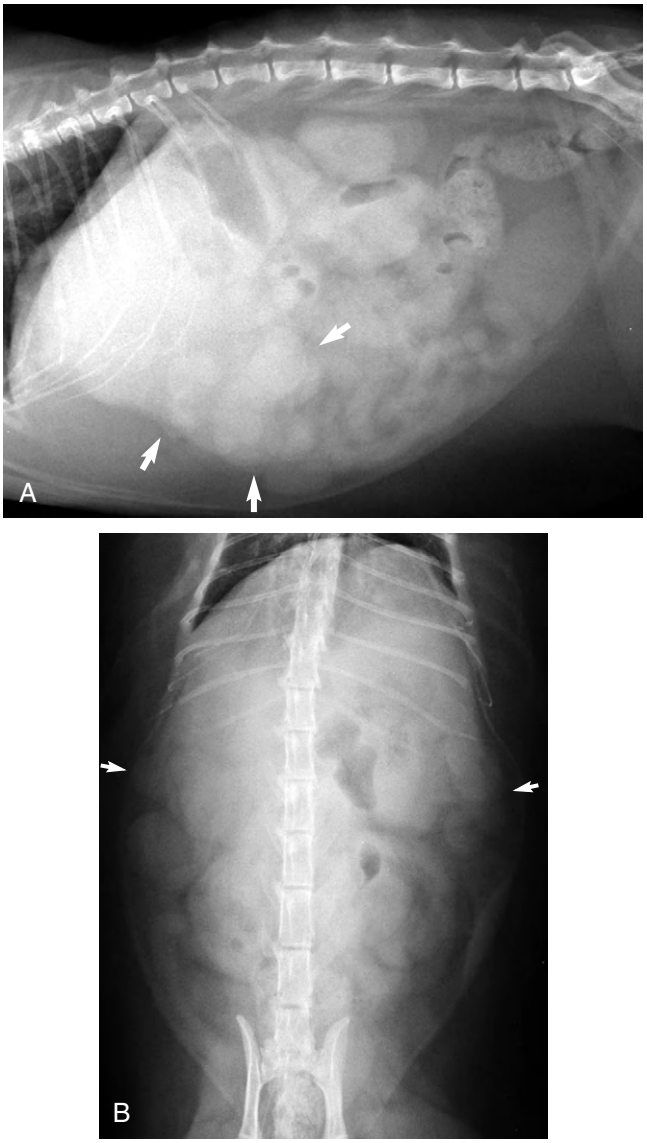


Figure 26-32 Hepatomegaly. (**A**) Lateral and (**B**) VD views of a cat with hepatomegaly. Note the very nodular margins of the liver (*white arrows*) as a consequence of a histologically confirmed metastatic pancreatic carcinoma.

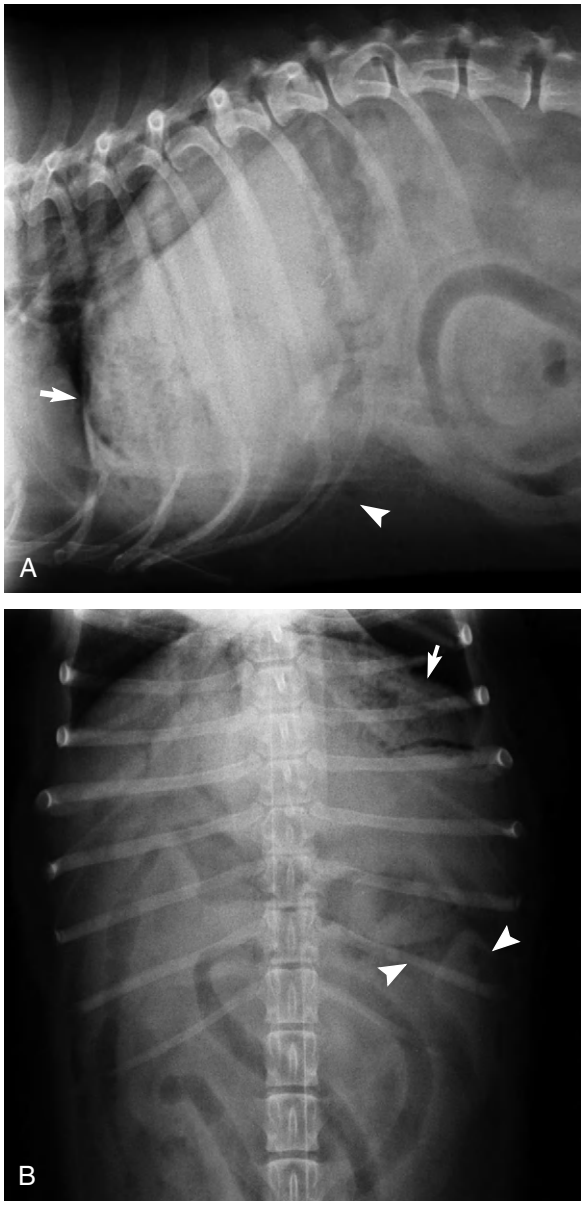


Figure 26-33 Hepatic abscess. (**A**) Lateral and (**B**) VD views of a dog with a hepatic abscess. Note the accumulation of gas in the left liver (*white arrows*). Note also the free peritoneal gas secondary to rupture of the abscess (*white arrowheads*).

signs, such as peritoneal effusion as a consequence of ascites, hemorrhage, or neoplasia, may also aid in refining the list of differential diagnoses.

Survey radiographs are not very sensitive for disorders of the biliary tract. Changes in opacity, such as those due to mineralization or gas may be seen. Regional loss of detail in the area of the porta hepatis or perigastric area may be the only finding in patients with cholecystitis, mucocele, gallbladder obstruction, or gallbladder rupture. Patients should be closely evaluated for an enlarged gallbladder, signs of peritonitis (i.e., effusion or sentinel intestinal loops), or causes of bile duct obstruction, such as stones, pancreatitis, or pancreatic masses.

Pancreas

Survey radiography is an inexpensive and noninvasive first-level diagnostic test for the workup of pancreatic disorders. Generally, patients with exocrine pancreatic disorders have a nonspecific history and clinical presentation related to the gastrointestinal tract. Survey radiographs are indicated in these patients and are useful in combination with biochemical testing to rule out nonpancreatic disorders such as disorders of the intestinal tract, the liver, the kidneys, the peritoneum, and other abdominal organs. Unless a patient is too compromised for positioning for survey radiography, there is no reason not to perform survey radiography consisting of a right lateral and VD view with a technique that provides good contrast of the abdominal organs. If a patient cannot tolerate being placed in a VD position, opposite lateral views are better than just one lateral view.

Anatomic Considerations

The normal pancreas is not generally visible on survey radiographs. However the knowledge of where the pancreas is located in normal

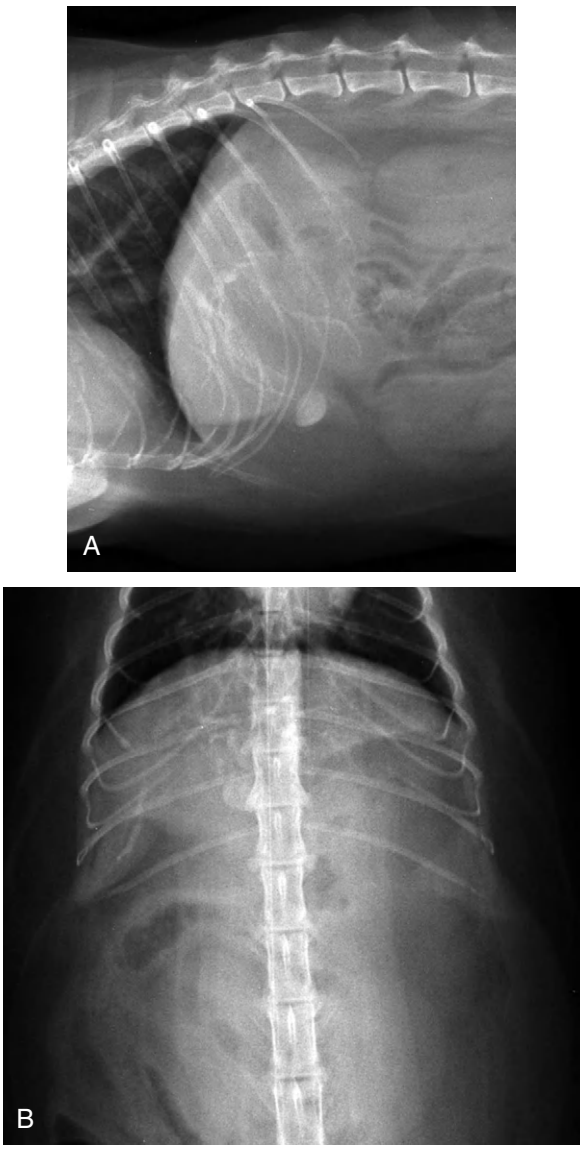


Figure 26-34 Cholelith. (**A**) Lateral and (**B**) VD views of a cat with mineralization of the biliary tract and a cholelith.

patients is crucial when evaluating for radiographic evidence of exocrine pancreatic diseases. The pancreas is divided into a body and right and left lobes. The right lobe lies in the mesoduodenum extending from the caudal thoracic to the mid-lumbar region along the right flank, and is usually medial to the descending duodenum. The body lies adjacent to the pyloric region of the stomach. The left lobe lies caudal to the greater curvature of the stomach ending in close relationship to the cranial pole of the left kidney and middle portion of the spleen. These boundaries describe the general location of the pancreas. The accessory pancreatic duct and the pancreatic duct serve as conduits for pancreatic secretions into the proximal duodenum. The pancreas is situated in close proximity to the following organs: the ventral aspect of the right kidney, the caudate lobe of liver, sublumbar fat (ureter), duodenum, cecum, ascending colon, gastric pylorus, dorsal wall of the body and fundus of stomach, cranial aspect of the left kidney, the middle portion of the spleen, and the transverse colon. Although the usefulness of survey radiography of the normal pancreas is limited, the left lobe of the pancreas can sometimes be seen radiographically in obese cats (Fig. 26-35).

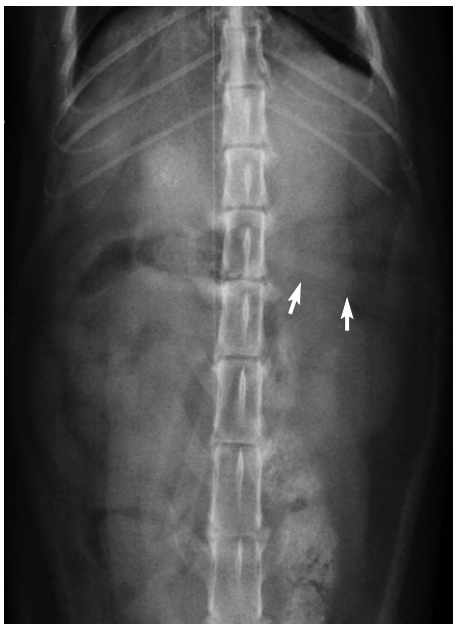


Figure 26-35 Pancreas. Ventrodorsal view of an overweight cat showing the left lobe of the pancreas (*white arrows*).

Functional Considerations

The major functions of the exocrine pancreas are secretory and include the secretion of digestive enzymes, bicarbonate, intrinsic factor, and antibacterial proteins (see Chapters 1 and 60). Diseases of the exocrine pancreas, such as pancreatitis, pancreatic abscess, pancreatic pseudocyst, and pancreatic carcinoma commonly cause survey radiographic changes. Exocrine pancreatic insufficiency (EPI) cannot be diagnosed radiographically, but in some patients may be associated with abnormalities of the GI tract on survey radiographs, such as excess bowel fluid and dilation, which may suggest malabsorption or bacterial dysbiosis. Endocrine disorders such as diabetes mellitus, insulinoma, and gastrinoma either do not cause primary macroscopic changes of the pancreas or cause changes that are too small to identify on survey radiography.

Abnormal Radiographic Signs

The normal soft-tissue shadow of the pancreas is not identifiable on survey radiographs, with the exception of the left pancreatic lobe in obese cats. In general, as the pancreas enlarges, there will be a poorly defined or well-defined soft-tissue mass or mass effect, dependent on the disease process (Fig. 26-36). Diseases with associated inflammation (i.e., pancreatitis, pancreatic abscess, or pancreatic pseudocyst), will be poorly defined because of regional effusion or peritonitis. The earliest detectable abnormal opacity with pancreatitis is often seen caudal to the stomach on the lateral view and in the right upper quadrant in the dog, and in the left upper quadrant in the cat on the VD view. The abnormal opacity is often granular in nature (ground-glass appearance). Rarely there will be dystrophic mineralization associated with pancreatic inflammation or gas associated with pancreatic abscessation. Enlargement of the pancreas on a survey radiograph is generally considered abnormal. A well-defined soft-tissue mass is more suggestive of a pancreatic pseudocyst or pancreatic carcinoma. Changes in the position or radiodensity of adjacent organs are also more suggestive of exocrine pancreatic disease. Pancreatic enlargement will cause organ displacements depending on the focal or diffuse nature of the enlargement. Focal

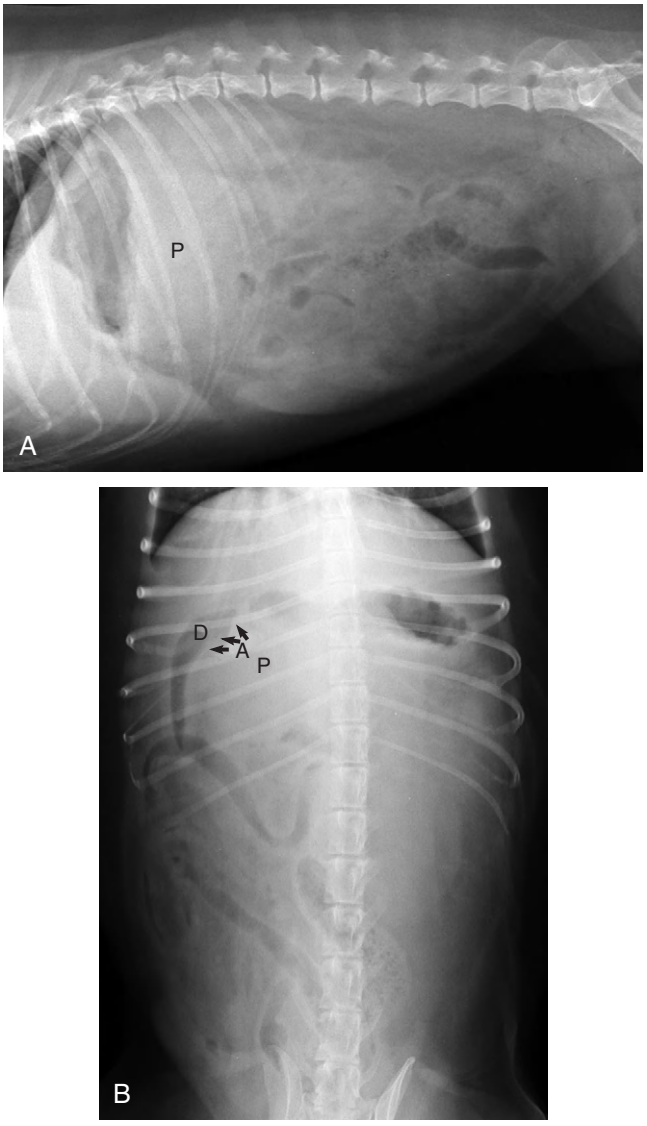


Figure 26-36 Pancreatitis. (**A**) Lateral and (**B**) VD views of a dog with severe pancreatitis. Note the poorly defined soft-tissue mass effect in the right upper quadrant displacing the pylorus toward the midline and increasing the cranial duodenal angle (*A*). The enlarged pancreas (*P*) is easily seen caudal to the stomach on the lateral view. Other findings include a dilated descending duodenum (*D*) and effusion. Other differentials for the pancreatic mass should include pancreatic abscess, pancreatic neoplasia, and pancreatic pseudocyst.

enlargements of the right lobe of the pancreas often displace the duodenum laterally and the cecum and ascending colon toward the midline. Focal enlargements of the body of the pancreas may enlarge the cranial duodenal angle by displacing the duodenum laterally and the pylorus or pyloric antrum toward the midline, and may displace the transverse colon caudally. Focal enlargements of the left limb of the pancreas may displace the transverse colon caudally, indent the body and fundus of the stomach, and displace the middle portion of the spleen laterally and caudally. Other indicators of pancreatic disease include changes caused by regional inflammation, such as persistent dilation of the descending duodenum and stomach with gas and/or fluid buildup. Survey radiographic may show findings that are suggestive of bowel wall thickening as a result of edema and/or inflammation due to pancreatitis. It is important to note that all of these radiographic findings are rather subjective and a definitive diagnosis of pancreatitis based on radiography alone is not possible.

Dysfunction and Special Procedures. In some patients, exocrine pancreatic disorders can be indirectly suspected through the use of an upper contrast GI study. As barium outlines the GI tract, the displacements described previously will be more easily recognized. Other findings may include delayed gastric emptying, diminished gastric peristalsis, persistent duodenal dilation secondary to regional inflammation, and thickened and rigid stomach and duodenal walls with or without thumbprinting. An uncommonly performed pancreatic special procedure in dogs and cats is endoscopic retrograde pancreatography (ERP),[29,30] utilizing endoscopy and fluoroscopy. Patients must be under general anesthesia for this procedure. Advanced imaging (e.g., US, CT, MR, nuclear scintigraphy) is generally necessary to further characterize exocrine pancreatic disorders.

Exocrine Pancreatic Diseases

Careful description of the radiographic signs in combination with signalment, history, and laboratory data should allow for the generation of an appropriate list of differential diagnoses. Additionally, the survey radiographic study is helpful for ruling out other gastrointestinal disorders, such as intestinal obstruction and intestinal perforation that may be associated with similar presenting clinical signs. In most cases, the disease will need further characterization with specific serum markers and ultrasound evaluation possibly with concurrent fine-needle aspiration for a definitive diagnosis.

Often the only radiographic finding associated with exocrine pancreatic disorders is a hazy or "ground-glass" loss of detail in the cranial abdomen in patients with acute or chronic pancreatitis. However this finding has been reported with other abdominal disorders, such as hepatic disease, biliary tract disease, peritonitis, intestinal perforation, and nonpancreatic effusions. A poorly or well-defined mass effect in the right or left cranial quadrant, which may be seen in patients with severe acute pancreatitis, pancreatic abscess, pancreatic pseudocyst, or pancreatic carcinoma, warrants further imaging with ultrasound. Any regional organ displacements indicating a potential pancreatic mass or mass effect should be noted. Supporting radiographic signs of possible exocrine pancreatic disorders include effusion, sentinel intestinal loops (a result of regional inflammation and wall edema), or regional lymphadenopathy. As mentioned previously, exocrine pancreatic diseases are rarely associated with gas or mineralization.

A specific presentation in cats warrants further mention. Common survey findings in cats with pancreatic carcinoma are marked accumulation of fluid, a nodular or irregular diffuse opacity, and/or ground-glass loss of detail in the area of the central omentum, which is consistent with carcinomatosis (Fig. 26-37A-B).[31] The origin of this opacity must generally be determined with ultrasound and cytology.[32]

ULTRASONOGRAPHIC IMAGING OF THE GASTROINTESTINAL TRACT

Lorrie Gaschen

The sonographic examination of the gastrointestinal tract should be interpreted in conjunction with the findings of abdominal radiographs in most instances. Abdominal radiography provides an

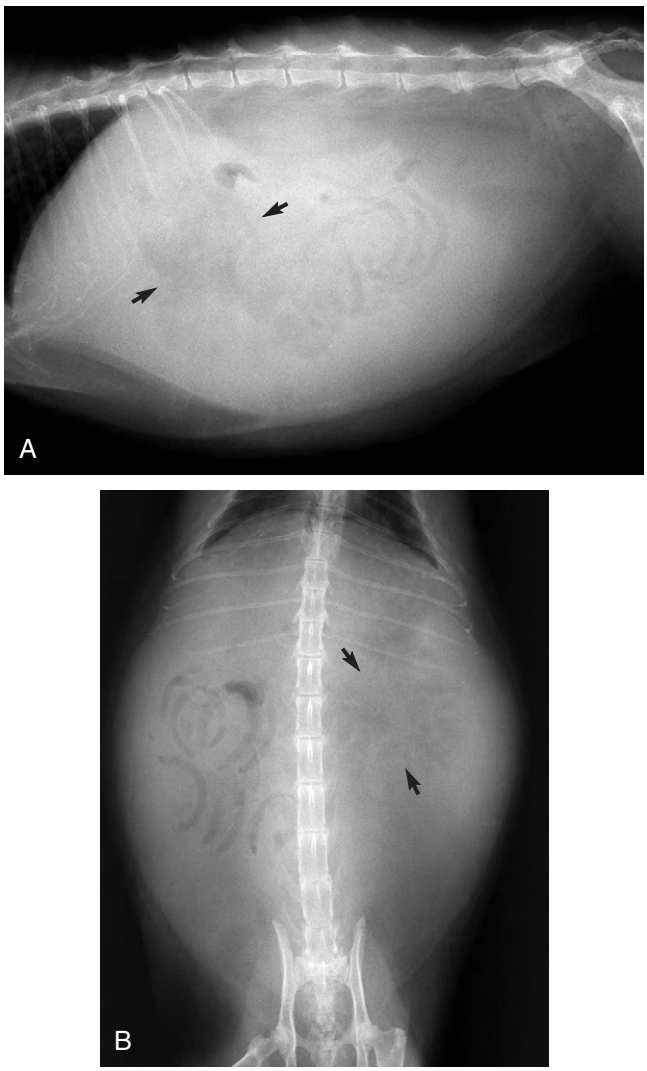


Figure 26-37 Carcinomatosis. (**A**) Lateral and (**B**) VD views of a cat with carcinomatosis. Note abdominal distention secondary to marked effusion. The effusion is asymmetrically distributed with a central area of ground-glass loss of detail (*white arrows*).

overview of the abdomen that the sonographic examination does not allow and can greatly aid in the understanding the sonographic features that are being observed. Patient preparation is another key to a successful ultrasonographic examination of the gastrointestinal tract. Dogs and cats should have food withheld for at least 12 hours prior to examination. This aids in the examination of the stomach, intestines, and adjacent structures and organs. Pressure exerted on the abdomen when the stomach is full results in patient discomfort and lack of compliance. In dogs and cats with a painful abdomen, analgesia or sedation may be necessary to perform a complete ultrasonographic examination. Some sedatives, however, can influence gastrointestinal motility, and this should be taken into account if assessing motility.

High-frequency curved- and linear-array transducers are best for examination of the gastrointestinal tract. Curved-array, 5 to 7.5 MHz transducers are best for the stomach, whereas either curved- or linear-array transducers of higher frequency (>10 MHz) are better suited for the small intestine and colon. High-frequency linear-array transducers are best suited for high-resolution imaging of the small intestinal and wall of the colon.

Patients may be positioned in dorsal, right, or left lateral recumbency for the examination based on the sonographer's preference and region being examined. By varying the position of the animal, gas is displaced to the nondependent region of the lumen and fluid can settle to the dependent regions for better visualization of the bowel wall.

Stomach

Five alternating hyper- and hypoechoic gastric wall layers are evident using high-frequency ultrasound: hyperechoic outer serosa, hypoechoic muscularis, hyperechoic submucosa, hypoechoic mucosa, and interface between mucosa and intestinal lumen (Fig. 26-38), which is hyperechoic. The stomach should be scanned in the axial and longitudinal planes, avoiding oblique planes, which can give the false impression of wall thickening. When empty, the stomach will be contracted and the close approximation of the rugal folds can also give the false impression of a thickened wall. Encouraging the animal to drink water will help to distend the stomach and allow reassessment of the area in question (Fig. 26-39). Gastric

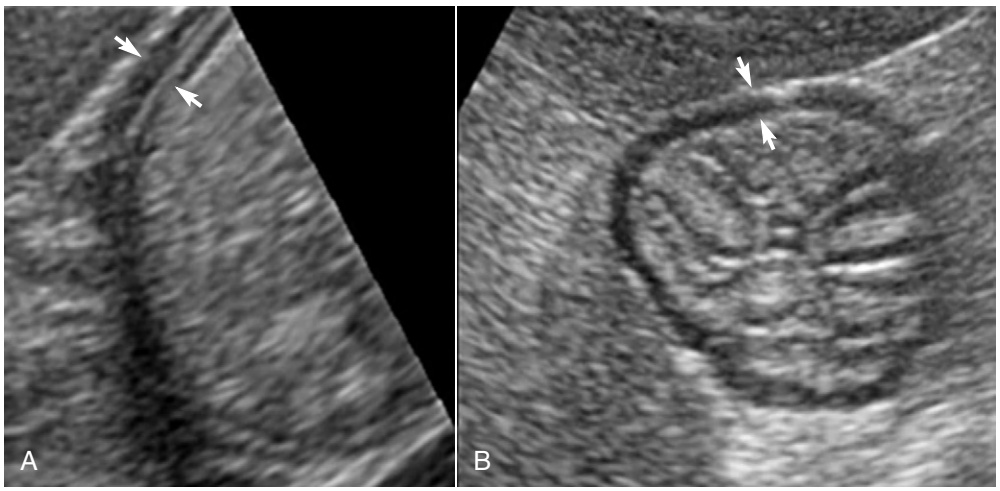


Figure 26-38 Normal canine gastric wall layering. (**A**) Food-filled stomach and (**B**) contracted stomach. The *arrows* mark the outer serosal and inner mucosal borders to show proper placement of calipers for measurement of wall thickness. Five alternating hyper- and hypoechoic layers of the gastric wall are identified.

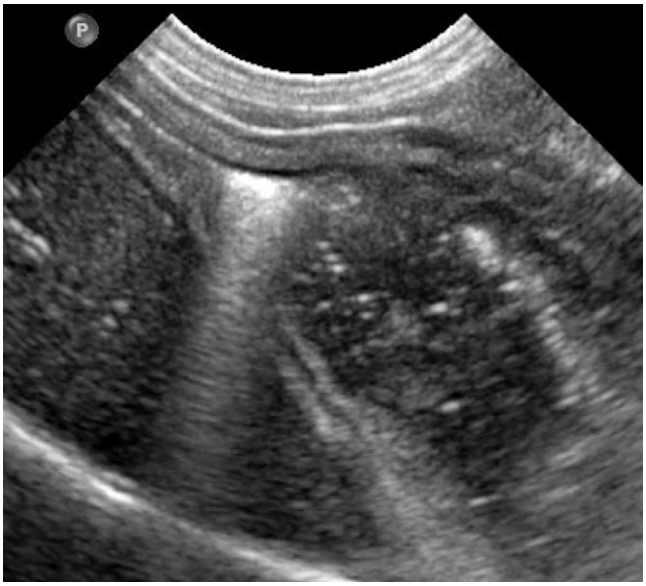


Figure 26-39 Normal canine stomach following oral fluid administration. The stomach is mildly distended and the wall appears thin with normal layering. Reverberation artifacts caused by gas are often present when the animal drinks water and can affect visualization of the wall in some regions.

content is typically gas, food, and/or fluid. Food particles produce a hyperechoic surface and distal shadowing, much like foreign material in the gastrointestinal tract. A recent dietary history is important for this reason. Repeat ultrasound examinations and abdominal radiography after withholding food are often necessary to confirm the presence of ingested food versus foreign material (Fig. 26-40). Gastric gas is common even when food has been withheld. Artifacts produced by gas make assessment of the wall and content more difficult. Gas causes reverberation artifacts, which can obscure the presence of fluid, wall thickening, or foreign material. For this reason, patients should be examined in several positions, and intercostal as well as substernal probe placement should be used. In general, a left intercostal approach is helpful for examination of the gastric fundus, whereas a right intercostal approach is useful for visualizing the duodenum and the pylorus.

Gastric wall measurements of thickness should be made between rugal folds. Normal gastric wall thickness in the dog is 3 to 5 mm, whereas in the cat it is less than 2 mm.[1] The number and prominence of the rugal folds decreases as one scans from the fundus toward the antrum. At the pylorus, the muscularis layer may appear more prominent in cats than in dogs, but this should not be mistaken for hypertrophy or infiltrative disease. At the cranial duodenal flexure there is a short zone where the wall appears diffusely hyperechoic with less distinct wall layering and is a normal finding in both dogs and cats (Fig. 26-41).

Gastric slow waves propagate at the rate of three to five contractions per minute in a stomach with some fluid or food content (see Chapter 1). However this may not be as apparent in the contracted stomach. Gastric emptying disorders can be assessed using a number of methods (see Chapter 26), including ultrasound. There are two main types of gastric emptying disorders: those that are anatomic or mechanical, and those that are functional or physiologic (summarized in Chapter 56). In general, diagnostic imaging should always begin with survey abdominal radiographs. Gastric size, position, and content can be rapidly assessed with survey radiographs. Barium contrast study, barium-impregnated polyethylene spheres (BIPs), gastric emptying scintigraphy, or ultrasound examination should follow abdominal radiography to diagnose the cause of a chronically dilated stomach.[2-6] Ultrasound is used to identify nonradiopaque foreign bodies, pyloric hypertrophy, and gastric wall–associated masses that are obstructing gastric outflow. The pyloric region in dogs can be very difficult to visualize sonographically and often depends on the operator's experience as well as patient conformation.[7] In cats, it is fairly consistently identified. Pyloric outflow obstruction should be suspected with any of the following findings:

- Abnormal gastric content with fluid and gas layers in the nondependent portion and particulate matter in the dependent portion;
- Contractions that do not propel gastric content into the duodenum;
- Circumferential thickening of the antral or pyloric wall;
- Wall-associated mass in the antrum, pylorus, or proximal duodenum;
- Extraluminal mass compressing the antrum or pylorus; or
- Intraluminal foreign body obstructing the pylorus or proximal duodenum.

Gastric foreign bodies can almost always be detected ultrasonographically. In most instances they have a hyperechoic surface with a strong acoustic shadow (see Fig. 26-40C). Their shapes are variable and dependent upon the nature of the foreign body. Wooden sticks, hard plastic, and balls have different shapes, but all exhibit strong acoustic shadowing (Fig. 26-42). Gastric trichobezoars can frequently be seen in cats and have a bright, hyperechoic surface with a clean acoustic shadow as a result of their compact nature. Food particles, such as pieces of meat and kibble, have variable sonographic appearances. Dense objects with smooth surfaces have bright reflective surfaces with clean acoustic shadow. Because of the variable and sometimes confusing nature of gastric content, radiography should be used as a comparative diagnostic tool and the patient should be held off food and reexamined sonographically before a definitive diagnosis is being made.

One of the most important indications for gastric ultrasound is for the detection of wall thickening. Detection of gastric wall thickening depends on extent and severity as well as patient condition. Gastric wall thickening can be characterized as focal, diffuse, concentric, or asymmetric, and with or without loss of wall layering. Loss of wall layering is commonly associated with neoplastic or fungal infiltration of the gastric wall as well as with gastric ulceration. Gastric wall thickening can also occur with gastritis, edema, neoplasia, fungal disease, congenital hypertrophic pyloric stenosis, and chronic pyloric hypertrophic gastropathy. Although ultrasonography is sensitive to gastric wall thickening, it lacks specificity.[8-10] Consequently, gastric biopsy is required for a definitive diagnosis of gastric wall thickening.

Gastric neoplasia typically leads to wall thickening and loss of layering, much like fungal infiltration.[8,11,12] Gastric neoplasia can be pedunculated and protrude into the lumen, to the extent of causing pyloric obstruction. Leiomyoma, leiomyosarcoma, carcinoma, and lymphoma are the most common types of gastric neoplasia in dogs and cats.[12] Gastric lymphoma is often typified by focal or diffuse transmural thickening with a hypoechoic wall, loss of wall layering, and regional lymphadenopathy (Fig. 26-43). Regional lymph nodes may become so enlarged that they create the effect of a midabdominal mass. Gastric carcinoma has an unusual ultrasonographic pattern of thickened alternating hypo- and hyperechoic layers that has been referred to as pseudolayering (Fig. 26-44).

Inflammatory diseases of the stomach include chronic gastritis caused by diseases such as eosinophilic, lymphocytic, and uremic

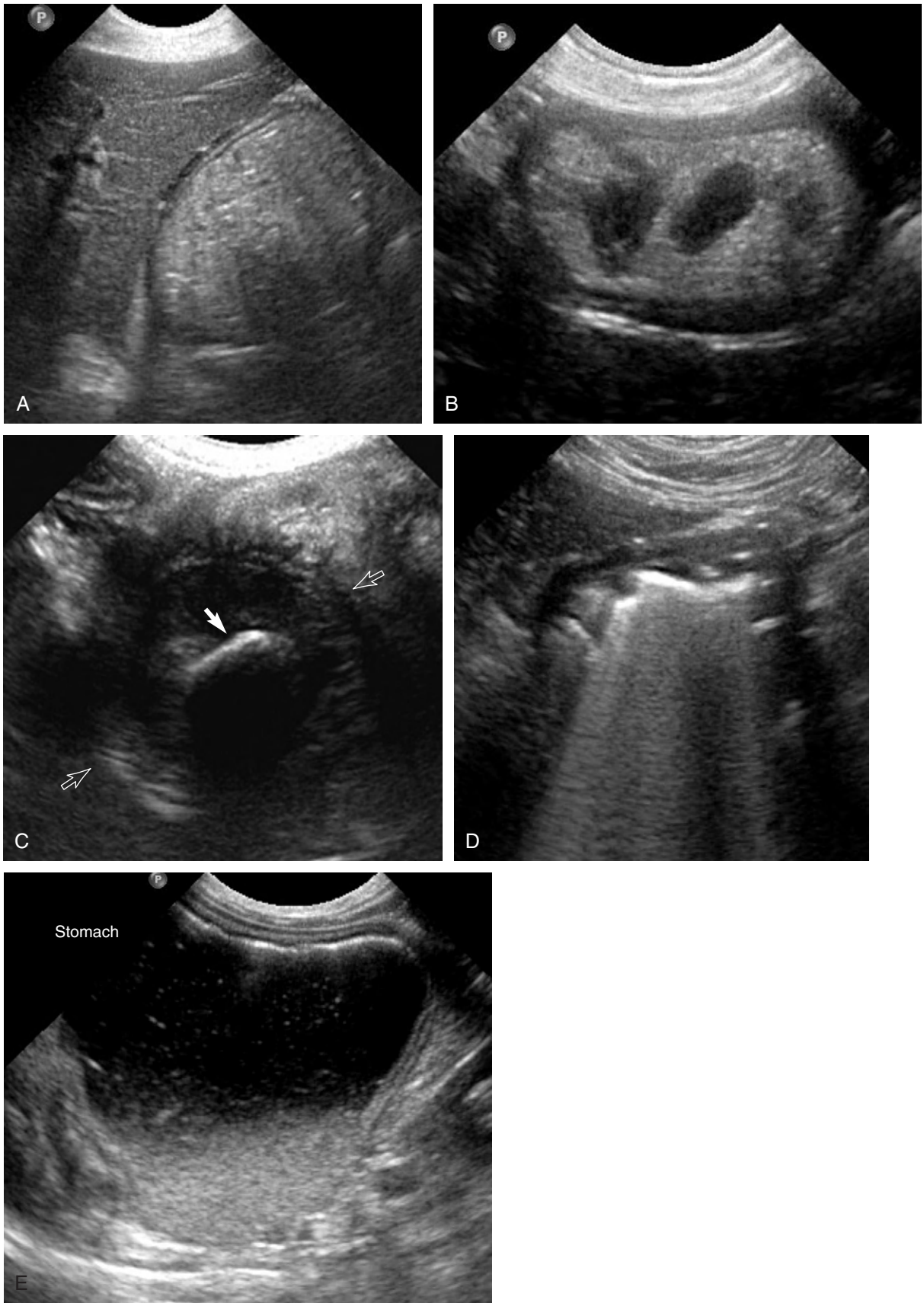


Figure 26-40 **A,** Appearance of a normal canine stomach with uniform food content. **B,** Appearance of a normal canine stomach showing large pieces of soft food (meat and potatoes). The hypoechoic mass-like appearance of the food should not be confused with wall infiltration or a gastric mass. Repeat ultrasound should be performed in the fasted state in such instances. **C,** Foreign body in the pylorus of a dog with chronic vomiting. Note the hyperechoic reflective surface and clean distal shadowing associated with the foreign material. Abdominal radiographs are indicated to further ascertain the type of foreign body (radiopaque versus radiolucent). **D,** Gas in the stomach. Gas creates dirty shadowing and reverberation artifacts that obscure most of the abdominal wall. In such instances, instilling water orally or changing the position of the dog helps to displace gas away from the region of interest in the stomach. **E,** Layered gastric content. The more dependent regions of the stomach have more echogenic layers whereas the nondependent region has less echogenic fluid content. This finding is indicative of a gastric outflow obstruction.

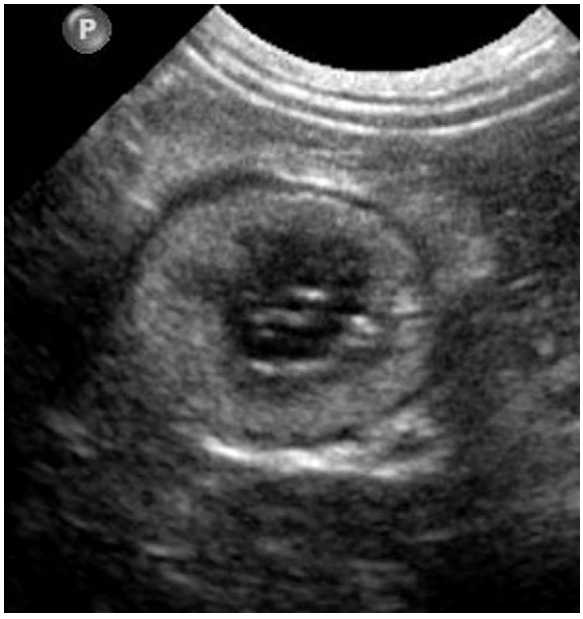


Figure 26-41 Cross-sectional ultrasound image of the normal canine cranial duodenal flexure. The wall appears diffusely hyperechoic over a very short length and should not be mistaken for a disease process.

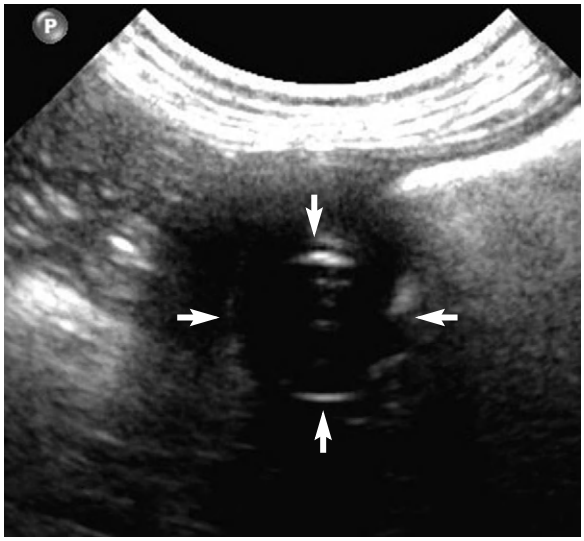


Figure 26-42 Gastric ball foreign body made up of a soft, gel-like substance in the pylorus of a Dachshund causing obstruction. The ball creates a hyperechoic rim as a result of its smooth surface (*arrows*) but is anechoic in the center because of the nonattenuating material.

gastritis.[13] An ultrasonographic change consistent with gastric inflammation is diffuse wall thickening without loss of wall layering. The stomach is usually distended with fluid accumulation and decreased peristaltic activity. Gastric rugal folds may appear enlarged and blunted. Dogs with hypoproteinemia as a consequence of protein-losing enteropathy (PLE) may develop gastric wall edema. In PLE disorders, the gastric wall is usually thickened with rounded rugal folds and altered wall layers (Fig. 26-45). Uremic gastropathy has many ultrasonographic features typical of inflammatory disease but may also include mineralization of the gastric wall.[13] Mineralization is often diffuse and appears as a hyperechoic layer along the gastric mucosa. Gastric mucosal biopsy is required to differentiate benign from malignant disease.

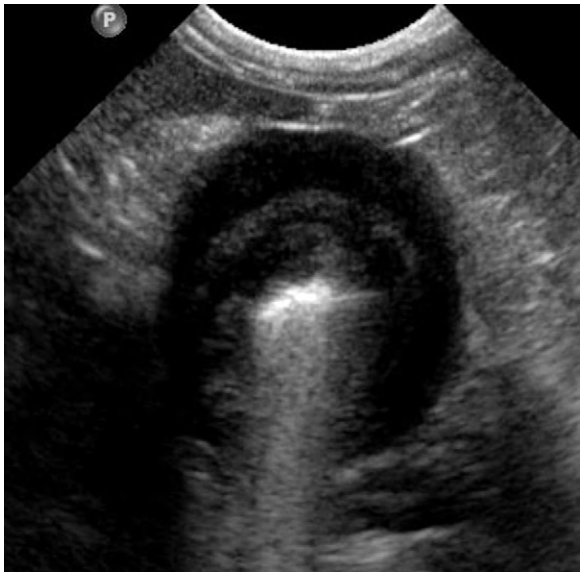


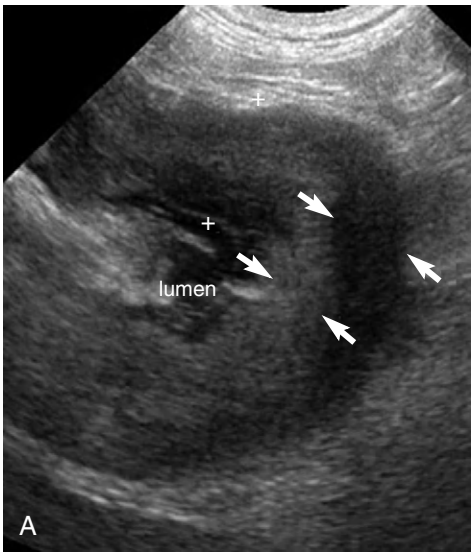
Figure 26-43 Transmural gastric thickening (1.5 cm) of the gastric fundus and body in a cat. The wall is diffusely hypoechoic with loss of wall layering. Histologic diagnosis: lymphoma.

Gastroduodenoscopy is clearly the diagnostic method of choice for detecting gastric ulcerative disease (see Chapter 27). However ultrasonography is a commonly used screening test for dogs with suspected gastric ulceration. Benign ulcers are often more difficult to detect ultrasonographically than malignant ones as they tend to be smaller in size and located in the pyloric canal. Malignant ulcers are generally larger and more readily detectable. They are associated with an adenocarcinoma, lymphoma, mast cell tumor, or gastrinoma. Gastric ulcers can lead to perforation, therefore abdominal radiographs should always be performed prior to the ultrasound examination in vomiting animals (Fig. 26-46). Depending on their size, location, and gastric content, some ulcers can be difficult to detect ultrasonographically. They appear as a focal wall thickening with loss of wall layering and a crater at the mucosal surface. The crater appears as a hyperechoic zone at the mucosal surface because of accumulation of necrotic debris and gas. The regional mesentery may appear hyperechoic and free fluid may be suggestive of peritonitis and a possible rupture. The nondependent region of the abdomen should be scanned for reverberation echoes adjacent to the peritoneal surface that could be consistent with pneumoperitoneum (Fig. 26-47).

Gastric intussusception is rare.[14] Gastrogastric, pylorogastric, gastroduodenal, and gastroesophageal intussusceptions have been reported and can be challenging to diagnose sonographically, as well.[14,15] The cause of most intussusceptions is unknown, but associations with vomiting disorders and gastric masses have been suggested. Gastric distention and a luminal gastric mass or concentric wall layers are potential sonographic findings. Gastric intussusceptions can be misdiagnosed as masses because of the presence of a thickened, edematous, and hypoechoic wall with indistinct layering.[16]

Small Intestine

The descending duodenum, ileum, and jejunum can be differentiated from one another ultrasonographically based on their location, wall layering, and communication with adjacent intestinal



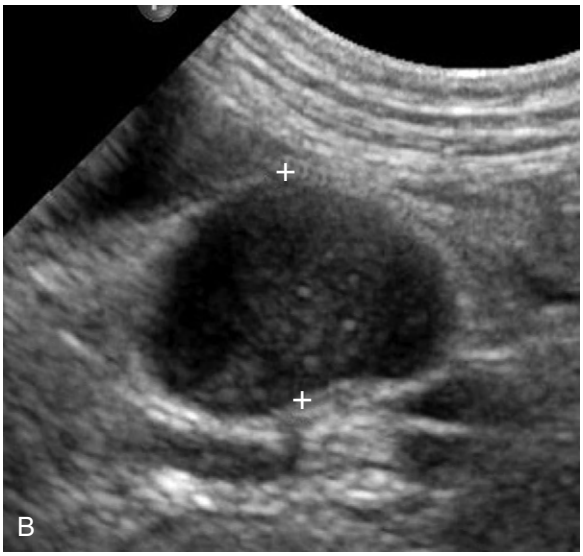


Figure 26-44 A, Transmural gastric thickening (1.2 cm marked on the image between the two "+" signs) of the gastric antrum in a dog with chronic vomiting and weight loss. Two thick layers (between *thin arrows*), one hypo- the other hyperechoic, replace the normal wall layering. **B**, The regional gastric lymph node is hypoechoic, enlarged (1.2 cm), and rounded. Histologic diagnosis: carcinoma with regional lymphatic metastasis.

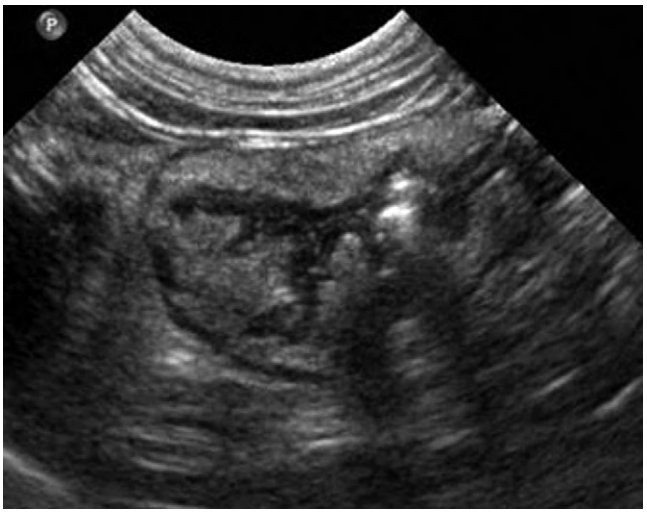


Figure 26-45 Gastric wall edema in a Yorkshire Terrier with protein-losing enteropathy. The gastric wall is thickened (8 mm), hyperechoic, and with blunted rugal folds.

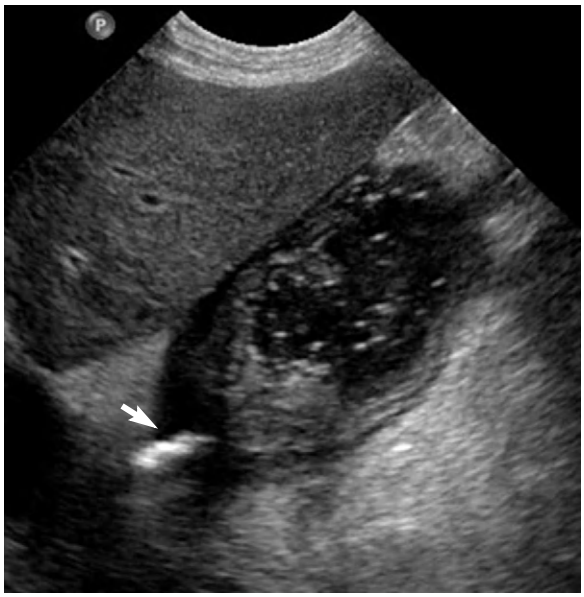


Figure 26-46 Benign perforating gastric ulcer in a dog caused by concurrent steroidal and nonsteroidal antiinflammatory drug therapy for orthopedic disease. The gastric antrum shows focal thickening and is hypoechoic with loss of layering. A "crater" can be identified (*arrow*) as a focal hyperechoic zone at the mucosal surface of the thickened region. The mesentery surrounding the stomach is diffusely hyperechoic and was a result of peritonitis.

segments. In dogs the duodenum is the most lateral intestinal segment in the right abdomen. The duodenum follows a straight course along the right body wall cranially to the cranial duodenal flexure where it abruptly turns toward the left to join the pylorus. The flexure is usually visible in all dogs, but may be difficult to locate in deep-chested breeds. The pyloroduodenal junction is not consistently identified in all dogs as a result of variability in thoracic conformation. A right intercostal approach may be necessary to examine it in some dogs. In cats, the duodenum has more of a midline location and the pyloroduodenal junction is just caudal to the hilus of the liver. A number of hyperechoic structures that appear like outpouchings of the lumen into the mucosa can often be detected at the antimesenteric border of the duodenal wall. These are normal structures associated with Peyer's patches and should not be misdiagnosed as ulcerations. Duodenal wall thickness varies with body size and weight.[17] In dogs weighing up to 20 kg, the jejunal wall thickness is less than or equal to 4.1 mm; dogs weighing between 20 and 39.9 kg have a thickness less than or equal to 4.4 mm; in dogs weighing more than 40 kg the thickness is less than or equal to 4.7 mm. Canine duodenal thickness is less than or equal to 5.1 mm for dogs weighing up to 20 kg, less than or equal to 5.3 kg for dogs weighing between 20 and 29.9 kg, and less than or equal to 6.0 mm for dogs weighing more than 30 kg. The normal feline duodenal thickness ranges from 1.9 to 3.8 mm.[18] The feline jejunum ranges from 1.6 to 3.6 mm. The luminal diameter is variable in

healthy dogs and cats, and depends on the duration of the period food has been withheld and gastric content at the time of examination. Small amounts of gas and fluid are normal findings. The walls of the duodenum and jejunum appear similar in dogs and cats (Fig. 26-48). The ileum can be recognized by its communication with the colon and its wall layering. The hyperechoic ileal submucosa is more prominent than that of the duodenum and jejunum (Fig. 26-49). In the transverse plane, the ileum has a rosette appearance because of its typically contracted state. The duodenum and jejunum should be observed for peristalsis, which occurs at the rate of approximately one per minute in normal animals (see Chapter 1).

The importance of the small intestinal ultrasound examination is to detect the extent and nature of anatomic and functional changes of the small intestine, and to determine if the changes are isolated to the gastrointestinal tract or involve other organ systems. When examining the small intestine with ultrasound, the wall thickness, wall layering, layer echogenicity, luminal content, and motility should be recorded. The length of an abnormality, the luminal diameter, regional lymph nodes, mesenteric echogenicity, and the presence of free fluid should be determined. Abnormalities should be characterized as focal or generalized.

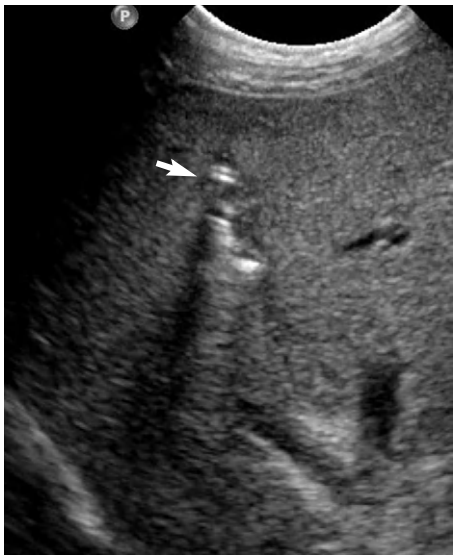


Figure 26-47 Ultrasound image of the same dog as in Figure 26-46 showing reverberation artifacts caused by the presence of gas (*arrow*) between the liver lobes following gastric ulcer perforation.

Inflammatory diseases of the small intestine are common in dogs and cats. Because they do not always induce changes that can be detected with ultrasound, diagnosis of this group of diseases generally requires intestinal biopsy for confirmation. Although generally diffuse, the disease can also be present focally or segmentally. Inflammatory disease generally leads to mild to moderate transmural thickening of the intestinal wall with preserved wall layering. Decreased intestinal motility because of wall thickening can also be seen with diffuse or segmental inflammatory disease. In cats, the disease is often associated with a selectively thickened muscularis, which is caused by lymphoplasmacytic and/or eosinophilic infiltration (Fig. 26-50).[19] However a thickened muscularis layer in the cat also has been associated with other disorders such as mechanical obstruction or lymphoma.[20] One study showed a significant association between muscularis thickening and T-cell lymphoma in cats.[21] The presence of regional lymphadenopathy was not significantly different in cats with inflammatory bowel disease versus lymphoma. When disease was only present in the mucosa and lamina propria histopathologically, there were no abnormalities ultrasonographically in the cats in that study. Because of the overlap of diseases associated with muscularis thickening and lymphadenopathy in cats, full-thickness intestinal biopsies are likely indicated to reach a definitive diagnosis.

Marked thickening of the muscularis layer may also be observed in cats with eosinophilic enteritis, a condition that has been reported to occur in association with feline hypereosinophilic syndrome. Although the changes are diffuse in almost all instances, a focal intestinal mass was reported in one cat.[22] Feline gastrointestinal eosinophilic sclerosing fibroplasia also has been described in 25 cats.[23] All of these cats had an intestinal mass at the pylorus, jejunum, ileum, ileocecocolic junction, and/or colon, with the pyloric location being most common. They are usually transmural

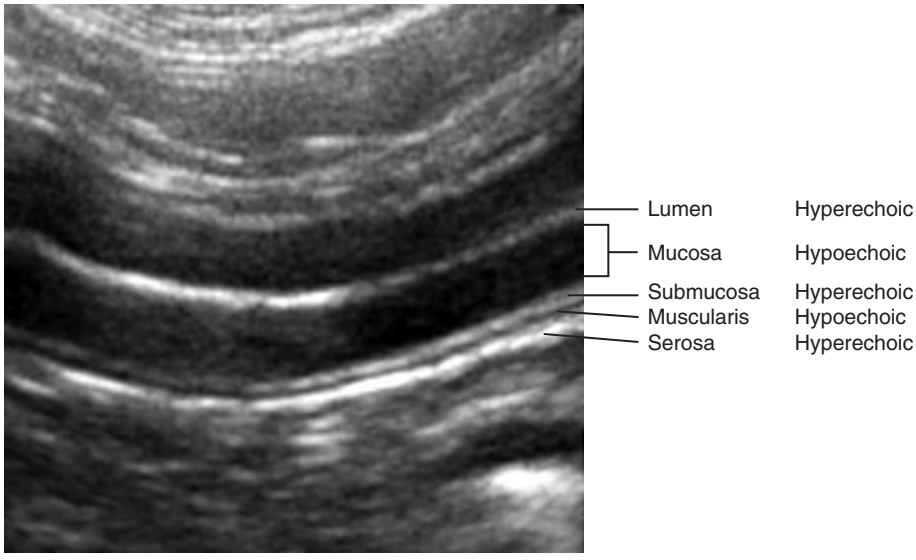


Figure 26-48 Normal small intestinal wall appearance showing the relationship of the layers and their echogenicity.

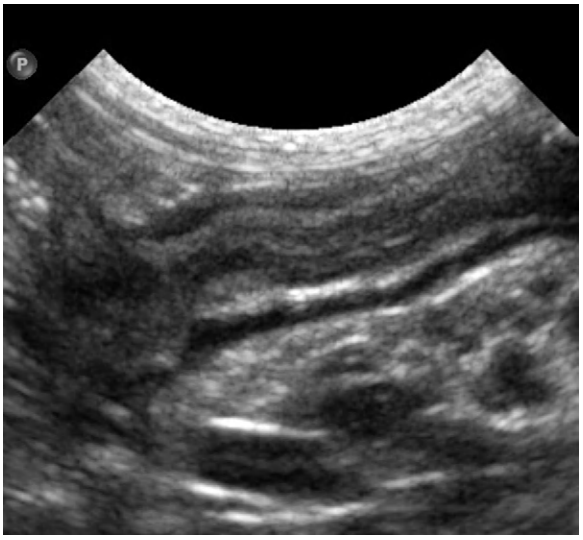
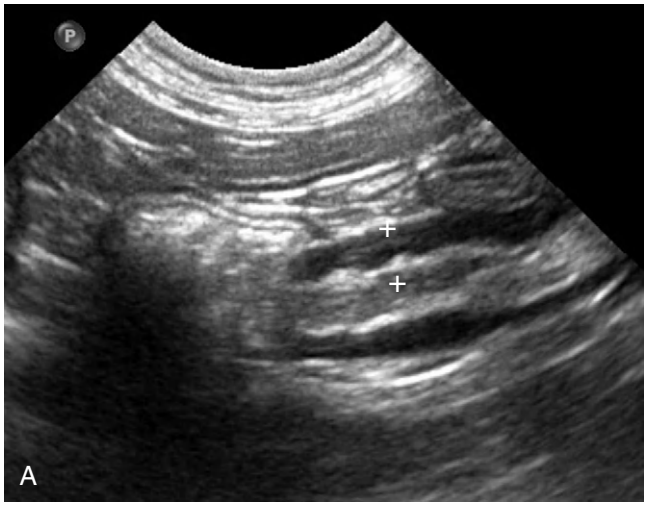


Figure 26-49 Normal feline ileum showing the ileocolic junction and prominent hyperechoic submucosal layer. The canine ileum shows a similar appearance.



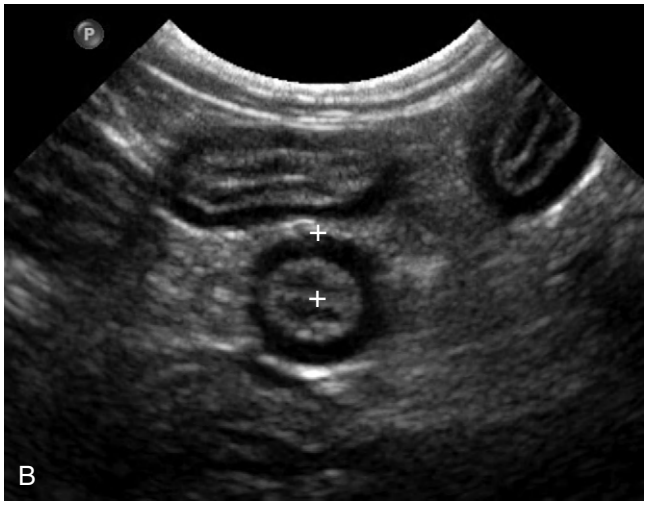


Figure 26-50 **A,** Feline ileum with inflammatory bowel disease. The muscularis layer is thickened. An eosinophilic and lymphocytic infiltration was found on histopathology. **B,** Feline jejunum with inflammatory bowel disease. Multiple transverse jejunal segments are shown with a thickened muscularis layer but normal total wall thickness.

lesions but can also be mucosal and none extend beyond the serosa. Although wall layering is generally preserved in inflammatory infiltration, in severe instances it can be indistinct or completely lost. As ultrasound findings of inflammatory and neoplastic infiltration may be similar, intestinal biopsy is always required to confirm and differentiate the two diseases. The relative thickness of the layers also may change while maintaining a normal total wall thickness. Lymphoma is the most common neoplastic cause of diffuse infiltration and wall thickening that can appear similar to inflammatory disease (Fig. 26-51).Chronic inflammatory disease in cats may also produce a distinct, thin, hyperechoic line within the mucosa that is associated with fibrosis histopathologically.[24] The clinical relevance of this sonographic abnormality is uncertain as it can be found incidentally in cats without gastrointestinal disease.

Few data are available concerning the ultrasonographic monitoring of chronic enteropathies. A two-dimensional ultrasound score has been established for canine chronic enteropathies.[18] The ultrasound score correlates with the clinical inflammatory bowel disease activity index (CIBDAI) for dogs at initial presentation.[18] However it is important to note that improvement in the CIBDAI does not correlate with improvement of the ultrasound score following therapy.[18,25]

Canine intestinal lymphangiectasia can occur as a consequence of inflammatory bowel disease or as a primary disorder. Ultrasonographically, mild thickening may be the only abnormality observed. The ultrasonographic diagnosis usually rests on the ability to demonstrate hyperechoic striations that are aligned parallel to one another and perpendicular to the long axis of the intestine (Fig. 26-52).[26] Generalized mild dilation of the intestine and increased fluid content is commonly present and regional lymph nodes may or may not be enlarged. Free peritoneal fluid is usually present in this disease and can be mild, moderate, or severe.

Corrugation of the small intestine can be seen with inflammatory disease within or surrounding the intestinal wall (Fig. 26-53). In dogs with pancreatitis, the duodenum can appear corrugated because of the surrounding peritonitis. Hemo- and uroabdomen result in similar findings.[27-29] With ultrasound, the sonographer can also detect spastic activity of the intestine in real time. These appear as intermittent contractions resulting in a corrugated appearance of the wall which, when relaxed, appears more normal.

Focal intestinal wall thickening can be a result of neoplastic and nonneoplastic lesions. Neoplastic masses often are associated with concentric or eccentric wall thickening with loss of wall layering. The presence of air within an abdominal mass is an indication that it could be of intestinal origin. In this situation, one should strive to find a communication between the air in the mass and adjacent small intestinal segments. In the axial plane, hyperechoic foci due to air may invade the mucosa. The most common intestinal wall tumors in dogs include carcinoma, lymphoma, and leiomyosarcoma.[30-33] Intestinal carcinoma typically develops into a focal mass with loss of wall layering, regional lymphadenopathy, and mechanical obstruction. In cats, the most common malignancies are lymphoma, mast cell tumor, and adenocarcinoma. Lymphoma can diffusely involve the intestine in both species. Lymphoma often appears as a decreased wall echogenicity with focally or diffusely altered wall layering and regional lymphadenopathy. It may also cause partial obstruction of the intestinal lumen (Fig. 26-54). The ileum is a predilection site for lymphoma in cats. Regional lymph nodes are commonly enlarged, rounded, and hypoechoic in patients with either neoplastic or fungal infiltrations of the intestines. Widespread infiltration of the tumor throughout the mesentery and organs can also occur and is referred to as

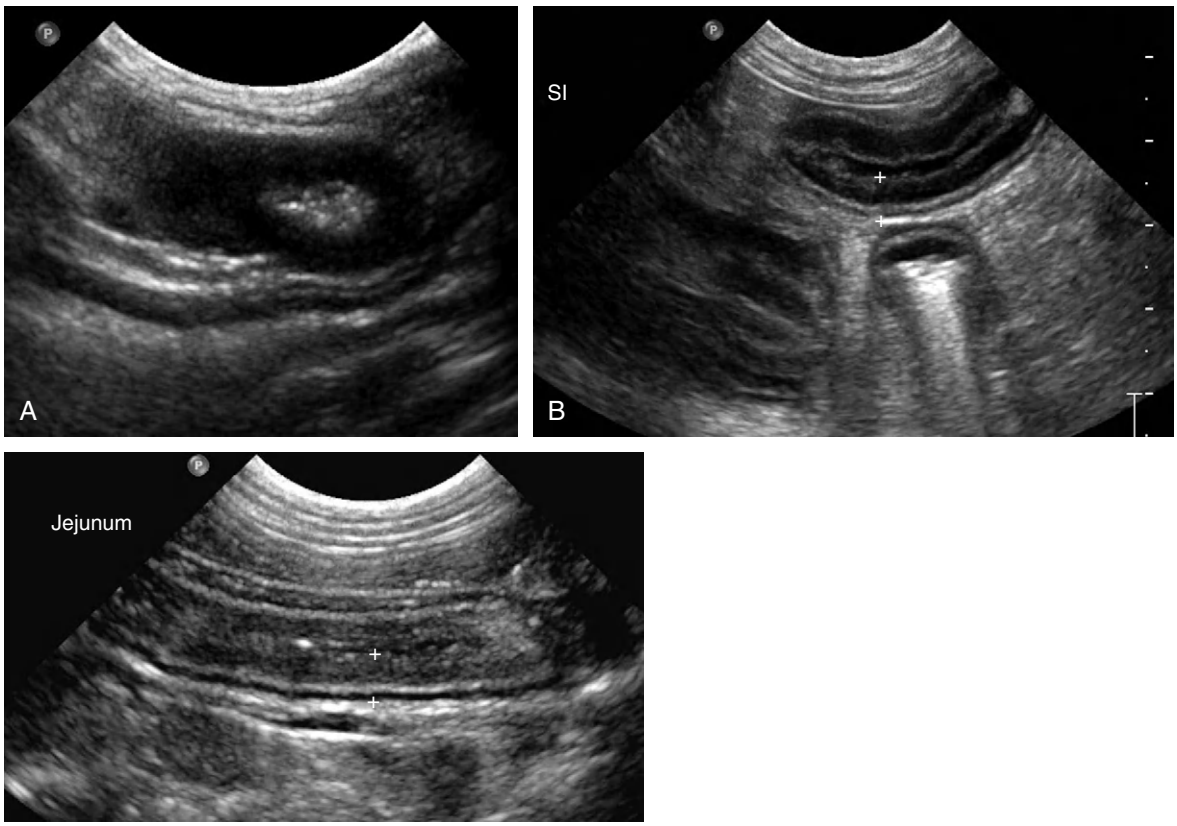


Figure 26-51 **A,** Feline small intestinal lymphoma. Focal transmural thickening with loss of wall layering. The wall appears diffusely hypoechoic and is a common appearance of gastrointestinal lymphoma. **B,** Canine inflammatory bowel disease caused by lymphoplasmacytic infiltration. The jejunum is mildly distended and has a stiff-walled appearance. The wall thickness was increased at 5.2 mm but there was normal wall layering. **C,** Canine inflammatory bowel disease caused by lymphoplasmacytic infiltration. The jejunum has a normal wall thickness but has a diffusely hyperechoic mucosa, in contrast to the dog in (**B**).

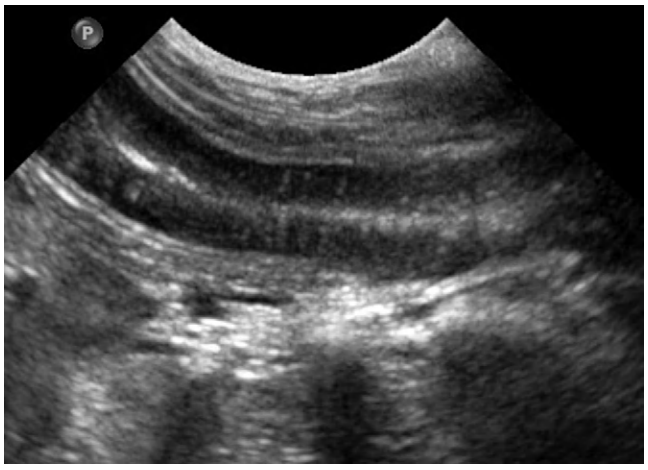


Figure 26-52 **Intestinal lymphangiectasia in a Yorkshire Terrier with protein-losing enteropathy.** Linear hyperechoic striations are aligned parallel to one another and perpendicular to the long axis of the small intestinal mucosa.

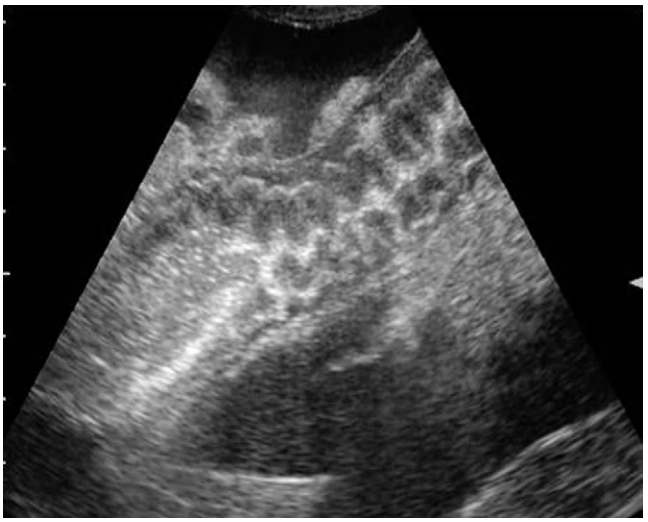
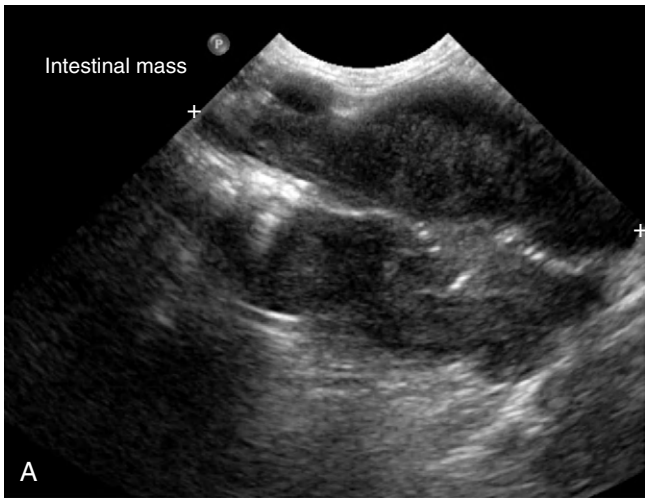


Figure 26-53 Corrugated duodenum in a dog with peritonitis.

carcinomatosis. Ultrasonographically it appears as hypoechoic foci, usually nodular, throughout the mesentery along with free fluid. When free fluid is present, the visceral peritoneal lining should be carefully scanned for irregularities in contour. Leiomyosarcomas tend to grow out from the periphery of the intestinal wall and appear as eccentric or extraluminal masses.

Nonneoplastic masses include fungal infections with *Pythium* and *Histoplasma*, abscessation, cysts, hematomas, ulcers, intussusceptions and foreign-body granulomas (Fig. 26-55). A focal mass with loss of wall layering is a nonspecific sign and can be present in any one of these conditions. *Pythium* and histoplasmosis can lead to either intestinal wall thickening infection with pseudolayering or



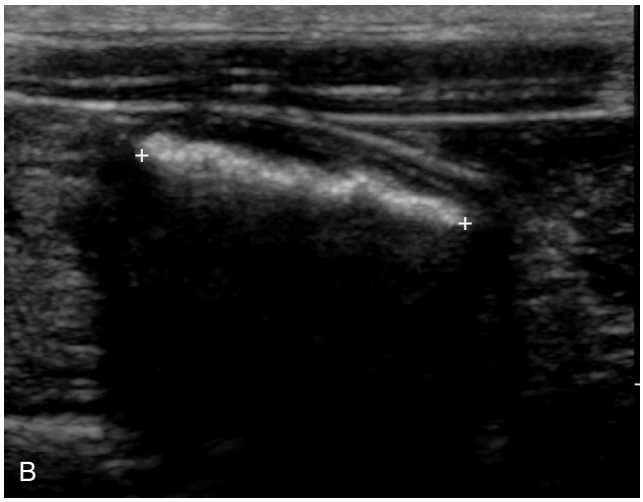


Figure 26-54 **A,** Feline intestinal lymphoma creating stenosis. The jejunal lumen is narrowed as a consequence of asymmetric thickening of the small intestinal wall that is hypoechoic and exhibits a loss of wall layering. **B,** Orad to the stenosis the jejunum contains hyperechoic foreign material with acoustic shadowing as a result of the accumulation of mineral food content over time.

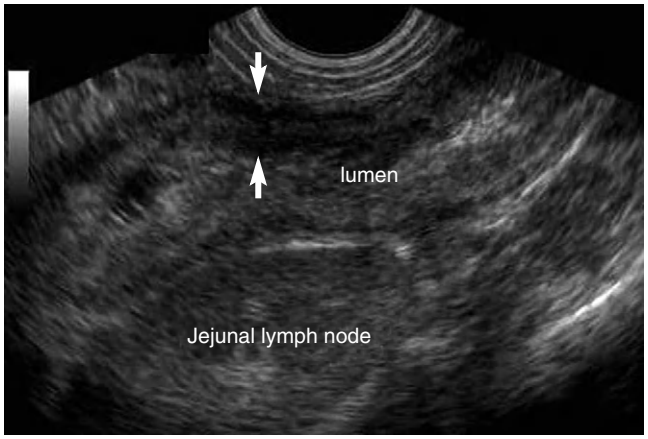


Figure 26-55 Diffuse intestinal thickening with transmural loss of wall layering and increased echogenicity of the wall and regional lymphadenopathy. Histologic diagnosis: pythiosis.

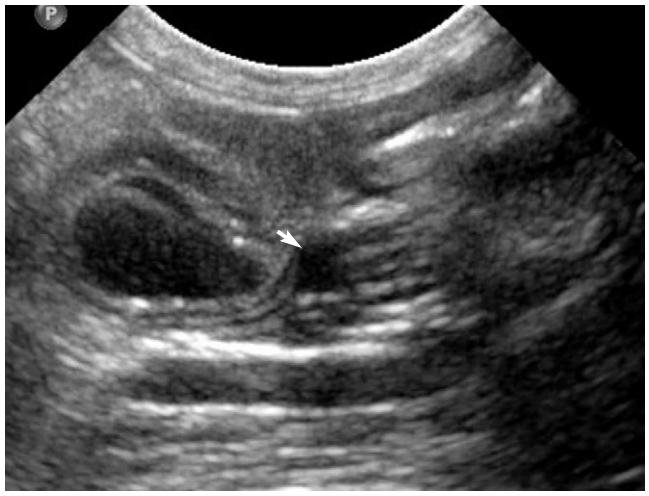


Figure 26-56 Mixed population of empty, contracted intestines adjacent to dilated, fluid-filled ones as a result of the presence of a small intestinal foreign body causing obstruction. The *arrow* shows a small amount of free fluid between the two intestinal segments.

transmural loss of layering as well as a focal mass (see Fig. 26-51).[9] Histoplasmosis has been reported in the cat and can spread throughout the entire abdomen and lungs.[34] Abdominal ultrasound of intestinal histoplasmosis can show lymph node enlargement, a mass of uncertain origin, thickening of the muscularis layer of the small bowel, focal thickening of the ileum with loss of layering, and free peritoneal fluid. These changes are similar to those of lymphoma and other neoplasms ultrasonographically. Histology is required for differentiation between neoplastic and nonneoplastic masses of the intestine.

Functional ileus is usually well-differentiated from mechanical ileus on ultrasound examination. Generalized, mild dilation of the intestinal lumen with fluid accumulation are the predominant features of functional ileus. Intestinal motility is decreased or absent and the intestinal walls may appear stiffened with to-and-fro movement of the fluid content. These changes may be observed with any cause of gastroenteritis, diffuse neoplasia, or peritoneal inflammation (see Chapter 57). An end-jejunal partial obstruction caused by a foreign body or stenosis caused by neoplasia can lead to similar findings.

Ultrasonography is often used in dogs and cats with suspected intestinal obstructions that are not evident radiographically. Similar principles are used as in radiography for diagnosing an obstructing foreign body (see Chapter 26). The gastrointestinal tract is scanned for small and large diameter intestinal segments. With mechanical ileus, the intestinal segments proximal to the obstruction usually show hyperperistalsis and are moderately to severely dilated whereas intestinal segments caudal to the obstruction are of small diameter (Fig. 26-56). Foreign-body material appears hyperechoic with shadowing. The uniformity of the shadowing is dependent on the material itself. With solid homogeneous material, the shadowing will appear more homogenous and anechoic. With heterogeneous material, the shadowing will also appear heterogeneous. If the material contains gas, reverberation artifacts may be present. Metallic foreign material is associated with "ring-down" artifacts (Fig. 26-57). Linear foreign bodies will cause plication of the intestine that should not be confused with corrugation (Fig. 26-58). Plication appears as bunching of the intestine and is static in nature. Occasionally a thin, linear echo representing the string may be seen.

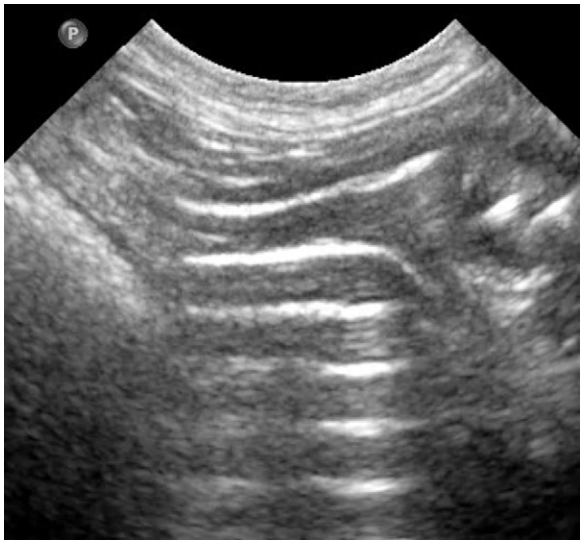


Figure 26-57 Alternating hyperechoic stacked bands can be seen emanating from a small intestinal segment. The intestine itself cannot be seen because of the artifact that was caused by the presence of two sewing needles in the midjejunum. Abdominal radiography was necessary to ascertain the source of the artifact.

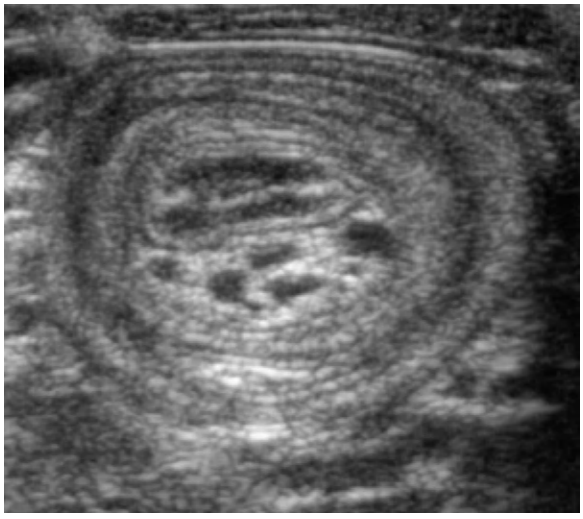


Figure 26-59 **Jejunojejunal intussusception.** Cross-section of the intussusceptions showing concentric rings of intestinal walls. The intussusceptum is in the center and is surrounded by hyperechoic mesentery and small round anechoic vessels. The outer wall or intussuscipiens has a less distinct wall.

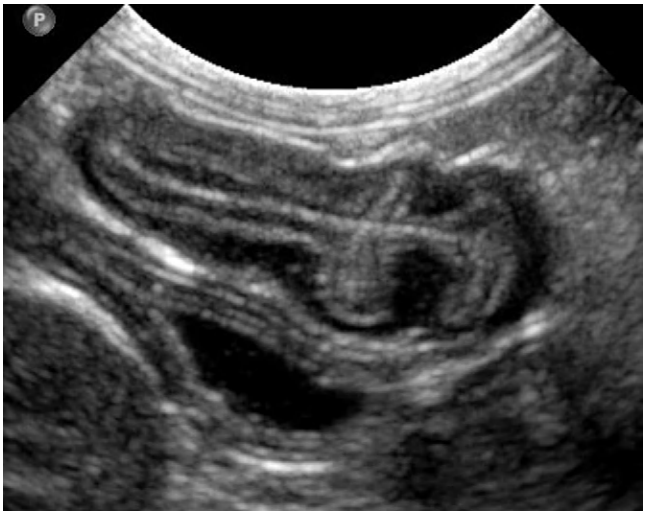


Figure 26-58 The jejunum in the same cat as in Figure 26-57 was found to be plicated. The sewing needles had a string attached and a linear foreign body was diagnosed ultrasonographically.

Intestinal intussusceptions cause a mechanical obstruction because of telescoping of the intestine. Underlying pathology such as a mass, particularly in cats, or segmental motility disorders may cause these intussusceptions. They can also be seen in patients with intestinal parasites, linear foreign bodies, and any disease associated with diarrhea. Ultrasonographically, a focal intestinal thickening with a multilayered or concentric ring appearance is diagnostic for intussusceptions in dogs and cats (Fig. 26-59).[35-37] The most common form is the ileocolic intussusception.[38] Intussusception occurs more commonly in young dogs at the ileocecocolic junction.[39-41] The intussusceptum is directed aborally to reside inside the cecocolic lumen. As intussusceptions can be intermittent, their presence should be confirmed immediately prior to surgery.[37] Color Doppler technology can be used to assess for ischemia in the mesentery of the intussuscepted bowel and is a useful technique for determining reducibility.[36]

Perforations of the intestine by a foreign body, ulcer, or neoplasia can also be detected with ultrasound. The perforation site may be observed directly or indirect signs of perforation such as regional accumulation of fluid and corrugated bowel may increase the suspicion for a perforation. Free peritoneal air may also be observed. Intestinal abnormalities are often present and include focal thickening and possible loss of layering at the site of the perforation. Postoperative ultrasound may be required in those patients manifesting abdominal pain post-enterotomy. Primary features used in identifying the surgical site include irregular hypoechoic serosal margins, a focally thickened bowel wall with altered to absent wall layering with adjacent hyperechoic fat and the presence of hyperechoic suture material.[42] Enterectomy sites are more readily visualized than enterotomy sites likely because of circumferential distribution and comparatively larger size of the surgical site.[42] Pneumoperitoneum, echogenic abdominal effusion, and hyperechoic mesenteric fat can be detected but should progressively resolve over 10 days in most patients.

Cecum and Colon

Ultrasonographically, the ileum, ileocecal junction, cecum, and ascending, transverse, and descending colon can be identified in the dog and cat. The bony pelvis limits examination of the colon, but the rectum as well as perirectal and perineal regions can be examined via perineal probe placement. If the region of interest within the pelvic canal cannot be assessed because of overlying bone, radiographic contrast studies or computed tomography can be helpful in determining the origin of soft-tissue masses causing displacement or compression of the colon. When distended, the wall should have the appearance of three layers and a thickness of 1 to 2 mm independent of the size of the animal. The empty colon will appear contracted and many layers can be appreciated. This should not be

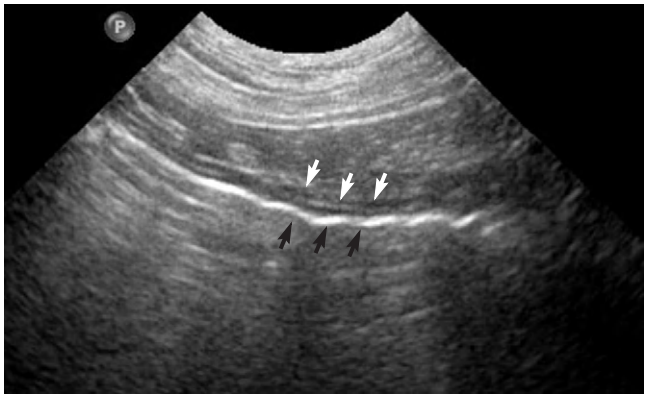


Figure 26-60 **Normal appearance of the colon.** The near wall (*white arrows*) is thin (1 to 2 mm) in dogs and cats and three distinct alternating layers (hyper-, hypo-, and hyperechoic) can be detected with high-resolution probes. Only the near wall is visible because of the hyperechoic reflective nature of the fecal and air content (*black arrows*).

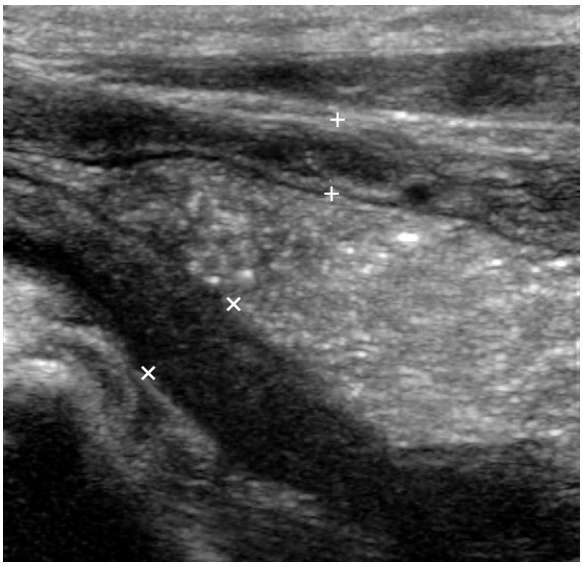


Figure 26-61 **Diffuse colonic wall thickening in a cat with tenesmus.** The colon wall ranges from 3 to 4.5 mm in thickness (delineated by the two "+" markers) and is diffusely hyperechoic such that the three thin layers are no longer visible. Histologic diagnosis: lymphoma.

misinterpreted as colonic wall thickening however. The large bowel is often filled with feces or air creating an artifact that permits only the wall closest to the transducer to be examined (Fig. 26-60). To differentiate dilated small intestines from the colon, the colon should be traced from the pelvic inlet cranially along the left abdominal wall to the stomach where it turns toward the right and courses caudally to the midabdomen. On the right side of the abdomen, the cecum and ileum can be identified medial to the midpoint of the descending duodenum. Upon visualizing the ileocecocolic junction, the large bowel can be traced cranially. The ileum is a short segment in the dog and cat and has a thicker wall and more prominent submucosa in both species (Fig. 26-61). Animals in which the right intercostal approach may prove most useful for examining the colon include large- and giant-breed dogs, deep-chested dogs, and dogs with gaseous distention of the stomach, duodenum, or colon.[43]

In dogs with diarrhea caused by colitis, the colon may appear normal or thickened ultrasonographically and the lumen may be filled with gas or fluid. In general, mild to moderate forms of colitis as a result of diffuse inflammatory infiltration often show no ultrasonographic changes, and colonoscopy is the diagnostic method of choice in both dogs and cats. Colonic wall thickening can be either focal or diffuse and a result of either neoplastic, benign inflammatory or granulomatous infiltration. Focal thickening or intramural masses of the colonic wall are associated with both neoplasia and granulomata. Both MRI and CT are alternative methods for examining the pelvic region or determining the involvement of the colon and surrounding tissues, especially when space-occupying lesions are present in that region.

Gastrointestinal Hemodynamics

Doppler ultrasound provides a noninvasive method of assessing gastrointestinal hemodynamics in dogs.[44] Assessment of systolic and diastolic arterial blood flow in the large upstream arteries supplying the gastrointestinal tract is aimed at detecting abnormally increased or decreased resistance to flow to the intestinal capillaries during digestion. The resistive and pulsatility indices (RI and PI, respectively) have historically been used to infer the degree of resistance to flow in downstream capillary beds. A lowered index indicates lowered resistance to flow and vice versa. The spectral waveforms of the celiac (CA) and cranial mesenteric arteries (CMA) in normal dogs have been described as being of moderately high resistance in the fasted state (CMA RI = 0.803 ± 0.029, CA RI = 0.763 ± 0.025, CMA PI = 2.290 ± 0.311, CA PI = 1.962 ± 0.216).[44,45] The CA and CMA feed two different capillary beds. The CA supplies the upper gastrointestinal tract, including the stomach and pancreas, whereas the CMA supplies the small intestine. Reference values for RI and PI in normal dogs both pre- and postprandial have been published.[45] The method involves measuring the RI and PI in the CA and CMA percutaneously at fasting (time 0) and at 20, 40, 60, and 90 minutes postprandially. Vasodilation during digestion leads to decreasing Doppler indices and increasing diastolic blood flow velocity, which infers decreased resistance to flow in the downstream capillary bed of the gastrointestinal tract. The effect lasts 40 minutes in the CA and 60 minutes in the CMA, and increased resistance to flow can be demonstrated at 90 minutes postprandially in normal dogs during reversion to the fasting state.[44] Prolonged vasodilation at 90 minutes has been demonstrated in normal dogs eating a high-fat diet compared with high-protein and high-carbohydrate diets that have the same response as a normal maintenance diet.[44]

In dogs with proven food allergies and clinical symptomatology, dietary provocation with the allergen results in prolonged vasodilation at 90 minutes postprandially.[46] Abnormal hemodynamics also have been shown in dogs with chronic enteropathies from other causes.[47] This noninvasive ultrasound method shows promise for assessing hemodynamic pathophysiology in dogs with adverse reactions to food and chronic enteropathies as a consequence of other causes, but further studies are required to determine the value of this technique in larger clinical populations.

Endoscopic Ultrasound

Endoluminal ultrasound (EUS; Fig. 26-62A) was developed in humans to overcome problems associated with transabdominal imaging difficulties including large penetration depths, presence of intestinal gas, and obesity.[48] Ultrasound endoscopes integrate endoscopic and ultrasonographic principles, permitting the mucosal

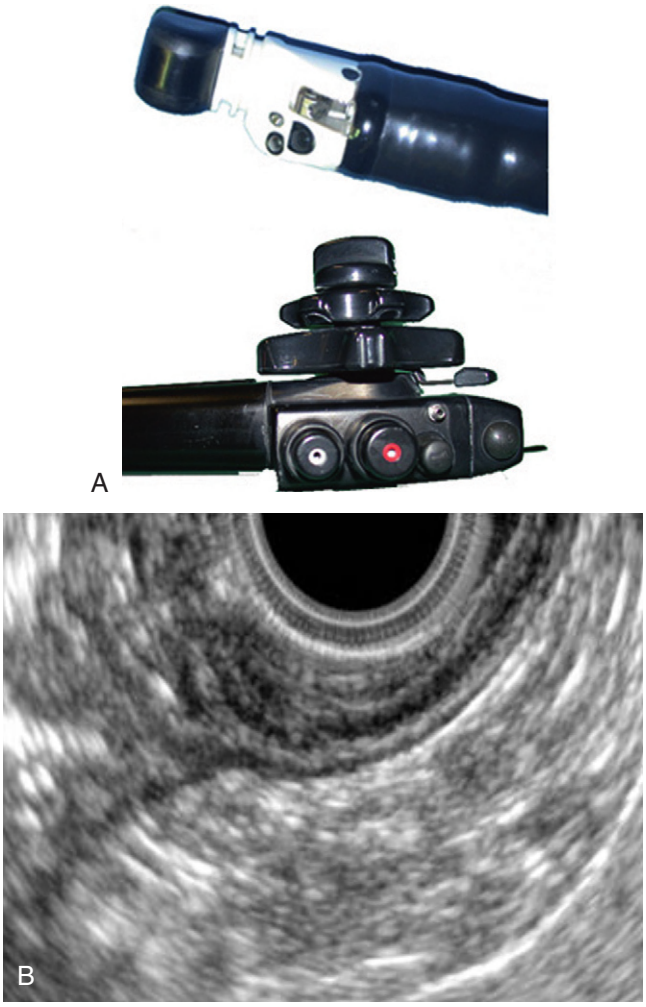


Figure 26-62 **A,** Ultrasound endoscope. The tip of the scope has a curved array transducer, optic, working channel, and a port for suction and fluid instillation. The handle has two dials, one for left–right movements and one for up–down movements of the ultrasound tip. The tip can be bent to 90 degrees. **B,** Endoscopic ultrasound image of the normal canine stomach.

surface to be visualized optically while the intestinal wall layering and contiguous organs are examined sonographically (Fig. 26-62B). In humans endoscopic ultrasonography is an accurate tool for staging malignant tumors of the esophagus, stomach, duodenum, rectum, major duodenal papilla, extrahepatic bile duct, and pancreas.[49]

A standardized EUS examination technique of the canine abdomen is possible by using five anatomic landmarks.[48] The upper gastrointestinal tract and cranial abdominal organs can be examined. EUS in dogs allows excellent visualization of the stomach from the distal esophagus to the proximal duodenum, independent of patient size, thoracic conformation, and body condition or luminal gas content. Because of the direct placement of the transducer on the stomach wall or with the aid of an inflated balloon, gastric wall layering can be visualized with excellent resolution (Fig. 26-63). EUS has potential for improving diagnostic capabilities for the gastrointestinal tract and assessment of wall layering when conventional transabdominal methods fail; however the equipment is costly and has limited availability.

Ultrasound-Guided Interventional Procedures

Ultrasound-guided fine-needle aspiration can be performed on the gastrointestinal wall and regional lymph nodes, as well as intestinal masses, to provide a cytologic diagnosis. Limitations to performing the procedure are size and location of the structure to be sampled, vascularity, and skill of the sonographer. Generally, a free-hand technique is indicated for fine-needle aspirations. However an ultrasound guide can also be used. Gastrointestinal masses are generally easier to sample than sites of mild intestinal wall thickening. The motility and mobility of the small intestine makes it more difficult to perform tissue aspiration. Furthermore, tissue aspiration of the intestinal wall to differentiate inflammatory from neoplastic disease has low sensitivity and specificity, and mucosal or full-thickness biopsy are still the best methods for differentiation of these two conditions.

For tissue aspiration of the gastrointestinal wall and regional lymph nodes, the skin should be clipped of hair, prepared aseptically, and the ultrasound probe should have a sterile cover. Alcohol is

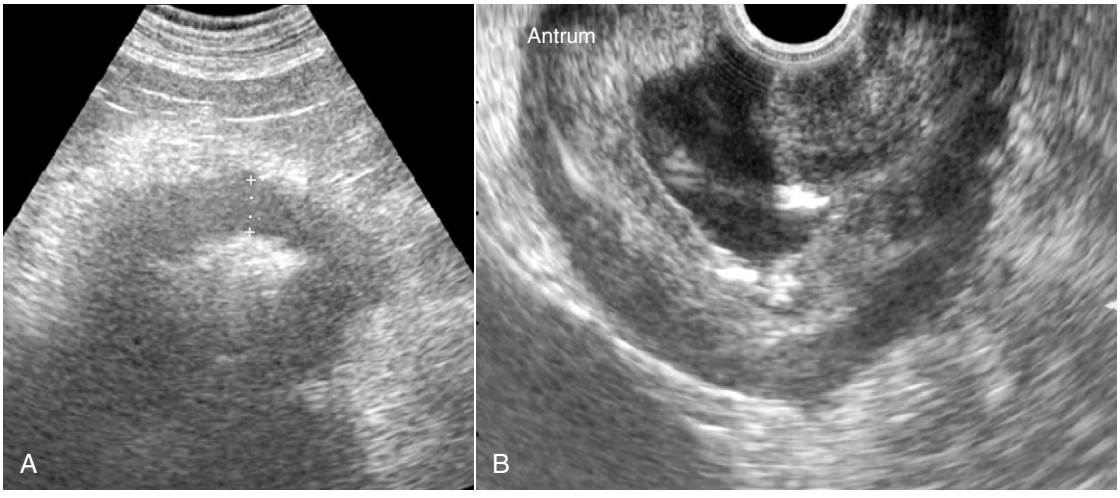


Figure 26-63 **A**, shows a transabdominal ultrasound image of the stomach in a dog with chronic vomiting and weight loss. There is poor visualization of the stomach wall as a consequence of the size of the dog and resulting poor resolution. **B**, The same dog examined with an echoendoscope. The wall can be well visualized and thickening with pseudolayering could be diagnosed. Histologic diagnosis: carcinoma.

generally adequate as a coupling agent. A 20- to 22-gauge (G), 2.5-inch needle is adequate in both small and large patients. For deeper-lying lymph nodes in larger animals, a spinal needle may be required. Tru-Cut biopsy for histology should generally be reserved for lesions greater than 2 cm in size. Biopsies can be performed with an 18 G spring-loaded or manual biopsy device.

ULTRASONOGRAPHIC IMAGING OF THE PANCREAS AND LIVER

Gabriela Seiler

Ultrasonographic Imaging of the Pancreas

Normal Ultrasonographic Anatomy

Technique

Ultrasonographic examination of the pancreas is challenging because of the small size and indistinct margins of the organ.[1] Additionally, deep-chested body conformation, overweight body condition, and a full gastrointestinal tract may hinder ultrasonographic visibility of the pancreas. However experience, excellent understanding of the anatomy, and use of different scan windows allow a thorough examination of the pancreas. Because it is small in size and superficially located, the highest possible transducer frequency should be used to assess the pancreas (usually 7.5 to 15 MHz).

Normal Pancreas

The normal pancreas has a fine texture and is iso- or slightly hypoechoic compared with the mesenteric fat.[2] Figure 26-64 shows schematic images of the canine and feline pancreas. In the dog, the right lobe of the pancreas is more easily seen than the body or the left lobe of the pancreas (Fig. 26-65A). It extends along the duodenum ventral and lateral to the portal vein. Because this right lobe of the pancreas is very superficial, using a high-resolution transducer (7.5 to 15 MHz) and application of minimal transducer pressure is important. In the transverse plane, the right lobe of the pancreas is triangular in shape and located between the duodenum and ascending colon. In contrast, the right lobe of the feline pancreas is very thin and not consistently or easily seen. In both species, the pancreatic body is found by following the right lobe of the pancreas cranially or by imaging it at the hilus of the liver just ventral to the portal vein and caudal to the pylorus. The left lobe of the pancreas is a small, triangular structure caudal to the greater curvature of the stomach in the dog, which is also located cranial to the transverse colon and cranioventral to the splenic vein. The left lobe of the feline pancreas is larger, often extending to the cranial pole of the left kidney (see Fig. 26-65B). Pancreatic thickness rarely exceeds 1 cm in dogs. Table 26-1 summarizes the normal dimensions of the feline pancreas. Pancreatic size and echogenicity have been reported to be unaffected by age in cats.[3] The pancreatic duct is not usually seen in dogs, but is visible in the center of the pancreatic parenchyma in cats (see Fig. 26-65B and Table 26-1). Ductal size increases with age, with a mean width of 0.13 cm (± 0.04 cm) in a group of older cats.[4] The pancreatic duct primarily enters the duodenum through the major (cats) or minor (dogs) duodenal papilla. In dogs the visible pancreaticoduodenal vessels may be used to confirm (i.e., blood flow can be confirmed by using color Doppler) identification of pancreatic tissue (see Fig. 26-65A).

Pancreatitis

Canine Pancreatitis

In the initial stage of severe acute pancreatic necrosis, the pancreas becomes thickened, hypoechoic and contains well-defined linear anechoic fissures and subcapsular stripes ("tiger-stripe" appearance), produced by pancreatic edema, which usually precedes necrosis

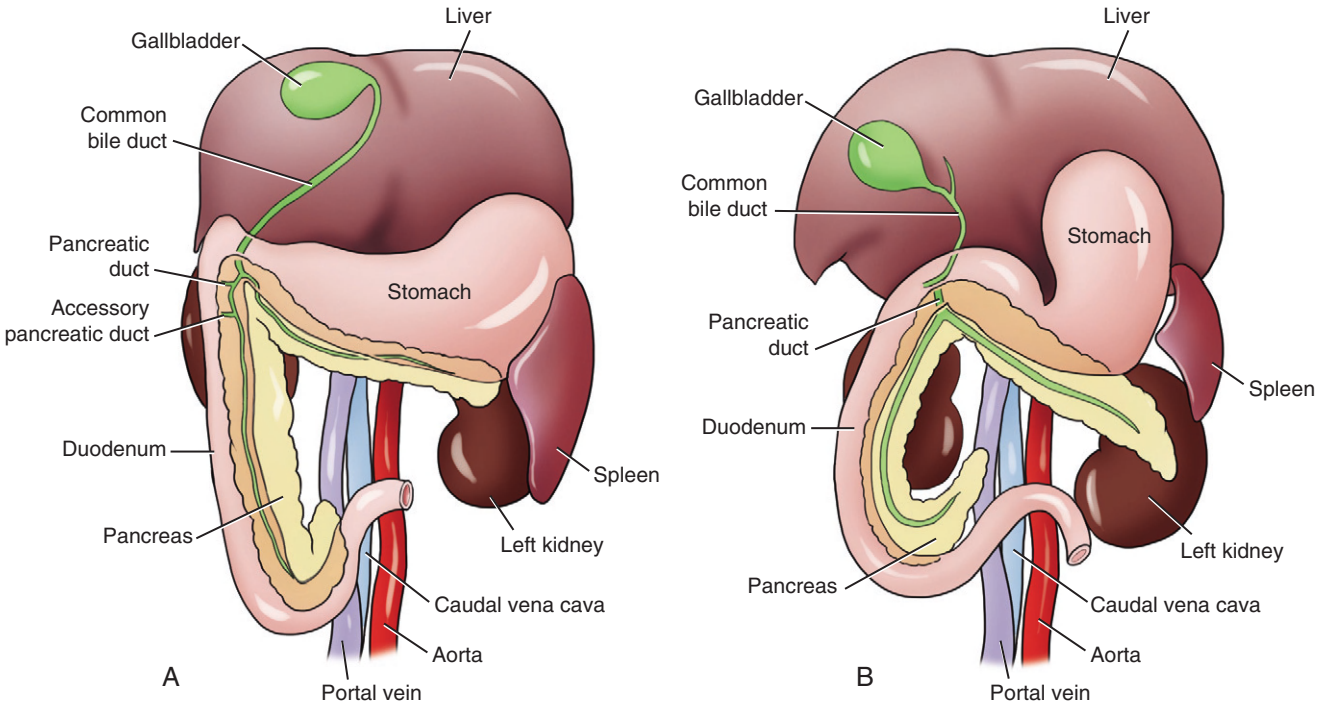


Figure 26-64 Schematic view of the ventral aspect of the (**A**) canine and (**B**) feline pancreas and adjacent organs.

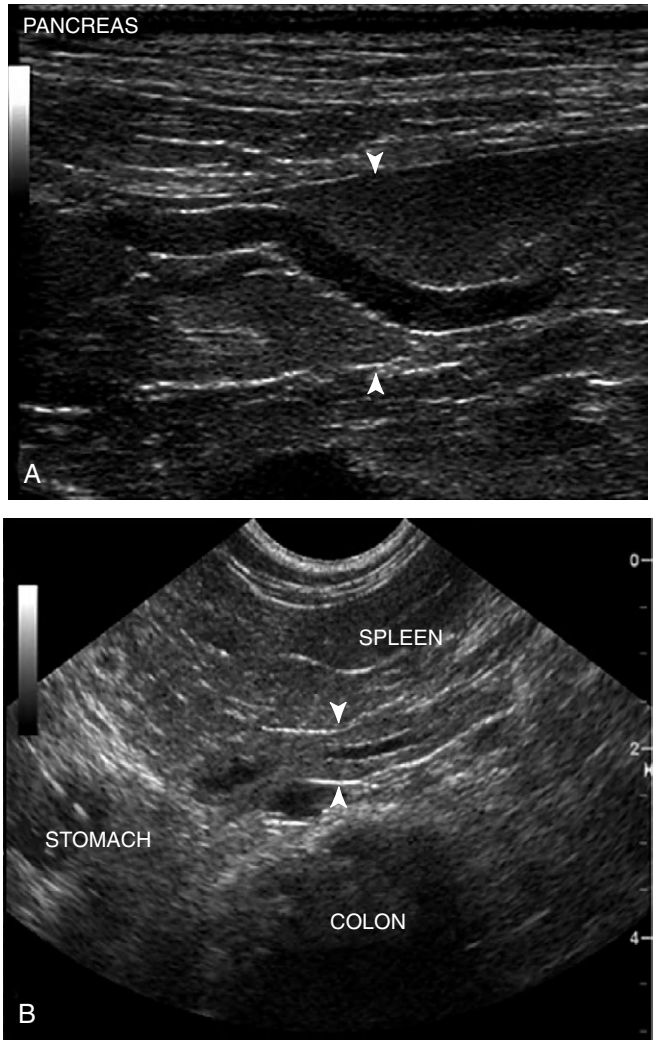


Figure 26-65 Long axis view of the (A) right lobe of a normal canine pancreas and the (B) left lobe of a normal feline pancreas. The pancreas is outlined by *arrowheads*. Note the smooth, uniform echogenicity and the regular surface of the normal pancreas. The echogenicity is slightly hypoechoic to the surrounding fat. The tubular hypoechoic structure in the center of the canine pancreas (**A**) represents the pancreaticoduodenal vein. The pancreatic duct in the center of the feline pancreas (**B**) has a similar appearance, but no flow is apparent when using color flow Doppler.

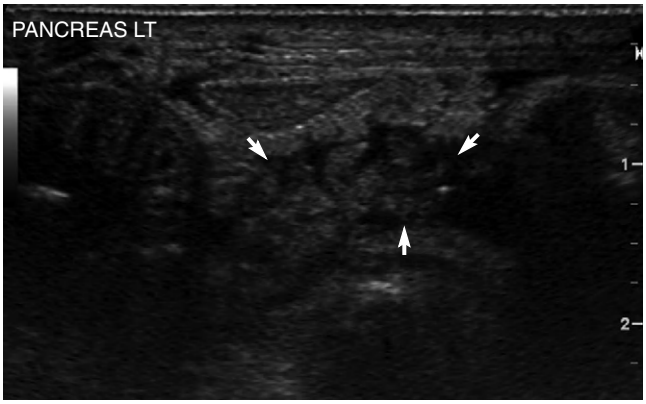


Figure 26-66 Long axis view of the left lobe of the pancreas of an 8-year-old female, spayed, Chihuahua dog with pancreatic edema. The pancreas is outlined by *arrows*. Note the hypoechoic fissures in the pancreatic parenchyma, resulting in a "tiger-stripe" appearance.

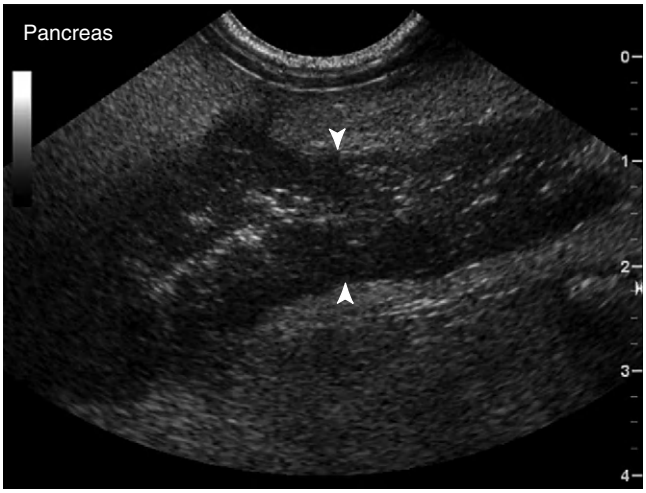


Figure 26-67 Long axis image of the right lobe of the pancreas of a 7-year-old male, castrated, Dachshund with acute pancreatitis. The pancreas is enlarged, hypoechoic, and irregularly outlined (*arrowheads*). Note the hyperechogenicity of the surrounding mesentery, indicating regional inflammation and peripancreatic fat necrosis. The hyperechoic area within the pancreas may represent fibrosis.

Table 26-1 Ultrasonographic Dimensions of the Normal Feline Pancreas

Anatomical Structure	Mean (mm)	Range (mm)
Left lobe	5.4	3.4 to 9
Body	6.6	4.7 to 9.5
Right lobe	4.5	2.8 to 5.9
Pancreatic duct	0.8	0.5 to 1.3

(Fig. 26-66). Irregular, hypoechoic tissue, representing necrotic, hemorrhagic pancreatic, and peripancreatic tissue is subsequently seen in the pancreatic region. The pancreas may not be seen distinctly or may appear mass-like.[5] Also, the pancreas is usually surrounded by hyperechoic peripancreatic mesentery, caused by inflammation, edema, and peripancreatic fat necrosis (Fig. 26-67). Other extrapancreatic changes include peritoneal effusion, a fluid- or gas-filled thick-walled atonic descending duodenum, pancreaticoduodenal lymphadenomegaly, and extrahepatic biliary obstruction. Mild acute pancreatic necrosis will have less-severe ultrasonographic changes; the pancreas is more distinct, contrasting with the slightly hyperechoic peripancreatic mesentery. Hyperechoic areas, which are consistent with fibrosis or saponification of fat may be present in the pancreas. Effusion, duodenal and biliary tract abnormalities are commonly absent. The sensitivity of ultrasound in the diagnosis of acute canine pancreatitis has been reported to be approximately 68%,[5] so an unremarkable ultrasonographic examination does not rule out pancreatitis. Pancreatic edema alone can also be encountered in canine patients with portal hypertension, hypoalbuminemia, or free peritoneal fluid in general.[6]

Feline Pancreatitis

Pancreatitis in cats is difficult to diagnose and the sensitivity of ultrasound for detection of feline pancreatitis is relatively low (most studies: 11% to 35%[7,8]; however, one small study reported a sensitivity of 80%).[9] The appearance of acute pancreatic necrosis and chronic nonsuppurative pancreatitis are not significantly different.[10] This is likely related to the fact that histologically, hemorrhage and edema, which are responsible for parenchymal hypoechogenicity, are less frequently seen in cats.[8] If present, an enlarged hypoechoic pancreas, hyperechoic peripancreatic tissue, free fluid, thickening of the gastric and duodenal wall, and extrahepatic bile duct obstruction all may lead to a diagnosis of pancreatitis. Concurrent diseases such as hepatic lipidosis, cholangitis, enteritis, diabetes mellitus, and interstitial nephritis are frequently present. Also, ultrasonographic evidence of hepatic lipidosis together with the presence of free fluid has been associated with acute pancreatitis.[11]

Chronic Pancreatitis

Chronic pancreatitis is characterized by interstitial fibrosis with acinar atrophy and often lymphoplasmacytic infiltrates. Ultrasonographic signs have not been well described and include a heterogeneous echogenicity, mineralizations, an irregular surface, and widening of the pancreatic duct. This form of pancreatitis is very difficult to differentiate from other pancreatic diseases, such as nodular hyperplasia.[2]

Cystic Pancreatic Lesions

Pancreatic abscesses or pancreatic pseudocysts are uncommon sequelae of pancreatitis. Both appear ultrasonographically as fluid-filled cavities with distal acoustic enhancement, but abscesses may also have a mass-like appearance (Fig. 26-68). Pancreatic pseudocysts are fluid accumulations within or adjacent to the pancreas with a capsule of granulation/fibrous tissue, which is thought to be the result of pancreatic duct rupture. Differentiation between a pancreatic abscess and a pseudocyst requires cytology or even histopathology.[12] Small cystic lesions without other pancreatic abnormalities are either congenital cysts or retention cysts caused by obstruction and focal dilation of the pancreatic duct. A rare anatomical variation with unknown clinical significance is called pancreatic "pseudobladder," an abnormal distention of the pancreatic duct.[13]

Pancreatoliths

Calculi, recognized as hyperechoic structures with distal acoustic shadowing, are occasionally seen in the pancreatic duct and are suggestive of chronic or intermittent pancreatitis.

Pancreatic Neoplasia

Pancreatic Carcinoma

Pancreatic adenocarcinomas arising from exocrine tissue or excretory ducts are rare in dogs and cats, but are highly malignant. The ultrasonographic findings are similar to pancreatitis: the pancreas is hypoechoic and enlarged, only occasionally a mass can clearly be delineated (Fig. 26-69). Metastasis disease to the liver, lymph nodes, and lungs is common and frequently already present at the time of diagnosis. Pancreatic adenocarcinoma is the most common primary pancreatic tumor, but the incidence of metastatic tumors appears to outweigh primary pancreatic tumors in both dogs and cats, and differentiation from nodular hyperplasia is difficult. Single masses larger than 2 cm have been reported to be more consistent with neoplasia.[14] Peripancreatic lymphadenopathy is commonly present but can be seen with various other abdominal diseases.

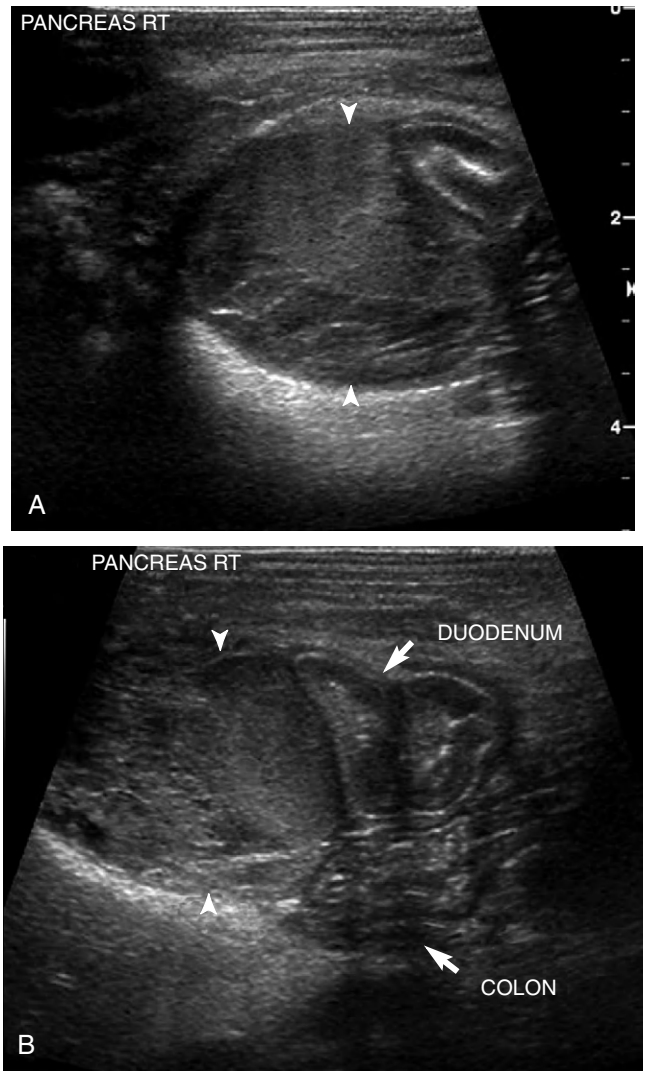


Figure 26-68 **A,** Transverse ultrasound image of the right cranial abdomen of an 8-year-old male, castrated, Miniature Schnauzer presented for vomiting of several days duration and a painful abdomen. In the right lobe of the pancreas there is a round cavitary lesion with echogenic material (*arrowheads*). The remainder of the right pancreatic lobe and the pancreatic body show signs of severe pancreatitis. **B,** The distortion of the shape of the adjacent duodenum and colon indicates presence of adhesions. Pancreatic abscessation and extensive adhesion formation were confirmed during surgical exploration.

Endocrine Tumors of the Pancreas

Gastrinomas, glucagonomas, and insulinomas are rare in dogs and cats. Insulinoma is the most common tumor type of this group and affects dogs more frequently than cats. If visible, pancreatic insulinomas appear ultrasonographically as well-defined hypoechoic round or lobulated nodules (Fig. 26-70). Nodules in the left lobe are harder to identify because of adjacent gastric and colonic gas. Metastatic disease is often present in the liver, seen as hypoechoic nodules or target lesions, and in the regional lymph nodes. Small pancreatic insulinomas, however, are poorly delineated from the pancreatic tissue and are not always visible ultrasonographically. The sensitivity of ultrasound for detection of primary lesions is quite low (35% in one study).[15]

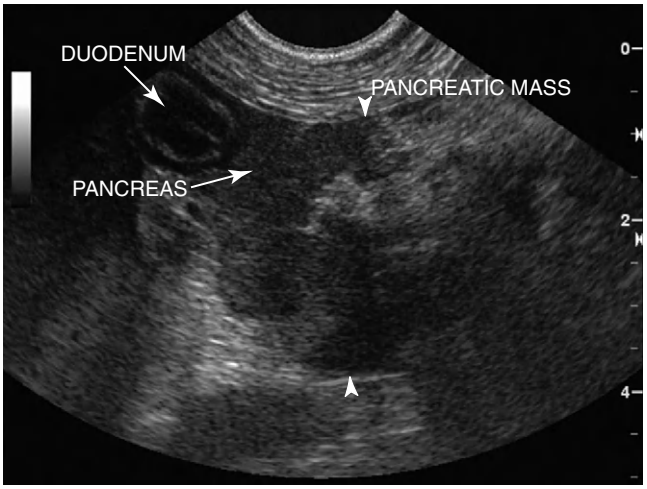


Figure 26-69 Transverse image of the right lobe of the pancreas of a 13-year-old male, castrated, Labrador Retriever. The duodenum is seen in cross-section in the *top left corner* of the image; the hypoechoic tissue next to it is the pancreas, which expands into a hypoechoic lobulated mass (*arrowheads*). The mass contains hyperechoic areas with some distal shadowing, likely representing some degree of dystrophic mineralization and necrosis. Pancreatic carcinoma was diagnosed histopathologically.

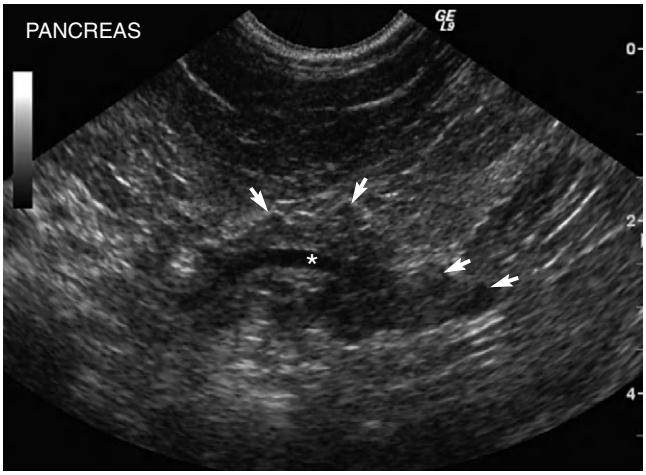


Figure 26-71 Nodular hyperplasia of the left pancreatic lobe in a 12-year-old Domestic Shorthair cat. The image shows a long axis view with the cranial aspect to the left. The pancreas is irregular in outline and multiple hypoechoic nodules are visible throughout the parenchyma (some are indicated with an *arrow*). None of the nodules were larger than 1 cm. The pancreatic duct is visible in the center of the pancreas (*asterisk*) and is normal in size for an older cat.

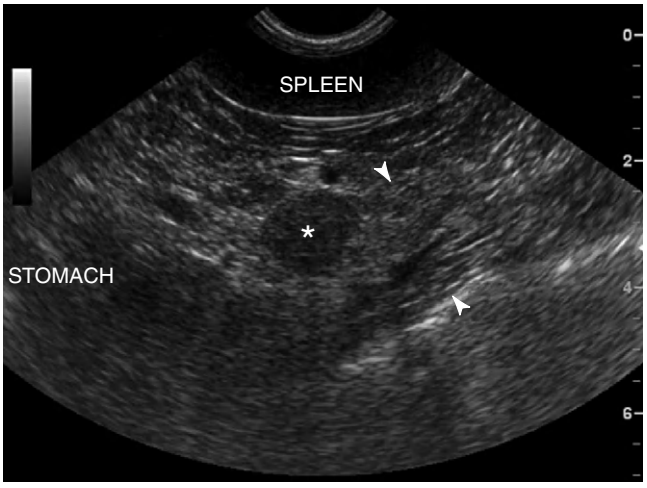


Figure 26-70 Long axis view of the left lobe of the pancreas of a 10-year-old female, spayed, mixed-breed dog presented with severe hypoglycemia. The pancreas is outlined by *arrowheads*. There is a 1-cm round, hypoechoic nodule present arising from the pancreatic tissue (*asterisk*). Histopathology confirmed the diagnosis of an insulinoma.

Nodular Hyperplasia

Nodular hyperplasia may be seen in up to 80% of older animals. Multifocal hypoechoic nodules may lead to an enlarged, hypoechoic, and irregularly outlined pancreas (Fig. 26-71). The nodules rarely exceed a diameter of 1 cm but can be poorly delineated. Fine-needle aspirates or pancreatic histopathology may be necessary to differentiate them from pancreatic neoplasia.[14]

Pancreatic Insufficiency

The ultrasonographic appearance of exocrine pancreatic insufficiency has not been described in dogs, but in cats it may lead to inhomogeneous pancreatic parenchyma or pancreatic nodules.[4] However in both species a diagnosis of EPI cannot be based on abdominal ultrasound alone and the functional reserve of the pancreas must be assessed with laboratory testing.

Fine-Needle Aspirate and Biopsy of the Pancreas

The main indication for fine-needle aspirates of the pancreas is the presence of a mass or cystic lesion. An ultrasound-guided tissue core biopsy is only recommended for larger masses. Pancreatitis as a complication has not been reported in cats or dogs, but has been described in humans; however, the complication rate for pancreatic fine-needle aspirates is very low.[16]

Contrast-Enhanced Ultrasound of the Pancreas

Ultrasound contrast media increase the sensitivity of ultrasound to image the blood supply to the pancreas. In human patients, contrast-enhanced ultrasound allows a distinction between malignant and focal inflammatory lesions and also the differentiation between hypoperfused adenocarcinomas and heavily vascularized neuroendocrine tumors.[17] The normal enhancement pattern of the feline pancreas has been described, and increased vascularity and perfusion have been reported for cats with pancreatitis.[18]

Endoscopic Ultrasound of the Pancreas

EUS is a potentially valuable method for investigation of the pancreas, as the ultrasound probe integrated into the endoscope is positioned within the stomach and therefore in close vicinity of the pancreas.[19] It has been suggested that EUS is superior in delineating focal nodular lesions, as well as imaging and measuring the right pancreatic lobe. However it should be noted that in one study findings on EUS were not different between healthy cats and cats with pancreatitis.[20]

Ultrasonographic Imaging of the Liver

Technique

Ultrasound provides information about the structure of the liver parenchyma, the biliary tract, the portal and hepatic vasculature, as

well as an opportunity to perform guided aspirates or biopsies. Consequently, ultrasound should be performed in patients with suspected hepatic disease even if no abnormalities are seen radiographically. Transducer choice largely depends on patient size; the highest possible frequency to still penetrate the depth of the parenchyma should be used (5 to 10 MHz). Most of the liver parenchyma can be imaged from an acoustic window just caudal to the xiphoid process. Subcostal and intercostal windows on both sides are then used to image the dorsal aspects of the liver. Curvilinear or sector probes are best for imaging these subcostal or intercostal windows. For a thorough interrogation of the hepatic vasculature a systematic approach and various image planes using grayscale imaging and color and spectral Doppler are used, protocols for which have been described in detail elsewhere.[21,22]

Normal Liver and Biliary Tract

Criteria for determining normal liver size ultrasonographically have not been well established. Hepatomegaly should be suspected if the liver lobes extend caudally well beyond the xiphoid process or if there is an increased distance between the diaphragm and the stomach. Similarly, microhepatia is suspected if the distance between the stomach and the diaphragm is decreased. Marginal changes in liver size require confirmation with abdominal palpation and conventional radiography.

The normal hepatic parenchyma has a homogenous texture, which is slightly coarser and less echogenic than the spleen. Echogenicity of the right renal cortex is less useful for comparison, as there is a large individual variability in the echogenicity of the renal cortex. The falciform fat is normally hyperechoic to the liver parenchyma in cats. The normal liver capsule is smooth and hyperechoic with sharp liver lobe margins.

The normal gallbladder has a very thin, smooth, and slightly hyperechoic wall, if it is visible at all. In cats, gallbladder wall thickness should be less than 1 mm.[23] The bile duct is rarely visible in dogs, whereas in cats it is usually seen and can be tortuous. Common bile duct diameter should not exceed 3 mm in dogs and 5 mm in cats.[24] In dogs, presence of biliary sludge is common and usually not associated with hepatobiliary disease.[25]

The portal vein is formed by the cranial and caudal mesenteric veins and the splenic vein, and is joined by the gastroduodenal vein from the right side just caudal to the porta hepatis. The diameter of the portal vein is largest at the porta hepatis. It is best visualized either from a ventral or a right intercostal approach. The normal ratio of the portal vein to the aorta ranges between 0.7 and 1.25.[26] Blood flow within the main portal vein is directed toward the liver with a normal mean velocity of 15 to 20 cm/sec in dogs and 10 to 18 cm/sec in cats.[26] The portal vein then divides into several branches that taper toward the periphery of the liver lobes. The intrahepatic portal veins can be distinguished from the hepatic veins by their hyperechoic wall structure.

Diffuse Liver Disease

A diffuse change in hepatic echogenicity usually represents diffuse infiltrative disease. However ultrasonographic findings are nonspecific and some diffuse hepatopathies may not be associated with any alterations in liver echogenicity. Attempts have been made to correlate ultrasonographic criteria with different groups of diffuse liver disease, but without much success.[27,28] The diagnostic accuracy for diffuse liver disease by abdominal ultrasound ranges between 36.5% and 39.1% in dogs and 54.6% and 57.7% in cats. The accuracy for differentiation between normal and diffusely abnormal hepatic parenchyma is also highly variable and ranges from 0% to 80%.[28] Consequently, histology is necessary for accurate diagnosis of diffuse liver disease.

Hypoechoic Liver

Decreased hepatic echogenicity (Fig. 26-72) has been reported with diffuse neoplastic infiltration, such as lymphoma or leukemia, but also with amyloidosis, acute hepatitis, or cholangitis in cats.[27] Right-heart failure with secondary hepatic congestion leads to hepatic hypoechogenicity, but also is characterized by distended hepatic veins and ascites. Focal hypoechogenicity or heterogeneity of a single liver lobe with a "lacy" pattern of the parenchyma and focal peritoneal effusion is consistent with a liver lobe infarction (Fig. 26-73) or liver lobe torsion. In this case, Doppler examination will reveal decreased blood supply and/or the presence of thrombi.[29]

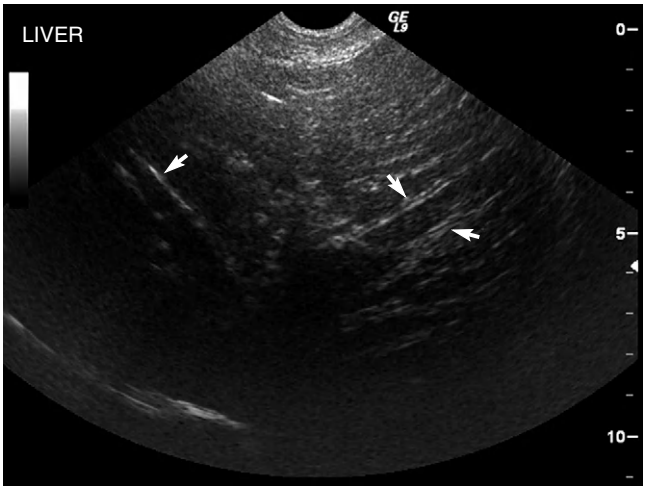


Figure 26-72 Long axis view of the liver of a 7-year-old Labrador Retriever dog with leptospirosis and acute hepatitis. The hepatic parenchyma is hypoechoic in this image, evidenced by the markedly hyperechoic portal vessel walls (*arrows*) compared with the surrounding liver parenchyma.

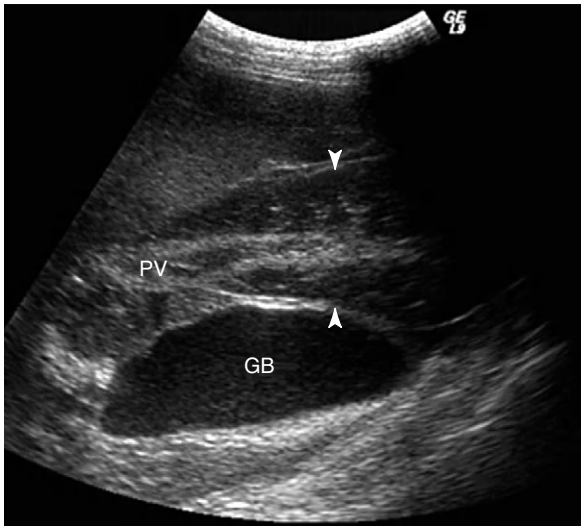


Figure 26-73 Acute infarction of the right medial liver lobe (between *arrowheads*). The infarcted liver lobe is hypoechoic compared with the adjacent normal right lateral liver lobe. The portal vein branch entering the affected lobe contains hyperechoic material; blood flow could not be detected with Doppler ultrasound. The infarcted lobe was surgically removed.

Hyperechoic Liver

A diffusely hyperechoic liver parenchyma is associated with a poor delineation of the walls of the portal vein and can give a false impression of a reduced number of hepatic vessels. Increased beam attenuation in the deeper portions of the hepatic parenchyma is consistent with fatty infiltration of the liver either caused by obesity, hepatic lipidosis (in cats), or diabetes mellitus (Fig. 26-74).[30] Other differentials for a diffusely hyperechoic and enlarged liver are steroid hepatopathy and diffuse hepatic lymphoma. A hyperechoic, but small and nodular liver is indicative of chronic liver disease (e.g., fibrosis, cirrhosis) (Fig. 26-75).

Mixed Hepatic Echogenicity

Neoplastic processes, such as metastatic disease or neoplastic round cell infiltrates, can lead to a generalized inhomogeneous echotexture. Other differentials include chronic liver disease of various etiologies with associated nodular hyperplasia. During early stages of chronic liver disease the liver may appear ultrasonographically normal, but as the disease progresses to cirrhosis, the hepatic surface tends to become irregular, and the parenchyma becomes heterogenic, with hyperechoic areas and hypoechoic regenerative nodules (see Fig. 26-75). Presence of microhepatia, ascites, and extrahepatic shunts is usually a sign of chronic "end-stage" liver disease.[31,32] Hepatocutaneous syndrome in dogs is characterized by a "honeycomb" appearance in which hypoechoic nodules are surrounded by a network of hyperechoic tissue.[33] The ultrasonographic appearance of hepatic amyloidosis in cats has been described as a diffuse process with heterogeneous echogenicity of the parenchyma with hypoechoic and hyperechoic foci. This process may also lead to spontaneous rupture of the liver.[34] Hepatic rupture should be suspected in patients with hemoabdomen and a focal area of overall hypoechoic but heterogeneous hepatic parenchyma.

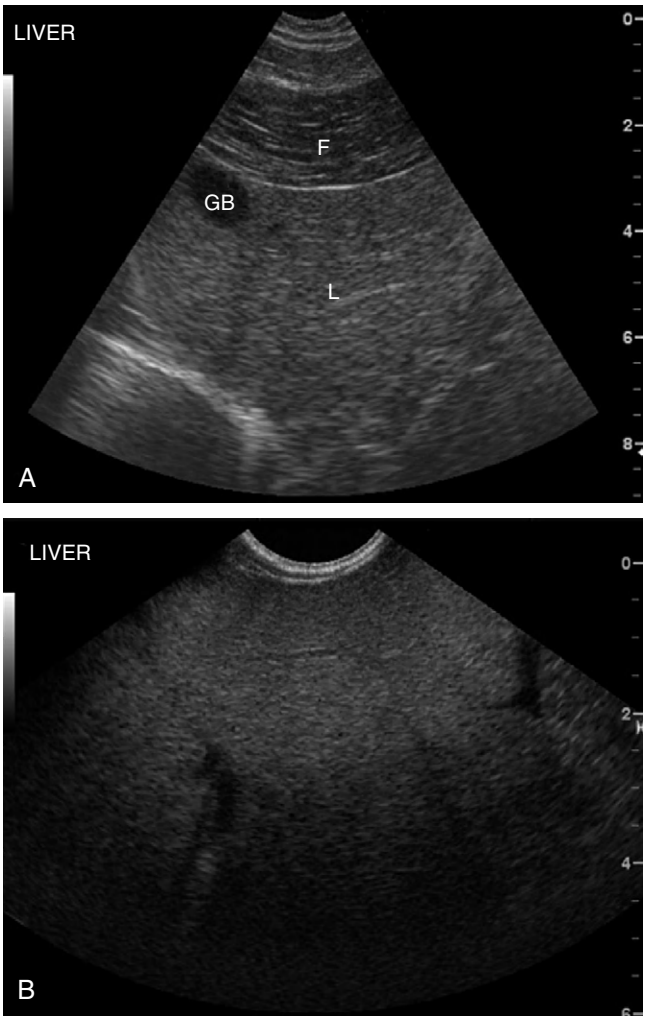


Figure 26-74 Ultrasonographic images of two different cats diagnosed with hepatic lipidosis. A, The liver (*L*) is hyperechoic compared with the falciform fat (*F*). The gallbladder (*GB*) is also labeled. **B,** The ultrasound beam is attenuated in the deeper portions of the liver, caused by the increased absorption and reflection of the sound beam as it penetrates the fatty tissue.

Focal and Multifocal Liver Disease

Masses and Nodules

Differential diagnoses for a solitary hepatic mass include primary hepatic neoplasia, focal hyperplasia, hematoma, or abscess, all of which can have a similar appearance and fine-needle aspiration or biopsy is required for a definitive diagnosis (Fig. 26-76). Hepatocellular adenomas and carcinomas have a similar appearance and typically present as solitary heterogenic or hyperechoic masses, often with a cystic component. Primary hepatic neoplasia can also present as multifocal hyperechoic or mixed-echoic nodules.[35] Histologically, nodular hyperplasia consists of hepatocytes (often vacuolated), blood-filled sinusoids, and areas of atrophic and necrotic tissue and most commonly results in multifocal uniformly hypoechoic nodules, which may be cavitated. Because of its similarity to the normal hepatic parenchyma, nodular hyperplasia is not always detected ultrasonographically. In contrast, extensive necrosis, fatty degeneration, or sinusoidal dilation may all result in heterogenic masses with or without cavitations, which may have a similar ultrasonographic appearance to hepatic neoplasia.[36] Appearance of metastatic liver disease ranges from hypoechoic to hyperechoic nodules surrounded by a rim of hypoechoic tissue (so-called target lesions). However there are also benign lesions that are reported to present as target lesions, including nodular hyperplasia, pyogranulomatous hepatitis, and chronic active hepatitis.[37]

Cystic Liver Lesions

Solitary or multifocal thin-walled cysts with a normal appearance of the surrounding hepatic parenchyma are occasionally seen within the hepatic parenchyma and often represent biliary cysts or may be

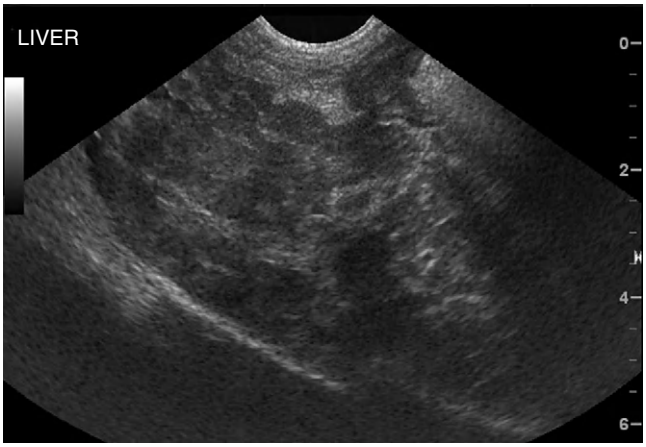


Figure 26-75 Long axis image of the liver of a 12-year-old male Beagle with liver failure. The liver is small and irregular. The parenchyma contains multiple hypoechoic nodules surrounded by hyperechoic tissue, consistent with cirrhosis.

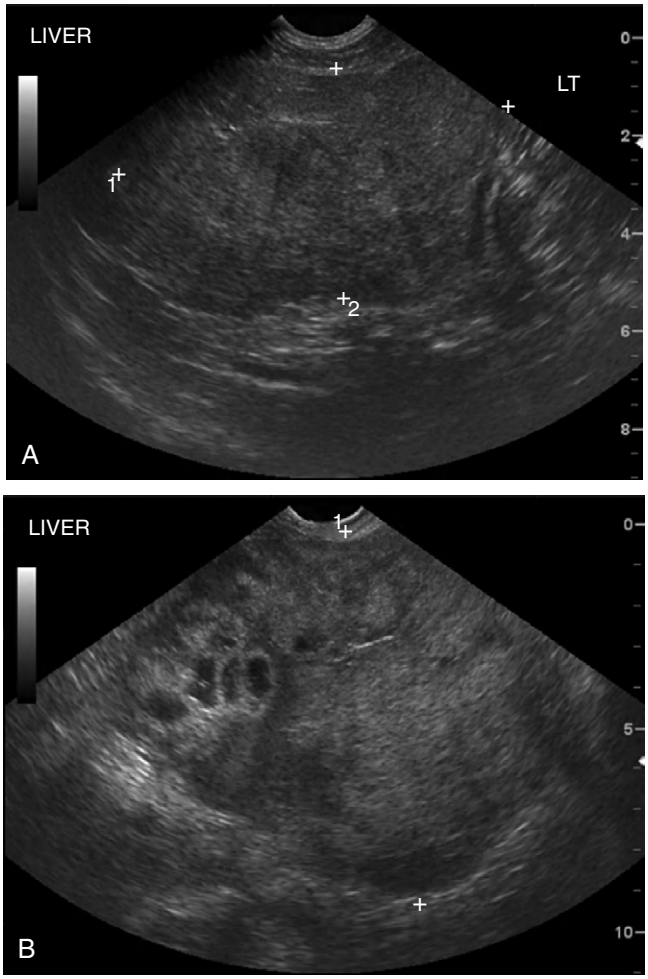


Figure 26-76 Long axis view of the liver of a (A) 12-year-old Bichon Frise with a hepatocellular adenoma and (B) a 13-year-old mixed breed dog with a hepatocellular carcinoma. The masses are outlined between the *cross-marks*. Note the similar appearance of the two masses: both are solitary, heterogenic, and with a lobulated appearance. The hepatocellular carcinoma also contain a few cystic areas as well.

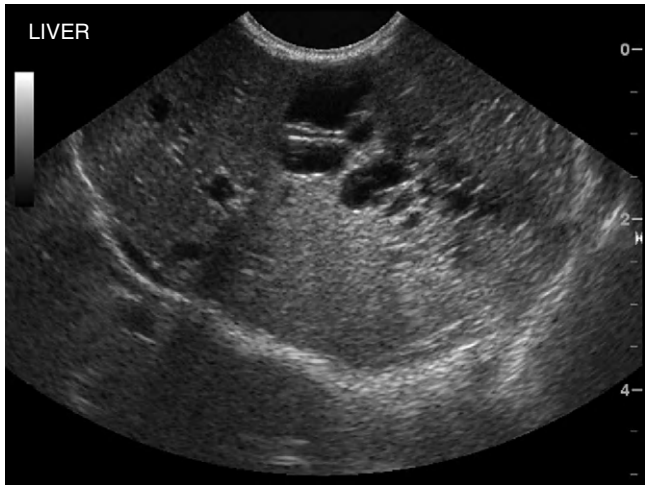


Figure 26-77 Multiple cystic lesions in the liver of an 8-year-old Domestic Shorthair cat with biliary cystadenomas. The hepatic parenchyma is hyperechoic distal to the cysts, consistent with acoustic enhancement.

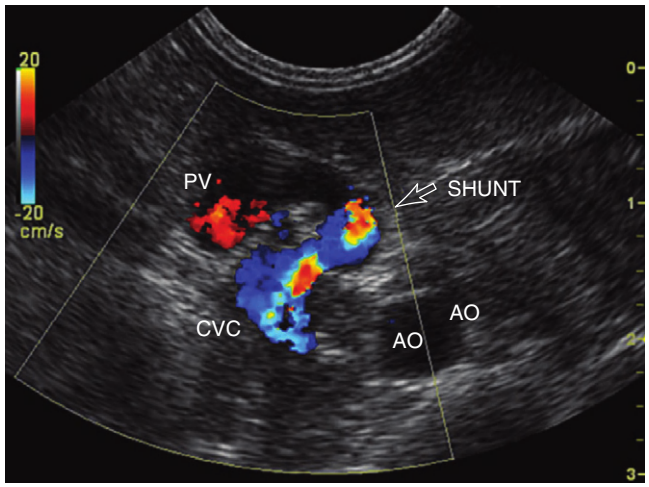


Figure 26-78 Transverse view of the right craniodorsal abdomen (dorsal to the right). The aorta (AO), caudal vena cava (CVC), and portal vein (*PV*) are labeled. A curvilinear shunt vessel connects the portal vein with the caudal vena cava (*arrow*).

a part of a polycystic disease process affecting the kidneys and the liver. Both types of cysts usually contain bile, and fine-needle aspiration can be used to differentiate them from other cystic liver lesions. Biliary cystadenomas are benign solitary or multifocal tumors mainly seen in older cats. The ultrasonographic appearance is variable, ranging from multiloculated masses composed of thin-walled cysts, hyperechoic or mixed echoic masses with cystic components (Fig. 26-77).[38] The hyperechoic portions of a mass are often composed of clusters of tiny cysts that are seen histologically but are not apparent ultrasonographically. The cysts contain clear or mucinous fluid when aspirated. Hepatic abscesses are more commonly solitary than multifocal in dogs and cats. The fluid-filled center of the abscess can appear echogenic if it contains a large amount of cellular debris, but can also appear anechoic. Similarly, not all abscesses have a thick wall. In some instances the wall is poorly discernible and the abscess has to be differentiated from other cystic lesions cytologically. Presence of gas within the lesion facilitates the diagnosis of an abscess.[39,40] Other differential diagnoses for cystic lesions include parasitic disease such as liver flukes or hydatid disease, which appears as thick-walled nodules with an echogenic center and occasional mineralizations. Echinococcosis is characterized by large cavitary masses predominantly in the portal hepatic region. The cysts have irregular walls with some echogenic material and possibly small mineralizations.[41] Hematomas, nodular hyperplasia, metastatic disease, or primary liver tumors all may be cavitated, and fine-needle aspiration or biopsy is required for definitive diagnosis.

Vascular Disorders of the Liver

Portosystemic Shunts

Portosystemic shunts can be congenital or acquired, and congenital shunts can be further differentiated into intra- and extrahepatic portosystemic shunts (Fig. 26-78). In patients with an intrahepatic shunt, the left or right portal branches run cranially and enter the caudal vena cava or the left hepatic vein at the level of the diaphragm. Blood flow in the main portal vein is often increased. Extrahepatic portosystemic shunts originate most commonly from

the splenic vein or left gastric vein and enter the caudal vena cava or the azygos vein. It has previously been reported that a PV:AO ratio of equal to or greater than 0.8 can be used to rule out an extrahepatic portosystemic shunt in both dogs and cats.[26] The portal blood flow at the hepatic hilus is often reduced as most of the portal blood is directed into the shunt vessel. Multiple acquired portosystemic shunts should be suspected if the left gonadal vein entering the left renal vein is dilated and if clusters of tortuous vessels are observed in the area of the left renal vein.[42]

Arteriovenous Fistula

Ultrasonographic findings in patients with arteriovenous fistulas include a dilated portal venous system with hepatofugal, pulsatile venous flow. Most animals have a reduced liver size and peritoneal effusion. Acquired extrahepatic portosystemic shunts as a consequence may also be observed.[43]

Portal Hypertension

Chronic liver diseases such as cirrhosis, surgical occlusion of a single shunt vessel, portal vein thrombosis, or arteriovenous fistulas can cause portal hypertension. Portal vein flow velocity is reduced below 10 cm/sec or may even be reversed. Persistent portal hypertension leads to opening of portosystemic collaterals or acquired portosystemic shunting.

Portal Vein Thrombosis

Portal vein thrombi are usually visualized as hyperechoic intraluminal structures in the main portal vein or one of the portal vein branches. Chronic thrombi may be mineralized. Doppler examination is used to determine if there is residual flow around the thrombus, and if there is any evidence of portal hypertension. Focal dilation of the vessel at the level of the thrombus is indicative of a tumor thrombus.[44]

Biliary Tract Disease

The main indication for the ultrasonographic evaluation of the biliary tree is to determine possible causes for icterus and to evaluate the gallbladder for signs of infection, cholelithiasis, or mucocele formation.

Cholecystitis

The main finding in patients with cholecystitis is a thickened gallbladder, and sometimes also a thickened cystic or common bile duct wall. Transhepatic fine-needle aspiration of the bile for culture and sensitivity testing has been shown to be safe and yield a significantly higher percentage of positive cultures than cultures of hepatic tissue.[45]

Cholelithiasis

Choleliths, a concretion of cholesterol, calcium, and bilirubin are uncommon in dogs and cats and are asymptomatic in many cases. However, they can also be a cause or consequence of bile duct obstruction. Calculi present as round or irregular hyperechoic structures with distal shadowing. Although rarely reported, bile duct obstruction secondary to choleliths can lead to bile duct rupture. In these cases, the choleliths may be found in the peritoneal cavity.

Mucocele

Mucinous gland hyperplasia and inspissation of bile can lead to formation of biliary mucoceles. The ultrasonographic appearance of the gallbladder is characteristic in these cases. The enlarged gallbladder is filled with immobile bile in a stellate, striated, or mixed pattern (Fig. 26-79). The gallbladder wall in patients with a biliary mucocele is prone to rupture and surgery for removal of the gallbladder is often indicated.[46,47] Evidence of gallbladder rupture includes focal peritonitis characterized by echogenic fluid and hyperechoic inflamed tissue in the gallbladder fossa of the liver, a discontinuous gallbladder wall, and in rare cases a clump of inspissated bile that may be observed free in the peritoneal cavity.[48]

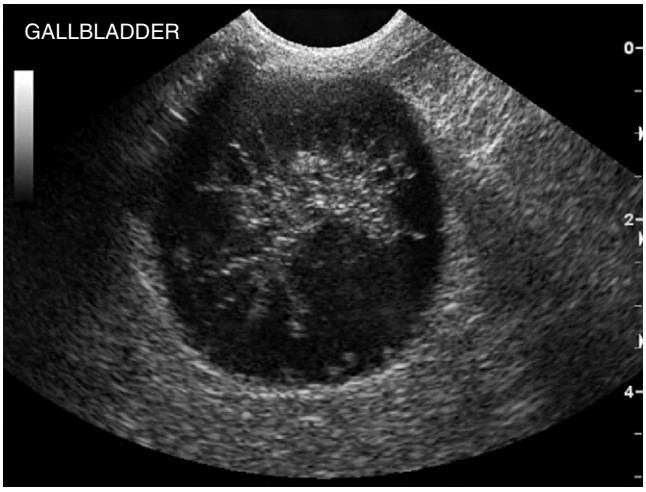


Figure 26-79 Gallbladder mucocele in a 14-year-old Bichon Frise presented because of several days of vomiting and anorexia. The gallbladder is filled with hypoechoic material peripherally and hyperechoic striations centrally, resulting in a "stellate" appearance.

Biliary Tract Neoplasia

Neoplasia of the gallbladder is extremely rare, and only a few cases of adenocarcinoma and neuroendocrine carcinoma have been reported,[49] but biliary adenomas and adenocarcinomas are more common, particularly in the cat.[50]

Bile Duct Obstruction

The most common cause for biliary tract obstruction is inflammation, often secondary to pancreatitis, cholelithiasis, or neoplasia. Bile duct enlargement is the main indicator of extrahepatic biliary obstruction. In cats with extrahepatic bile duct obstruction, 97% were found to have a common bile duct diameter greater than 5 mm (Fig. 26-80).[51] Dilation of the gallbladder and/or intrahepatic bile ducts is seen in a percentage of animals and is likely related to location, duration, and severity of the obstruction. Nevertheless, the appearance of an enlargement of the biliary system always has to be interpreted in light of clinical and blood chemistry findings, as common bile duct dilation can persist after a previous obstruction. Sequential measurement of serum bilirubin concentration should be monitored to determine if an obstruction is currently present.

Fine-Needle Aspiration and Ultrasound-Guided Biopsy

Fine-needle aspirates or biopsy of the liver is required for a definitive diagnosis of most hepatic lesions. Fine-needle aspiration is easy to perform and associated with a low risk for complications. The accuracy of cytologic diagnosis is limited, although agreement between histopathology and cytology was found in only 30% of canine and in 51% of feline liver samples in one study.[52] Agreement between the morphologic diagnosis determined from needle biopsies and wedge biopsies was reported to be between 56% and 67% in another study.[53]

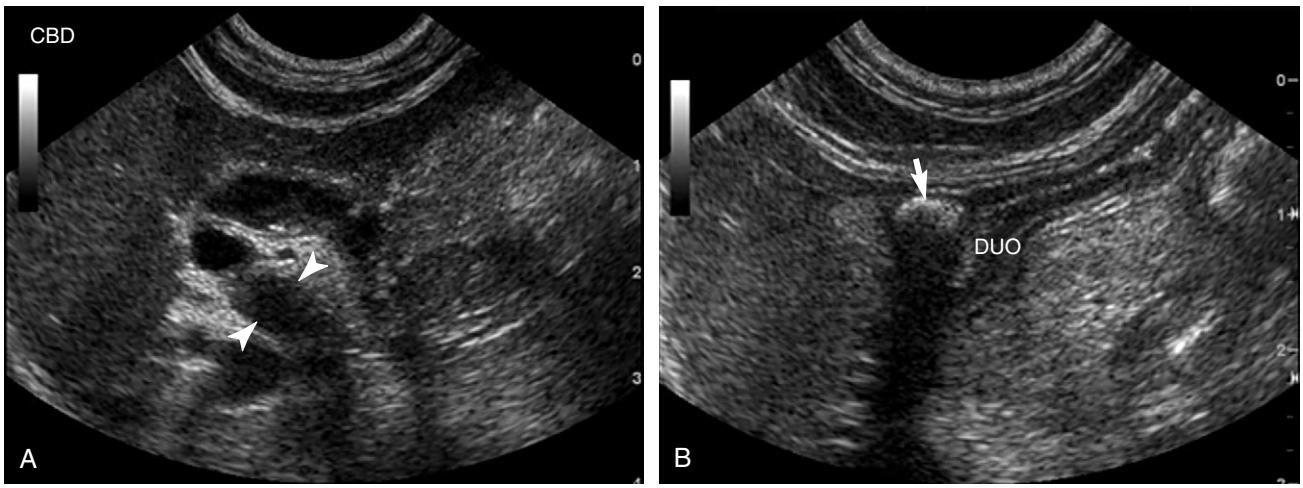


Figure 26-80 Common bile duct obstruction in a 12-year-old Domestic Shorthair cat with icterus. A, The bile duct is enlarged with a diameter of 8 mm (outlined by *arrowheads*). **B,** At the level of the papilla duodeni, a round hyperechoic structure with distal shadowing (*arrow*) could be seen lodged in the common bile duct and papilla. A cholelith was removed surgically.

Contrast-Enhanced Ultrasound

Unlike other contrast agents used for diagnostic imaging, microbubble ultrasound contrast medium does not leave the vascular system and is therefore useful to assess hepatic perfusion and vascularity. Lesion detection is improved after contrast application, and differentiation of benign and malignant hepatic nodules is possible with a high accuracy.[54,55] Benign liver nodules have a similar blood supply and vascularity and therefore show similar enhancement compared with the normal liver parenchyma, whereas malignant nodules lack the extensive venous sinusoids and remain relatively hypoperfused at peak liver enhancement (Fig. 26-81). When using contrast-enhanced ultrasound, the accuracy for detecting metastatic liver disease was very high (97% to 100%).[54,55]

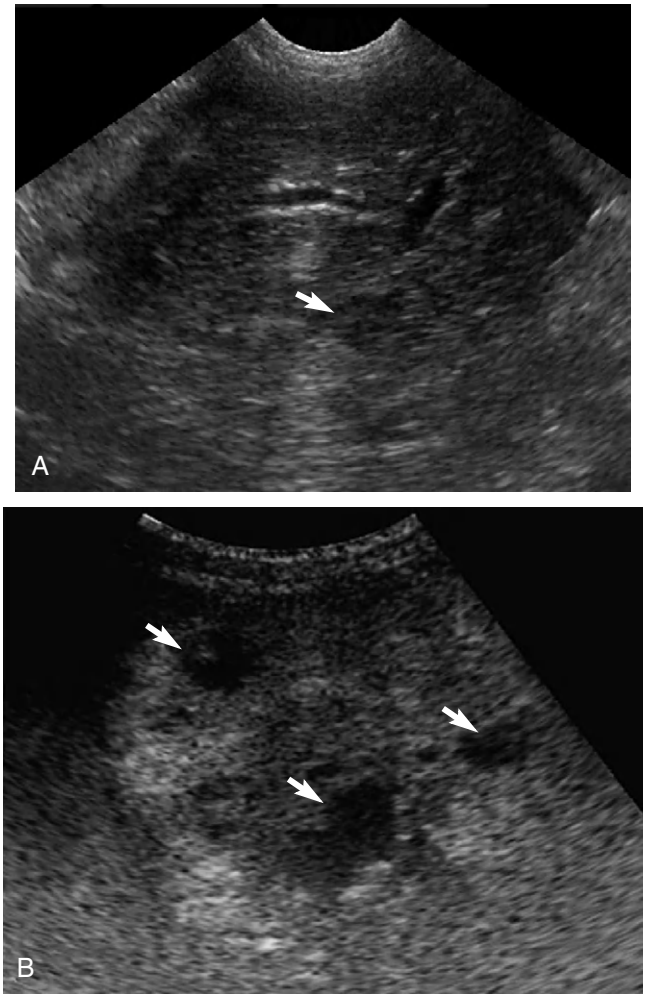


Figure 26-81 (**A**) Conventional and (**B**) contrast-harmonic ultrasound images of the liver of a 12-year-old mixed-breed dog with a metastatic hemangiosarcoma. The image was recorded during the portal phase of the contrast enhancement. In the precontrast image (**A**) the liver is mottled and a hypoechoic nodule is visible (*arrow*). After injection of microbubble contrast (**B**) there are multiple hypoperfused nodules seen throughout the parenchyma; the three largest ones are marked by *arrows*.

NUCLEAR SCINTIGRAPHY

Federica Morandi

Scintigraphy is a medical imaging modality utilizing radiopharmaceuticals (compounds containing a radioisotope bound to a pharmaceutical) that concentrate in a specific region of interest, ideally involving one specific physiological function, and relies on the detection of radioactive decay in the diagnosis of disease. Following administration, the radiopharmaceutical distributes within the body according to its specific mechanism of localization and emits gamma radiation, which is detected by a scintillation camera, thereby creating an image that depicts distribution of radioactivity within the body. The most commonly used isotope is technetium-99m (^{99m}Tc), which is very suitable for diagnostic imaging because of its short half-life ($T_{1/2}$, the time it takes for the initial activity to decrease by 50%: 6.02 hours for ^{99m}Tc) and ideal energy emission (140 KeV) for detection by a gamma camera. The use of scintigraphy is well established for the evaluation of portosystemic shunts[1-9] and the hepatobiliary system.[10,11] Scintigraphy has also been used to evaluate gastrointestinal blood loss,[12-14] esophageal motility, gastric emptying time,[12] and pancreatic inflammation in cats.[15,16]

Hepatobiliary Scintigraphy

Principles, Indications, and Radiopharmaceuticals

Hepatobiliary agents are lidocaine analogues, exploiting the fact that lidocaine's primary site of metabolism is the liver.[10] Lidocaine, however, cannot be directly bound to ^{99m}Tc, therefore iminodiacetic acid (IDA) analogues (mebrofenin or disofenin) are used as bifunctional chelates, bound to lidocaine on one side of the molecule and ^{99m}Tc on the other.[10] After intravenous (IV) injection, ^{99m}Tc-IDA agents are transported to the liver loosely bound to serum albumin. They dissociate in the space of Disse, where they come in contact with membrane receptors on the hepatocyte, and compete for dye anion class receptors. ^{99m}Tc-IDA agents are taken up by hepatocytes in a carrier-mediated, non–sodium-dependent transport mechanism similar to that of bilirubin, and are secreted into the bile and small intestine in their native form. Thus, ^{99m}Tc-IDA uptake is dependent upon serum albumin binding, systemic circulation, hepatic arterial blood flow, serum bilirubin concentration, hepatocyte function, and biliary secretion. Of these multiple sequential processes, ^{99m}Tc-IDA handling depends primarily on hepatocyte uptake and biliary secretion. Normal hepatocytes extract the radiopharmaceutical rapidly from the blood pool, whereas poorly functioning hepatocytes do not extract the radiopharmaceutical as efficiently. In the presence of severe hepatocellular disease, the urinary system becomes the primary route for excretion.[10] Although hepatobiliary scintigraphy permits the evaluation of hepatic morphology, its primary uses are in the determination of hepatic function and biliary tract patency.[10,11]

Technical Considerations

In dogs and cats, a dose of 2 to 6 mCi (74 to 222 MBq) is used. Static 60-second lateral and ventral images are acquired at 5, 10, 15, 30, 45, 60, 90, and 240 minutes following IV injection. If activity is not seen in the intestines by 240 minutes, images at 8 and 24 hours should be obtained in all cases to evaluate for extrahepatic obstruction.[10] For quantification of the hepatic extraction index, a dynamic acquisition is obtained, starting the acquisition just prior to injection.[10]

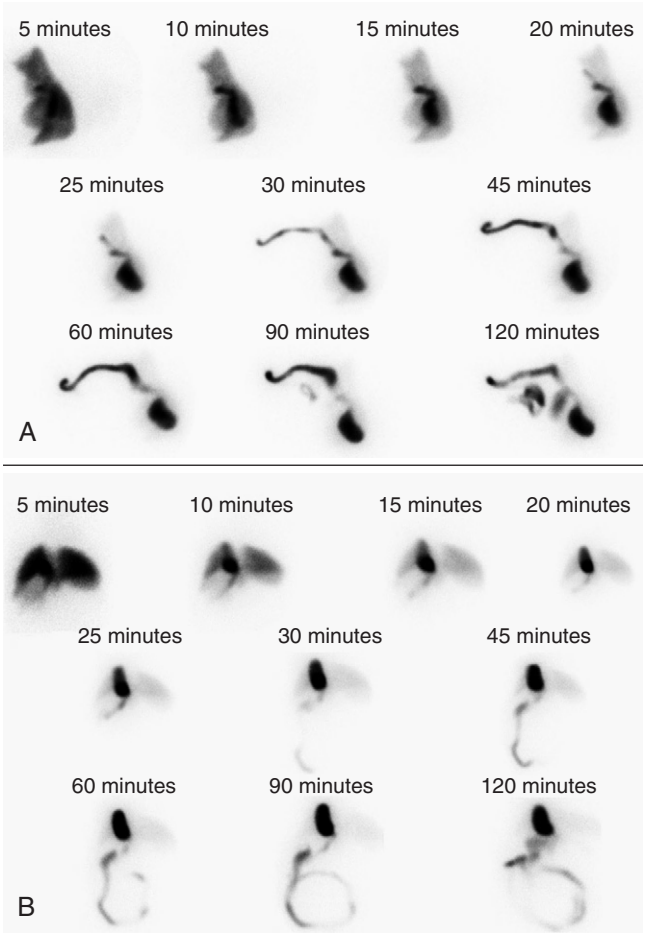


Figure 26-82 Right lateral (**A**) and ventral (**B**) views after IV injection of ^{99m}Tc-mebrofenin. Notice the absence of blood pool and cardiac activity at 5 minutes, and the progressive and rapid clearance of hepatic activity into the gallbladder, which is already visible at 10 minutes. On the 20-minute images, hepatic counts have dropped more than 50% compared with the 5-minute images, indicating normal hepatic half-life. Activity is then visible in a tubular structure consistent with the common bile duct at 20 minutes, and is clearly visible in the duodenum at 30 minutes.

Interpretation

As for any scintigraphic study, the raw images should be evaluated first, before any quantitative analysis is done (Fig. 26-82). In a normal dog, the 5-minute images provide the best assessment of hepatic morphology, Hepatic extraction is characterized by rapid radiopharmaceutical uptake by the liver, with clearance of the blood pool and washout of cardiac activity by 5 minutes, and peak liver uptake at 6 to 8 minutes. Hepatic excretion is characterized by a $T_{1/2}$ of 19 minutes.[10] In other words, the 20-minute image should show approximately 50% of the liver activity seen on the 10-minute image. Although gallbladder activity and intestinal activity should be visible within an hour, it is the author's experience that in dogs with large amounts of biliary sludge, the gallbladder may never be visible. However there should be progressive centralization of activity around the area of the gallbladder, followed by visible intestinal activity. Quantification of hepatic function requires the calculation of the hepatic extraction fraction (HEF), which is the percentage of radiopharmaceutical removed by the liver on each circulatory pass. In normal dogs, the HEF is on average 95%.[10]

The presence of hepatocellular disease is characterized by decreased hepatic radiopharmaceutical uptake (HEF <90%), prolonged blood pool and cardiac activity (visible beyond 5 minutes), intrahepatic cholestasis ($T_{1/2}$ >19 minutes), delayed excretion into the intestinal tract, and visualization of the kidneys and urinary bladder as alternate routes of excretion.[10] Complete extrahepatic obstruction is characterized by normal to decreased hepatic uptake and excretion (depending on the duration of obstruction) and no visible intestinal activity at any time, including the 24-hour images.[10,11] In cases of partial extrahepatic obstruction, the appearance of gastrointestinal activity can be markedly delayed (>18 hours), and the volume of activity present may be very small (Fig. 26-83).[10,11] It was initially reported that lack of GI activity at 3 hours was indicative of complete obstruction.[17] A more recent study[11] found that the 3-hour cutoff overestimates the frequency of complete obstruction, resulting in high sensitivity (100%) but very low specificity (33%), while the 24-hour cutoff yields improved specificity (83%) with good sensitivity (83%), thereby minimizing the number of unnecessary surgeries in animals with partial obstructions.

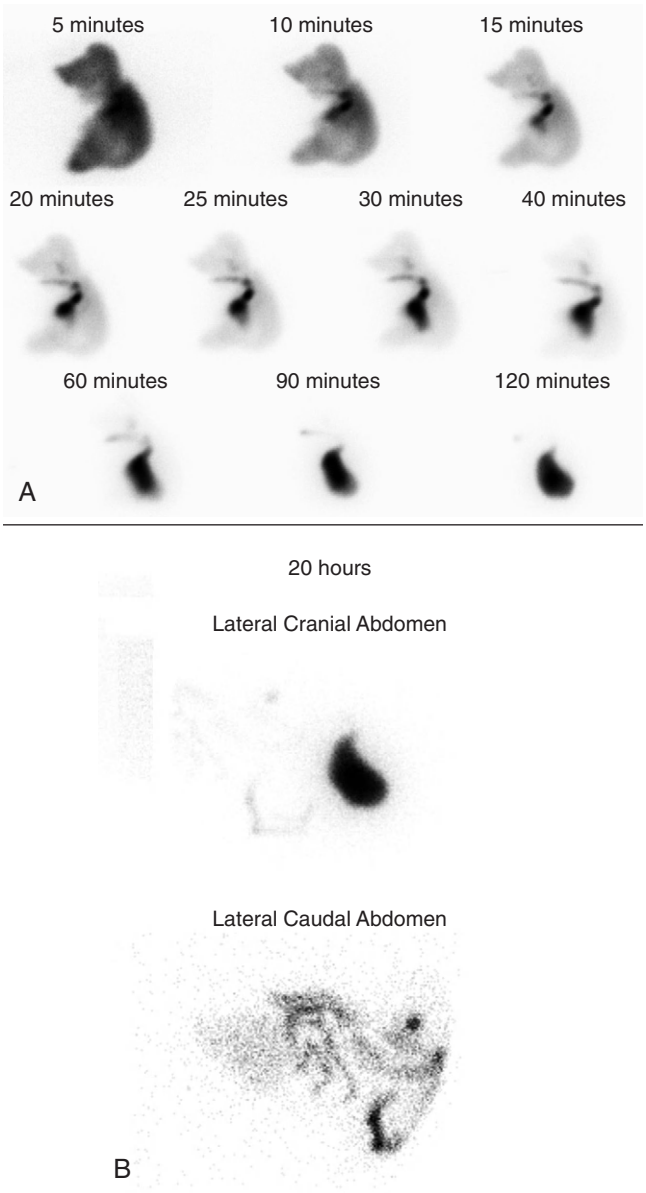


Figure 26-83 Right lateral views after IV injection of ^{99m}Tc-mebrofenin in a dog with partial biliary obstruction. A, Images obtained up to 3 hours and 40 minutes after injection, documenting mild hepatomegaly, rounded liver margins, normal hepatic uptake and secretion into the gallbladder and proximal aspect of the bile duct, with lack of progression of the radiopharmaceutical in the intestinal tract. **B,** Lateral views obtained the following morning (20 hours postadministration) that show a small amount of activity with linear distribution in the mid to caudal abdomen, consistent with passage of ^{99m}Tc-mebrofenin in the intestinal tract.

Portosystemic Shunt Imaging

Principles, Indications, and Radiopharmaceuticals

Scintigraphy has been used to evaluate dogs and cats with macroscopic portosystemic shunts (PSSs) since the early 1980s.[1] It was not until the early 1990s that the development of per-rectal portal scintigraphy (PRPS) provided a highly sensitive and specific technique in the diagnosis of PSSs. PRPS exploits the unique ability of ^{99m}Tc in the form of pertechnetate to be absorbed through the colonic mucosa into the portal venous system.[1-4] With normal portal venous circulation, activity appears first in the liver followed by the heart, after a delay of approximately 8 to 12 seconds. With portal venous shunting, activity arrives in the heart before or at the same time as it appears in the liver.[1-4] PRPS has some distinct disadvantages, chiefly the inability to identify the morphology and location of the shunt.[1,5] This study therefore provides a simple "yes" or "no" answer to the question, "Is there a macroscopic PSS?" Another limitation of PRPS is that study quality is extremely variable and depends on the degree of isotope absorption from the colon. Colonic absorption of pertechnetate is often poor (<15%). Consequently, high doses of isotope (10 to 20 mCi, or 370 to 740 MBq) are needed to achieve a diagnostic study. Such a high dose, however, results in higher patient and personnel exposure.[5]

In recent years, transsplenic portal scintigraphy (TSPS) was developed to overcome the limitations of PRPS.[5-7] This technique requires an ultrasonographically guided injection of a small volume of ^{99m}Tc (either pertechnetate or ^{99m}Tc-mebrofenin) into the splenic parenchyma. In normal dogs, the radiopharmaceutical is rapidly absorbed in the splenic vein, emptied into the portal vein, reaching the liver first, and appearing in the heart thereafter with a delay of approximately 7 seconds.[5] Because of the much higher tracer absorption from the spleen compared with the colon (53% vs. 9% in a recent study),[5] TSPS requires a much smaller ^{99m}Tc dose and therefore decreased patient and personnel exposure compared with PRPS. TSPS is as sensitive and specific as PRPS for the detection of PSS, but, because it provides a nuclear angiogram and studies of consistently higher quality, it has the further advantage of enabling identification of the number and termination of shunting vessels.[8] The ability to differentiate between single and multiple shunts is especially important, because the latter are managed medically, while the former require surgical occlusion.[8] At the author's institution, TSPS has replaced PRPS, and since 2004 we have performed more than 700 TSPS studies with no significant complications and a rate on nondiagnostic studies (mostly because of leakage of tracer from the spleen into the peritoneum or nonabsorption) of <5%.

Technical Considerations

Either pertechnetate[5] or ^{99m}Tc-mebrofenin[7] can be used, at a dose of 0.5 to 2 mCi (18.5 to 74 MBq) in 0.2 to 0.5 mL volume. The animal is placed on the gamma camera in right lateral recumbency, and a dynamic acquisition at 4 frames/sec is started at the time of needle placement (22 G) in the splenic parenchyma.[5,7] If ^{99m}Tc-mebrofenin is used, a static right lateral image is also obtained 5 minutes after transsplenic injection.[7]

Interpretation

As mentioned previously, in normal dogs undergoing TSPS with pertechnetate, the radioactive bolus will be rapidly absorbed from the splenic injection site, outlining the splenic and portal veins, reaching the liver first, and being visible in the heart after an average delay of 7 seconds.[5] If the study is done using ^{99m}Tc-mebrofenin, the radiopharmaceutical will remain trapped within this organ as a result of the high first-pass extraction of this IDA compound by normal hepatocytes after it reaches the liver. From there it will be gradually cleared into the biliary system (Fig. 26-84).[7]

In dogs with macroscopic PSS, three patterns of uptake are easily distinguished. With portocaval shunts the radioactive bolus is transported in a linear fashion toward the caudal vena cava, entering the heart from its caudal aspect (Fig. 26-85). With portoazygos shunts, the bolus is transported dorsally, running parallel to the thoracic spine, and enters the heart from the craniodorsal aspect with a 90°

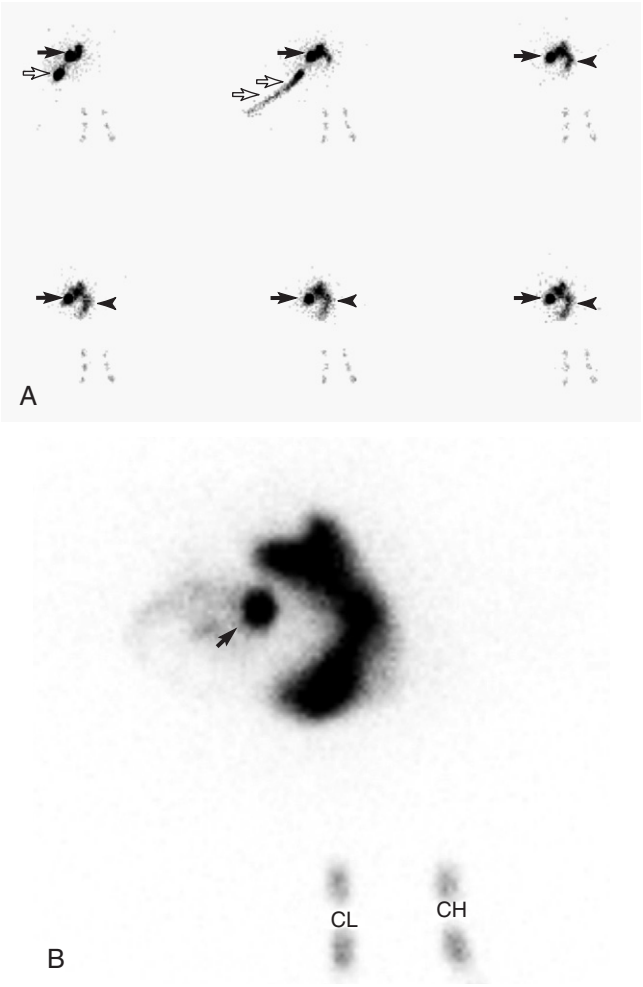


Figure 26-84 Right lateral reframed dynamic images, each representing 0.5 seconds of data (**A**) and a static 5-minute image (**B**) in a normal dog after transsplenic injection of ^{99m}Tc-mebrofenin. The *white arrows* indicate the tip of the syringe, which is removed on the second image. After injection into the spleen (*black arrow*) the radiopharmaceutical travels slightly dorsally, then curves ventrally and becomes trapped in the liver (*black arrowhead*). On the 5-minute image, there is no residual blood pool or cardiac activity, and only the liver and spleen are visible. The dotted area of activity ventral to the dog represent ^{57}Co markers, one placed ventral to the liver region (*CL*) and one ventral to the apex of the heart (*CH*).

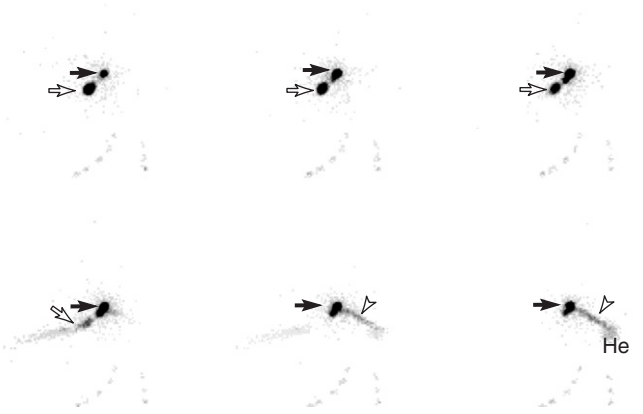


Figure 26-85 Right lateral reframed dynamic images, each representing 0.5 seconds of data, after transsplenic injection of ^{99m}Tc-mebrofenin in a dog with a splenocaval shunt. The *white arrows* indicate the tip of the syringe, which is removed on the fourth image. After injection into the spleen (*black arrows*), the radiopharmaceutical travels immediately cranioventrally (*white arrowhead*) entering the heart (*He*) from the caudal aspect.

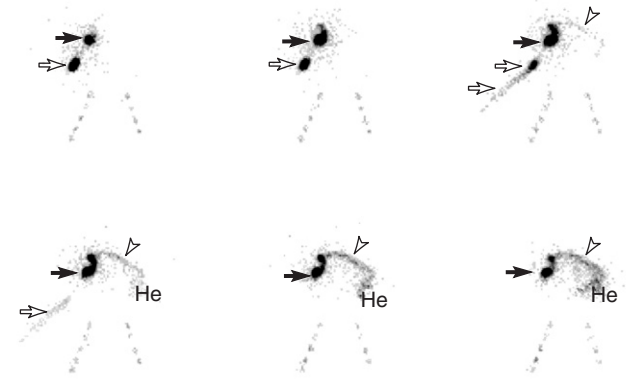


Figure 26-86 Right lateral reframed dynamic images, each representing 0.5 seconds of data, after transsplenic injection of ^{99m}Tc-mebrofenin in a dog with a portoazygos shunt. The *white arrows* indicate the tip of the syringe, which is removed on the fourth image. After injection into the spleen (*black arrows*) the radiopharmaceutical travels immediately dorsally, then cranially in a vessel along the dorsal aspect of the thorax (*white arrowhead*), and enters the heart (*He*) from the dorsal aspect with a 90° angle.

angle (Fig. 26-86). With internal thoracic shunts, the bolus is transported ventrally along the thorax and abdomen entering the cranial aspect of the heart.[6] Most multiple acquired shunts are easily identified because the bolus outlines a well-defined plexus of vessels in the mid to caudal abdomen (Fig. 26-87).[6,9] Not all multiple shunts, however, show this typical pattern, most likely because some acquired shunts are smaller than the limit of resolution of the gamma camera, and may therefore appear as a single vessel. A recent study found that a plexus of anomalous vessels was visible in 64% of cases of multiple acquired shunts, while hepatofugal flow caudal to the cranial margin of the kidneys was present in 93% of cases, indicating that the latter is the most reliable imaging feature in cases of multiple acquired shunts.[9]

^{99m}Tc-mebrofenin has two distinct advantages over pertechnetate. First, mebrofenin is actively extracted by the hepatocytes, and liver size and shape are more easily identified, compared with a study done with pertechnetate.[7] This is a useful characteristic in that it permits the accurate tracing of regions of interest (ROIs) over the liver and heart for determinations of shunt fraction (SF). Net hepatic and cardiac counts are calculated in the ROIs in a 7-second time frame (normal hepatic to cardiac transit time for TSPS), and SF is determined by calculating the ratio of cardiac counts to cardiac plus hepatic counts; normal mean SF with TSPS is 2.6%.[5] It is important to note that, other than confirming the presence of a PSS, SF values do not have any prognostic or predictive value.[1] A second advantage of ^{99m}Tc-mebrofenin is in the use and interpretation of the 5-minute static image. In a normal dog, this image will show activity limited to the normal-size liver, some residual activity at the site of splenic injection, but no blood pool or cardiac activity.[7] Animals with PSS, on the other hand, show variable amounts of blood pool and cardiac activity, as well as decreased hepatic volume.[7]

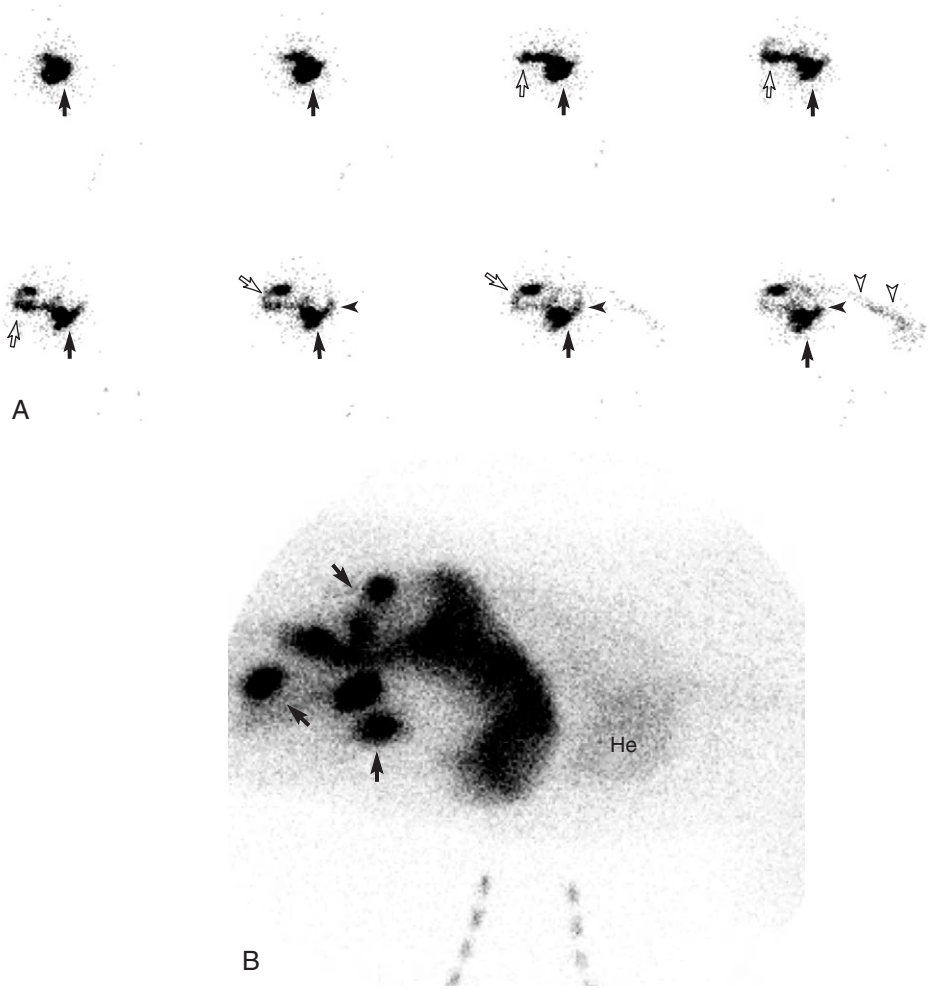


Figure 26-87 Right lateral reframed dynamic images, each representing 0.5 seconds of data (**A**) and a static 5-minute image (**B**) after transsplenic injection of ^{99m}Tc-mebrofenin in a dog with multiple acquired shunts. After injection into the spleen (*black arrows*) the radiopharmaceutical travels caudally with marked hepatofugal flow before curving in a cranial direction (*white arrows*); a second vessel travels from the injection site cranially and dorsally (*black arrowhead*). Activity from these two anomalous vessels enters the caudal vena cava (*white arrowheads*) bypassing the liver and reaching the heart from its caudal aspect. On the 5-minute image, there is moderate residual blood pool and cardiac (*He*) activity.

Animals with underlying hepatocellular disease but without macroscopic PSS will show persistent blood pool and cardiac activity, but the dynamic acquisition will have excluded a macroscopic PSS. They often show increased hepatic size and rounded liver margins.

Because TSPS requires injection into the spleen, some shunts originating distal to the splenic vein might not be identified using this technique, although this has not been the author's experience. The flow of the small volume of injected radiopharmaceutical likely occurs preferentially through the shunt. Furthermore, extrahepatic portosystemic shunts arise from the main portal, left gastric, or splenic veins, and empty into the caudal vena cava cranial to the phrenicoabdominal vein, and would not be missed with TSPS.[5]

Gastrointestinal Bleeding

Principles, Indications, and Radiopharmaceuticals

Scintigraphy can be used to document gastrointestinal bleeding, by detecting the accumulation of either ^{99m}Tc-sulfur colloid or ^{99m}Tc-labeled red blood cells (^{99m}Tc-RBCs) into the gastrointestinal tract lumen.[12-14,17] The technique does however have two limitations. It does not accurately localize the precise anatomic site of bleeding, and active bleeding must be present at the time of the imaging procedure.[12] ^{99m}Tc-sulfur colloid is more sensitive to small volumes of blood loss (down to rates of 0.1 mL/min) because of the absence of background activity. ^{99m}Tc-RBCs require greater rates (3 mL/min) because of the presence of higher background activity, but allows delayed imaging at 24 hours postinjection when labeled red blood cells (RBCs) can be more readily identified in the colon.[12,13]

Technical Considerations

For both radiopharmaceuticals, a dose of 5 to 20 mCi (185 to 740 MBq) is injected intravenously and static lateral and ventral images are acquired at 0, 5, 15, and 30 minutes. For ^{99m}Tc-RBCs, additional images are obtained every 30 minutes for 4 hours, followed by a final set of images at 24 hours.[12] Two methods, in vivo and in vitro, for labeling RBCs are available.[12,14] The in vivo method is easy, quick, and requires only an IV injection of stannous chloride followed by pertechnetate.[14] Despite these advantages, the in vivo method yields a comparatively low labeling efficiency of approximately 90%. The

in vitro method requires collection and incubation of the patient's RBCs, which are reinjected into the patient after the labeling process is completed. Although more time-consuming, the in vitro method yields labeling efficiency of greater than 98%, thereby minimizing background activity.[12]

Interpretation

Gastric, intestinal, or colonic radioactivity is indicative of gastrointestinal hemorrhage (Fig. 26-88).[12,14]

Pancreas

Leukocytes labeled using ^{111}In-oxine, ^{111}In-tropolone, or ^{99m}Tc-hexamethylpropyleneamine oxime (^{99m}Tc-HMPAO) can be used to image inflammation. ^{99m}Tc-HMPAO-labeled granulocytes have been used in one confirmed case of feline pancreatitis.[16] Although in normal cats there is no visible accumulation of ^{99m}Tc-HMPAO in the region of the pancreas,[15] progressive radiopharmaceutical uptake, first visible at 2 hours, most intense at 4 hours, and persisting at 17 hours postinjection,[16] was documented in one case of pancreatitis. The time-consuming procedure to label feline granulocytes and the variable labeling efficiency of ^{99m}Tc-HMPAO (15% to 42%) have been limiting factors for the clinical use of this technique, and this diagnostic test would be most useful for research purposes rather than for routine clinical cases of suspected feline pancreatitis.

Esophageal Motility and Gastric Emptying Studies

Esophageal transit and gastric emptying times (solid and liquid phases) can be quantified using scintigraphy with radiolabeled meals or liquids.[12] Because of the broad range of normal values and the variable protocols reported in the literature, the usefulness of these studies is generally limited to research settings. The best clinical application of scintigraphic motility studies is perhaps when serial studies are performed on the same animal, as a tool to monitor response to therapy.[12]

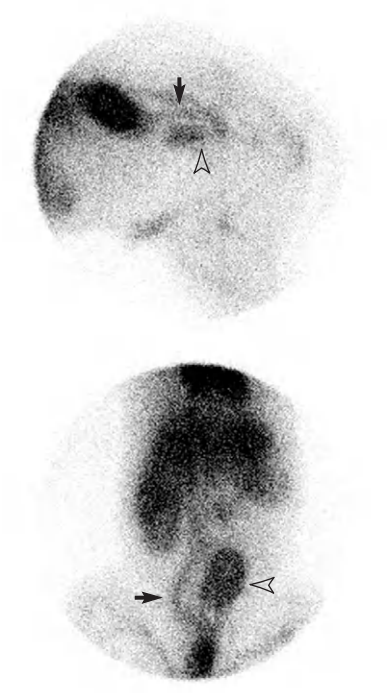


Figure 26-88 Left lateral and ventral views of a dog 20 hours after IV injection of ^{99m}Tc-RBCs. There is abnormal activity in a linear structure in the caudodorsal abdomen (*black arrow*) consistent with colon, indicating that the study is positive for GI blood loss. Activity is also present in the urinary bladder (*white arrowhead*), because of dissociation of ^{99m}Tc from the erythrocytes.

COMPUTED TOMOGRAPHY/MAGNETIC RESONANCE IMAGING

Travis C. Saveraid

The clinical use of CT and MRI in companion animal diagnosis has increased dramatically in the last decade. CT and MR scanners are now available at nearly all academic hospitals and many specialty centers. However there are still relatively few studies describing the clinical use of CT or MRI in the medical investigation of hepatobiliary, pancreatic, and gastrointestinal tract diseases. The majority of publications are restricted to single case reports or descriptions of normal anatomy.[1-6] CT and MR imaging studies of the abdomen in general, and the hepatobiliary, pancreatic, and gastrointestinal systems in particular are poised to become increasingly relevant imaging tools in the next 5 to 10 years.

Advantages

CT and MRI allow complete visualization of organs of interest and adjacent regional structures without the visual obstructions prevalent with radiographs and US images. Both modalities allow for multiplanar display of the anatomy of interest. Because of superior anatomic resolution, normal and abnormal anatomic structures are more intuitively obvious even to the inexperienced observer. In addition, both modalities can be used for dynamic functional assessment of organs and vessels through various contrast (CT and MRI) and advanced imaging techniques (MRI).

Disadvantages

Two significant disadvantages to CT and MRI are the requirement for general anesthesia and the cost of higher technology compared with other imaging modalities. In many situations, however, general anesthesia may be a benefit as it allows for greater control of the patient's respiration and decreases gastrointestinal movement. Patient immobility improves cranial abdominal imaging studies. With the advent of more advanced multidetector CT scanners, the speed of image acquisition may obviate the need for general anesthesia and heavy sedation protocols may prove sufficient in the future.

CT and MRI have higher capital expense costs and exam charges will likely always be higher than for other imaging studies, but when appropriately used, a CT or MRI study may save the cost of multiple less-definitive diagnostic tests. Continuous improvements in computer hardware and the introduction of newer technologies have created an active secondary market of refurbished systems more economically competitive for the veterinary market.

A more insidious disadvantage is the lack of understanding and interpretation of CT and MR images. Clinicians often need confidence building in a new imaging method before recommending a more expensive diagnostic test. In that regard, there is a general perception of higher comfort level with CT imaging as it is a technology that is loosely based on x-ray technology. MR image interpretation is not necessarily more difficult than that of CT images,

but MRI physics is based on detection of protons in a magnetic field, and is unique from other imaging modalities. Despite a number of advantages of MRI in certain situations, many clinicians continue to choose traditional imaging methods because of their discomfort with newer technologies.

Methods and Techniques

Because of the great technical variation in CT and MR systems available to veterinary medicine, detailed specific protocols for imaging the hepatobiliary, pancreatic, and gastrointestinal systems are beyond the scope of this book. Generally speaking, for abdominal imaging, faster scanning techniques combined with respiratory pause methods are ideal. Respiratory pause methods include hyperventilation prior to scanning, controlled ventilation (e.g., breath holding), or controlled ventilation combined with pharmacologic paralysis. Faster scanning techniques can be accomplished in a variety of ways depending on the modality system but may include adjustments to the slice thickness (CT and MR), pitch (CT), sequence selection (MR), phase-encoding steps (MR), parallel imaging (MR), or scanning smaller selected regions of interest (CT and MR).

Computed Tomography

Specific protocols vary depending on the scanner type and regions of interest. Single-detector/single-slice systems with and without helical option or multidetector/multislice systems are now widely used in academic and specialty hospitals. With single-slice scanners, 3- to 5-mm transverse slices with overlap in image reconstruction are usually adequate for the liver, pancreas, gastrointestinal tract, and abdominal vasculature. With multidetector systems, slice thickness and acquisition times can be greatly reduced with significant improvements in spatial and temporal resolution. Many of the multidetector systems can scan and reconstruct images using isotropic voxels allowing for pixel-perfect multiplanar reconstructions (MPRs). Pixelated MPRs with poor image resolution have historically been a detriment for CT studies as compared with the native multiplanar acquisition methods of MRI. With improved multidetector CT technologies, MPRs have greatly improved. Viewing CT images in the original transverse and multiplanar reconstructions are essential for complete evaluation of the study.

Early studies of the utility of abdominal CT focused primarily on CT angiography (CTA). Single-phase and dual-phase (arterial and venous) angiographic techniques have been successfully applied in the examination of the portal, hepatic, and pancreatic vasculatures.[6-10] The timing of the contrast injection is a critical part of this exam. Newer CT systems with dynamic bolus tracking technology have simplified this process. A new contrast injection and angiography technique has shown great promise in providing sustained contrast within the arterial and venous vasculature for the duration of the angiography study regardless of patient size.[11]

Magnetic Resonance Imaging

With MRI studies of the abdomen, particularly of the liver, pancreas, and gastrointestinal tract, multiple planes should always be employed. These planes should include at least one sequence in all three of the standard planes: sagittal, dorsal, and transverse. Dorsal plane and transverse plane images are the most commonly used. Dorsal plane images have the distinct advantage of providing a larger field of view per unit acquisition time thereby facilitating more rapid imaging and initial anatomy interrogation compared with transverse images. Sagittal plane images have similar advantages and can be used if preferable. Once appropriate anatomy or lesions of interest are identified with dorsal plane images, transverse images of the region of interest are then prescribed. While the field of view can be focused over the area of interest, for example, liver or pancreas, the images will typically encompass the cranial half of the abdomen when evaluating for pancreatic and hepatobiliary disease. General sequences for abdominal imaging include T2-weighted and T1-weighted pre- and postcontrast with fat saturation techniques applied on at least one of the postcontrast planes. If fat saturation is ineffective or unreliable, additional short tau inversion recovery (STIR) sequences will be necessary. Many scanners can take advantage of more rapid imaging methods such as three-dimensional (3D) volumetric acquisition, variations of gradient recalled echo (GRE) and echo planar sequences, and parallel imaging techniques, to create sequences, which rapidly cover the region of interest and avoid respiratory motion artifacts. Higher field scanners (1 Tesla and greater) have superior fat-saturation techniques compared with low-field scanners. When using a high-field scanner the author prefers using a T2-weighted sequence with fat saturation in at least the dorsal plane, followed by a T2-weighted transverse sequence and T1-weighted pre- and postcontrast sequences in the area of interest.

Similar to advances with CT angiography of the portal and hepatic vasculature, high-field MR systems can create excellent vascular roadmaps of the abdomen. An early MR angiographic technique called two-dimensional (2D) time-of-flight was used successfully to characterize canine portal vasculature and portosystemic shunting.[12,13] More recently, a faster, more robust, and technically easier method of multiphase time-resolved contrast-enhanced MR angiography (CE-MRA), has been used to characterize normal and abnormal portal and hepatic vasculature.[14,15]

Indications

Under ideal circumstances, a lesion or abnormality would be identified with more common imaging methods such as radiography or ultrasound, and then CT and/or MRI could be used for greater clarification, narrowing the list of differential diagnoses, or establishing a specific imaging diagnosis. Where appropriate, multiple imaging tests are preferable, but often not feasible because of escalating cost to the client. The clinician is then faced with the difficult question of selecting one or two imaging modalities that will best reveal the clinical diagnosis (Boxes 26-1 and 26-2).

In the author's opinion, if abdominal imaging beyond radiography is required for evaluation of a mass, metastasis, intraabdominal vasculature, or preoperative planning in canine patients weighing more than 50 lbs (23 kg), the clinician should strongly consider the use of CT or MRI rather than abdominal ultrasound. A recent abstract supports this opinion when comparing helical CT versus US.[16] In ultrasonography exams, the ultrasonographer must make simultaneous interpretation while dealing with the challenges of gastrointestinal gas, limited patient cooperation, near and far field artifacts, and demanding, repetitive physical actions. Detailed evaluation of dorsal liver regions, complete biliary system, entire pancreas, and entire gastrointestinal tract is vastly improved and less distracting in CT and MRI exams compared with US. In situations where fine-needle aspiration or needle core biopsy is required after CT or MRI, US can be employed for rapid, guided sampling.

Box 26-1 Conditions for Which CT or MRI Should Be Considered Instead of Ultrasound for the Evaluation of Hepatobiliary, Pancreatic, or Gastrointestinal Disease

- Patient weighs more than 50 lbs (23 kg)
- Evaluation for portosystemic shunt (PSS)
- Investigation of non-PSS vascular lesions such as arteriovenous shunts, other anomalous vessels, and mesenteric vessels
- Determination of the dynamic contrast enhancement of a mass
- Evaluation of entire GI tract
- Patient with excessive GI gas on radiographs
- Surgical assessment of known large masses including involvement of regional vasculature
- Assessment for anatomic extent of a mass including metastases

Box 26-2 Preferences for CT Versus MRI in the Imaging of Hepatobiliary, Pancreatic, and Gastrointestinal Disease

CT preferred
- Primary GI tract evaluation, especially if extensive gas is present or a perforation is suspected
- When rapid results are required, such as in a sedated patient or critical care patient unstable for anesthesia

MRI preferred
- Evaluation of primary neoplasia or other known mass, especially in the liver
- Assessment for metastatic neoplasia, especially in the liver
- Investigation of regional inflammatory disease, such as pancreatitis with adjacent peritonitis

Either CT or MRI
- Angiography for portosystemic shunt evaluation
- Angiography for hepatic, pancreatic, or mesenteric vessels

*Assuming a high field (1 Tesla or greater) MR system.

Hepatobiliary Computed Tomography and Magnetic Resonance Imaging

MRI allows for highly accurate differentiation of benign and malignant neoplasia of the liver.[17] Evaluation of hepatic masses with multiple sequence types and pre- and postcontrast sequences permits more specific clarification and easier surgical planning, particularly with regard to the location and involvement of the main hepatic vasculature (Fig. 26-89). In human medicine, MRI is considered superior to CT for detection of focal liver lesions. In veterinary medicine, MRI and CT have been used for the evaluation of primary and metastatic hepatic lesions.[12,17,18] CT is an excellent method for the assessment of liver volume before and after correction of portosystemic shunting.[19,20] Preliminary MR studies showed that it underestimates liver volume compared with CT, but these studies were likely limited by magnet field strength. Clinical imaging of the gallbladder and biliary tract has not yet been described. Anecdotally, both modalities provide excellent visualization of the gallbladder wall, cholecystoliths, and the common bile duct, although MRI has superior tissue contrast.

Pancreatic Computed Tomography and Magnetic Resonance Imaging

CT has been used for the evaluation of pancreatitis in both dogs and cats.[21-24] However in two separate feline studies, in which patients had a definitive diagnosis of pancreatitis, only 20% had lesions consistent with pancreatitis on CT examination.[21,22] In a case report of two dogs with acute pancreatitis, contrast-enhanced CT identified changes of pancreatitis, central regions of necrosis, and sites of regional vascular thrombosis.[24] Evaluation of the pancreas for endocrine neoplasia, specifically insulinomas,[23-25] has been described several times but there are no case series describing CT or MRI findings of pancreatic exocrine neoplasia.[25-27] Evaluation of the normal pancreatic vasculature has been reported using dual-phase CTA.[1] In practical use, the entire pancreas is more consistently visible on CT and MRI than with US.

Intestinal Computed Tomography and Magnetic Resonance Imaging

The use of MRI to evaluate intestinal disease has not yet been reported in companion animal medicine, but CT has been used as a primary or ancillary imaging technique to evaluate suspected intestinal or peri-intestinal lesions.[28-30] In a recent case series of intrapelvic masses identified with CT, four of 14 masses were identified with imaging characteristics strongly supportive of benign intramural neoplasia of the colonic wall and were subsequently histopathologically proven as leiomyomas.[29] Anecdotally, CT has also been used in the evaluation of gastric masses and intestinal masses and intestinal foreign bodies. Imaging of the intestinal tract with CT, and especially MRI, is likely underused and underreported. Intestinal wall imaging using CT and MRI for mural infiltrates or mural masses is increasingly reported in the medical literature.[31-35] Identification of intestinal foreign bodies and mesenteric vascular disease using CT is also described.[35-39]

In veterinary medicine, there are many unexplored uses for CT and MR in intestinal tract evaluation, particularly in the mid and distal small intestine, for infiltrative disease, focal masses, intestinal foreign bodies, and mesenteric vascular disease. The use of general anesthesia in veterinary patients will be beneficial to imaging of the gastrointestinal tract because of decreased motion and the opportunity for instillation of gastrointestinal contrast via orogastric or orointestinal deposition for optimal distention (enteroclysis). CT or MR enteroclysis or enterography has not been published in veterinary medicine but has potential for future application in intestinal imaging.

Angiography of the Hepatic and Portal Vascular System

The most commonly reported use of CT and MR in the abdomen has been in the CT and MR angiographic evaluation of the hepatic and the portal vascular systems. CTA and MRA have a high success rate at finding extrahepatic versus intrahepatic shunting, single versus multiple shunts, and areas of arterial venous fistulas (Fig. 26-90).[7,9,10,13,14,40-42] CTA and MRA provide a vascular roadmap allowing for more rapid and precise surgical intervention. One of the great strengths of CTA and MRA is the ability to identify not only single versus multiple shunts, but also the end location of the shunting vessel. This is particularly important for left gastric shunts as they frequently pass dorsal to the stomach and liver and then course ventrally ending in the caudal vena cava immediately prior to passage through the diaphragm. The terminus of these shunts is difficult to identify with ultrasound or during surgery. Depending on the availability of the type of CT or MR system, both systems have

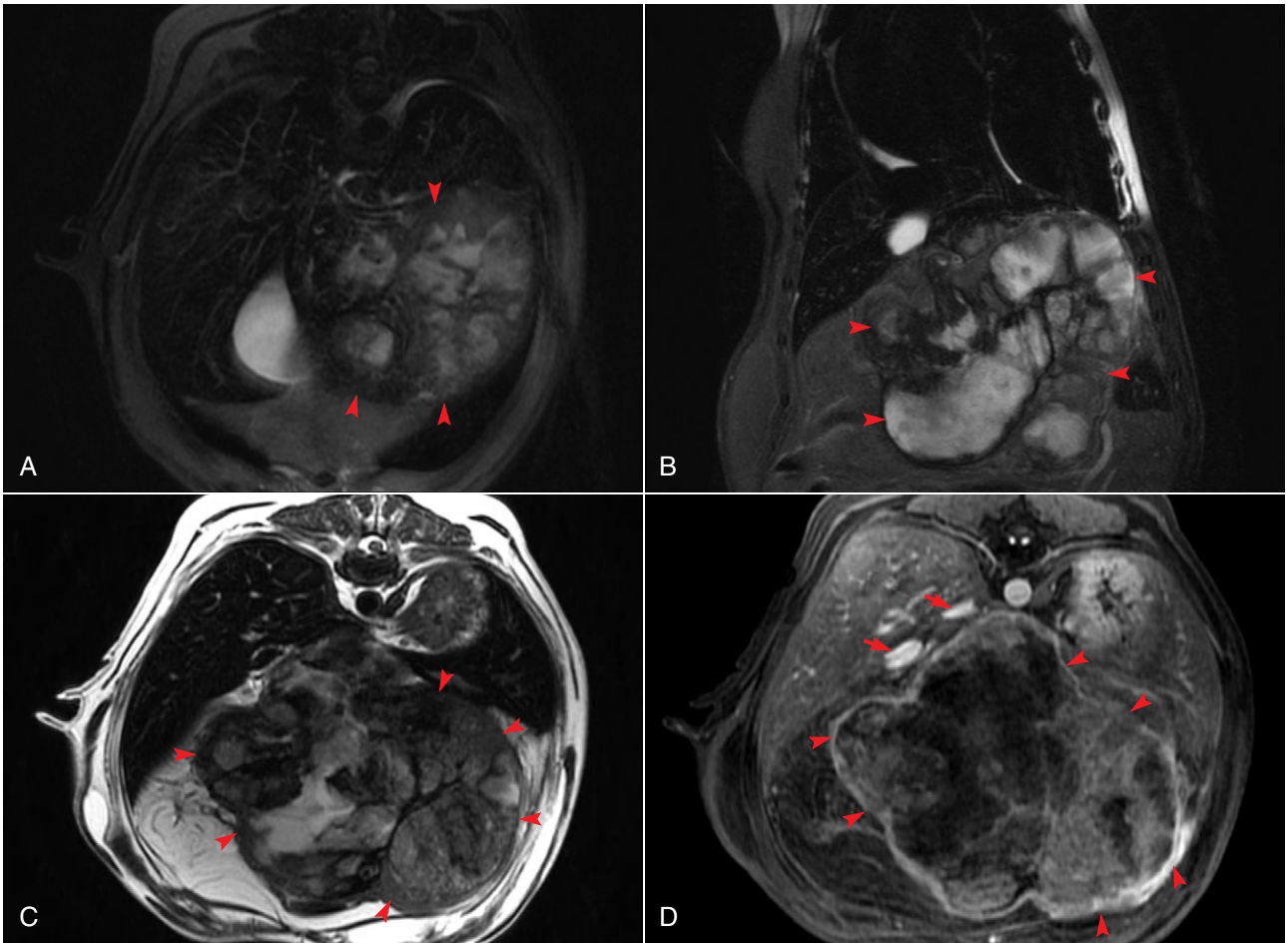


Figure 26-89 Transverse and dorsal plane MR images at the level of the mid liver. The images were acquired on a high-field scanner. A 12-year-old male neutered, mixed breed dog was positioned in dorsal recumbency. **A,** Transverse T2-weighted with fat saturation; **B,** dorsal T2-weighted with fat saturation; **C,** transverse T2-weighted; **D,** transverse spoiled gradient recalled echo (SPGR) early after IV gadolinium contrast. The *arrowheads* outline a large hepatocellular carcinoma with chaotic internal architecture. The gallbladder and the majority of the normal liver are displaced cranially. Postcontrast images show early peripheral contrast enhancement and large, central, nonvascularized regions. The *arrows* on the postcontrast image show the displacement and compression of the portal vein and caudal vena cava.

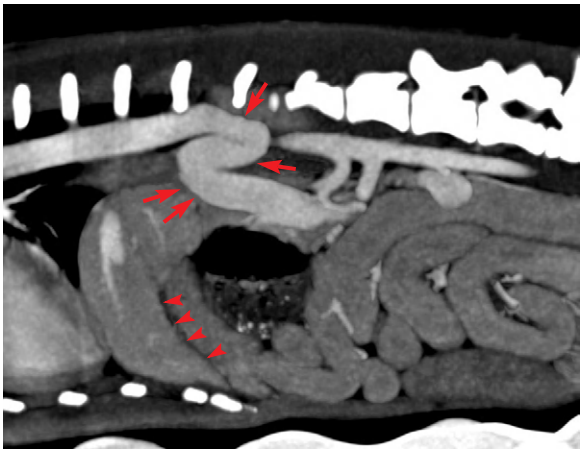


Figure 26-90 Oblique sagittal plane, maximal intensity projection CT angiography image of the cranial abdomen of a 1.5-year-old, spayed female Shih Tzu positioned in ventral recumbency. The *arrows* depict a single, large, portoazygos vascular shunt. The *arrowheads* outline the small liver. Multiple other major abdominal vessels, such as the aorta, celiac artery, and cranial mesenteric artery are also easily visualized.

been used to create high-resolution, relatively rapid images (less than 15 minutes total study time) of the abdominal vasculature. Multidetector helical CT is preferable to single-source helical for these studies. MRA is best performed with a high-field system. Low-field systems, generally 0.3 Tesla or smaller, are incapable of creating an adequate abdominal angiographic study. In the author's opinion, if there is access to a capable CT scanner or high-field MRI system, these imaging systems are the best choice for verification and identification of suspected portosystemic shunts.

ASSESSMENT OF GASTROINTESTINAL MOTILITY

Robert Washabau

Disorders of Gastrointestinal Motility

Disorders of gastrointestinal motility represent a diagnostic and therapeutic challenge. Gastrointestinal motility disorders may result in delayed transit, accelerated transit, impaired relaxation, or inappropriate relaxation.[1] The delayed transit disorders are the most

important motility disorders of companion animals and may involve the esophagus (e.g., idiopathic megaesophagus), stomach (e.g., delayed gastric emptying), small intestine (e.g., ileus or pseudoobstruction), or colon (e.g., constipation) independently, or as a more generalized and diffuse gastrointestinal motility disorder (e.g., dysautonomia).[2]

Idiopathic Megaesophagus

Idiopathic megaesophagus is the most common form of regurgitation in the dog. The disorder is characterized by esophageal hypomotility and dilation, progressive regurgitation, and loss of body condition. Several forms of the syndrome have been characterized, including congenital, acquired secondary, and acquired idiopathic megaesophagus.[2-4]

Gastric-Emptying Disorders

Gastric-emptying disorders are fairly common in dogs and cats and are an important cause of nausea and vomiting. Primary conditions that have been associated with delayed gastric emptying include infectious and inflammatory disease (e.g., inflammatory bowel disease [IBD]), ulcer, and postsurgical gastroparesis, while secondary conditions include electrolyte disturbances, metabolic disorders, concurrent drug usage (cholinergic antagonists, adrenergic agonists, opioid agonists), acute stress, and acute abdominal inflammation.[5] Recovery from gastric dilation volvulus (GDV) is almost always associated with significant myoelectrical and motor abnormalities in the dog.[6]

Small Intestinal Transit Disorders

Several small intestinal transit disorders have been described in the dog and cat, including IBD, postsurgical pseudoobstruction, nematode infection, intestinal sclerosis, and radiation enteritis.[2] Vomiting and diarrhea are the most important clinical signs associated with these disorders. Dysbiosis of small intestinal bacteria, a common sequela to disordered motility, may contribute to these clinical signs.

Colonic Motility Disorders

Constipation, obstipation, and megacolon are primarily disorders of the domestic cat.[2,7,8] An extensive list of differential diagnoses (e.g., neuromuscular, mechanical, inflammatory, metabolic, endocrine, pharmacologic, environmental, and behavioral causes) has been proposed, but most (>96%) cases are accounted for by idiopathic megacolon (62%), pelvic canal stenosis (23%), nerve injury (6%), or Manx sacral spinal cord deformity (5%).[7]

Dysautonomia

Dysautonomia is a generalized autonomic neuropathy that was originally reported in cats in the United Kingdom, but that has now been documented in dogs and cats throughout Western Europe and the United States. The clinical signs reflect a generalized autonomic dysfunction, including megaesophagus and esophageal hypomotility, gastric dilation and delayed gastric emptying, ileus and intestinal pseudoobstruction, and megacolon and obstipation.[4,9]

Methods for Measuring Gastrointestinal Motility

Methods available for the evaluation of gastrointestinal motility include (a) radiography—survey, barium contrast, and radiopaque-indigestible solids (e.g., barium-impregnated polyethylene spheres [BIPSs]); (b) quantitative videofluoroscopy; (c) ultrasonography; (d) nuclear scintigraphic imaging; (e) tracer studies; (f) manometry; and (g) functional MRI (Table 26-2).

Survey Radiography

Survey abdominal radiography provides very little information about GI motility, but it is the imaging technique of choice in the initial assessment of any gastrointestinal disorder. Survey radiographs are useful in providing information about gastrointestinal tract position and content that may help to delineate mechanical obstruction from functional motility disorders. Survey radiographs are also helpful in determining the size and shape of other abdominal organs (e.g., spleen, liver, biliary tract, and urogenital tract) and their relationship to the gastrointestinal tract.

Contrast Radiography

Liquid Barium

Barium-contrast radiography is often used in clinical practice to detect gross abnormalities of esophageal peristalsis, gastric emptying (Table 26-3), intestinal transit (Table 26-4), and colonic motility, but the technique does have some distinct limitations.[10,11] In gastric-emptying studies, for example, gastric emptying of a radionuclide was markedly delayed in a group of dogs with pyloric hypertrophy although liquid emptying of barium was thought to be normal.[12] Similarly, the barium-swallow technique used to assess esophageal

Table 26-2 Methods Available for the Assessment of Gastrointestinal Transit in Dogs and Cats

	Esophagus	Stomach	Intestine	Colon
Survey radiography	+	+	+	+
Liquid barium contrast radiography	+	+	+	+*
Barium meal contrast radiography	+	+	+	–
BIPS contrast radiography	–	+	+	+
Ultrasonography	–	+	–	–
Nuclear scintigraphy	+	+	+	+
Tracer studies				
Gastric	–	+	–	–
Plasma	–	+	+	–
Breath	–	+	+	–
Manometry	+	–	–	–
Functional MRI	–	–	–	–

*Rarely performed.

Table 26-3 Gastric-Emptying Times of Solids and Liquids in Dogs and Cats

Solids	50% GET	75% GET	95% to 100% GET	Substrate	Method	Species	Reference
	–	–	5.6 ± 0.25 h	Hill's P/D + ^{99m}Tc	Nuclear scintigraphy	dog	28
	2.5 ± 0.3 h	–	–	Dinty Moore + ^{99m}Tc	Nuclear scintigraphy	dog	29
	1.1 ± 0.3 h	–	–	Eggs, starch, glucose	Nuclear scintigraphy	dog	30
	1.3 ± 0.34 h	–	–	Mighty Dog + ^{99m}Tc	Nuclear scintigraphy	dog	23
	2.5 ± 0.71 h	–	–	Purina + ^{99m}Tc	Nuclear scintigraphy	cat	31
	1.9 ± 0.78 h	–	–	Bread, egg, milk	Ultrasound	dog	21
	6.5 ± 1.2 h	–	–	Food + 1.5 mm BIPSs	Radiography	dog	32
	6.5 ± 3.2 h	–	–	Food + 1.5 mm BIPSs	Radiography	dog	33
	6.9 ± 1.3 h	–	–	Food + 1.5 mm BIPSs	Radiography	dog	34
	7.7 ± 0.7 h	–	–	Food + 1.5 mm BIPSs	Radiography	dog	35
	3.5 h	5 h	5 h	Hill's Sci. Diet + markers	Radiography	dog	36
	–	–	7.0 ± 1.86 h	Ground kibble + barium	Radiography	dog	16
	–	–	5.43 ± 1.0 h	Beef stew + barium	Radiography	dog	37
	–	–	10.9 ±0.76 h	Purina + barium	Radiography	dog	17
	7.7 h	–	12 h	Whiskas + 1.5 mm BIPSs	Radiography	cat	38
	8.1 h	–	10 h	Whiskas + 5 mm BIPSs	Radiography	cat	38
	5.36 ± 3.62 h	5.89 ± 4.06 h	6.54 ± 3.68 h	Hill's R/D + 1.5 mm BIPSs	Radiography	cat	19
	3.4 ± 0.50 h	–	–	Bread, egg, margarine	^{13}C breath test	dog	39
	3.4 ± 0.48 h	–	–	Bread, egg, milk	^{13}C breath test	dog	21
Liquids	**50% GET**	**75% GET**	**95% to 100% GET**	**Substrate**	**Method**	**Species**	**Reference**
	0.2 ± 0.05 h	–	–	Saline + ^{99m}Tc	Nuclear scintigraphy	dog	40
	–	–	0.66 ± 0.15 h	Saline	Ultrasound	dog	41
	–	–	1.05 ± 0.29 h	12.5% Soup solution	Ultrasound	dog	41
	–	–	0.90 h	3% Phenol red	Dye dilution	dog	42
	0.16 ± 0.02 h	–	–	Saline	Duodenal recovery	dog	43
	0.67 ± 0.12 h	–	–	3% Psyllium + saline	Duodenal recovery	dog	43
	0.57 ± 0.08 h	–	–	1.5% Guar + saline	Duodenal recovery	dog	43
		–	1.27 ± 0.29 h	60% $BaSO_4$	Radiography	dog	11
	–	–	3.5 h	Liquid barium	Radiography	dog	44

50% GET, 50% gastric-emptying time, or the time it takes to empty 50% of the ingested/fed meal; 95% GET, 95% gastric- emptying time; 100% GET, 100% gastric emptying time; BIPSs, barium-impregnated polyethylene spheres.

Table 26-4 Orocecal Transit Times in Dogs and Cats

OCTT	Substrate	Method	Species	Reference
3.4 ± 0.75 h	Mashed potatoes	Sulfapyridine transit	Dog	24
3.7 ± 0.9 h	Dog food	Sulfapyridine transit	Dog	45
3.0 ± 0.9 h	Dog food	Sulfasalazine transit	Dog	25
2.3 ± 0.8 h	Dog food	Breath H_2 excretion	Dog	25
1.6 ± 0.4 h	Lactulose	Breath H_2 excretion	Cat	46
2.8 ± 0.34 h	Cat food	1.5 mm BIPSs	Cat	19
3.0 ± 0.23 h	Cat food	1.5 mm BIPSs	Cat	47

BIPSs, Barium impregnated polyethylene spheres; OCTT, orocecal transit time is the time taken from the oral administration of the test meal to the time when the first portion of the meal reaches the colon.

peristalsis provides only a qualitative assessment unless it can be coupled with quantitative videofluoroscopy.[13,14] The latter technique requires sophisticated equipment and computer software that are generally not available in most clinical practices. Barium enema is now rarely performed in clinical practice, and has been superseded by other imaging techniques. In general, liquid barium studies will be useful only in documenting gross abnormalities of gastrointestinal motility.

Barium Meal

Esophageal peristalsis, gastric emptying (see Table 26-3), and intestinal transit (see Table 26-4) are affected by the physical properties of the meal (solid vs. liquid), size of the ingested particles (large vs. small), and chemical composition (lipids vs. proteins vs. carbohydrates)[5,15]; consequently, barium mixed with food is thought to be a better contrast agent for the determination of gastrointestinal transit. Despite this, barium can dissociate from the food and redistribute into the liquid phase of the ingested meal, which likely accounts for the wide variability in reported transit times. For example, the gastric-emptying time of ground kibble (8 g/kg) mixed with barium sulfate suspension (5 to 7 mL/kg) was reported in the range of 5 to 10 hours in mature Beagles,[16] while total gastric-emptying time ranged from 7 to 15 hours in another study.[17] As with liquid barium studies, GI motility disorders can be diagnosed only if the transit/emptying times are markedly prolonged.

Barium-Impregnated Polyethylene Spheres

Small, indigestible radiopaque markers such as BIPSs have been used to quantitate gastric emptying (see Table 26-3) and intestinal transit times (see Table 26-4) in dogs and cats.[18,19] BIPSs are administered in food as recommended in the manufacturer's package insert, and

two to four abdominal radiographs are taken at convenient intervals over the next 13 to 24 hours.[18,19] The percentage of BIPSs that have transited the stomach and intestine is calculated and compared with standard emptying and transit curves (provided in the manufacturer's package insert). Unfortunately, interpretation of BIPSs emptying and transit data has some of the same limitations as liquid barium and barium meal studies. However because of the widespread availability of radiographic equipment and practitioner expertise, radiographic methods employing liquid barium, barium meal, or BIPSs will continue to be the methods of choice for most practitioners.

Ultrasonography

Ultrasonographic equipment is now more widely available in veterinary practice, and recent studies suggest that US may be a useful noninvasive method for quantitative assessment of gastric emptying (see Table 26-3) in dogs and cats.[15,20] In healthy dogs fed a solid meal labeled with ^{13}C-octanoic acid, there was a strong correlation between the rate of solid-phase gastric emptying assessed by use of gastric emptying ultrasonography and the ^{13}C-OBT (carbon 13-labeled octanoic acid breath test) in dogs.[21] Further research is necessary to validate this method against nuclear scintigraphic imaging and to describe reference ranges for healthy and diseased animals.

Nuclear Scintigraphy

Nuclear scintigraphic imaging is a very effective means of evaluating gastrointestinal motility and is now considered to be the standard method of assessment.[12,15,21-23] ^{99m}Technetium (bound to sulfur or albumin colloid, disofenin, or mebrofenin) and ^{111}indium (bound to diethylene triamine pentaacetic acid [DPTA]) are the radioisotopes most widely used because they are safe, simple to use, and nonabsorbable. Two radionuclide markers can be tracked simultaneously, which allows solid and liquid emptying to be assessed during the same test period. Animals are fasted for 12 to 24 hours after which a test meal is fed incorporating one or two radioisotopes. Left lateral, right lateral, and ventral images are acquired with a gamma camera and integrated nuclear medicine computer system. Gastric, intestinal, and/or colonic regions of interest are identified, and the radioactive counts in these regions are recorded, usually at regular intervals for 6 to 9 hours (gastric emptying), 12 to 24 hours (intestinal transit), or 24 to 36 hours (colonic transit). The expense, limited availability, and radiation hazards associated with this method have limited its widespread clinical application in dogs and cats.

Tracer Studies

Several kinds of tracer studies, including gastric, plasma, and breath tracers, have been developed for the assessment of gastric emptying and/or intestinal transit (see Tables 26-3 and 26-4).

Gastric

Gastric tracer studies involve the serial aspiration of gastric contents after administration in food or by gastric intubation of a known concentration of a nonabsorbable marker substance.[15] Chromium oxide, polyethylene glycol, and phenol red have all been used to assess solid- (chromium oxide) or liquid-phase (polyethylene glycol or phenol red) gastric emptying. The invasive nature of this method precludes its use in anything other than the research setting.

Plasma

Plasma tracer studies take advantage of the site-specific absorption of orally administered drugs following gastric emptying (acetaminophen) or orocecal transit (sulfasalazine). Acetaminophen is poorly absorbed in the stomach and rapidly absorbed in the duodenum, and the appearance of acetaminophen in plasma therefore reflects the gastric-emptying time of acetaminophen.[15] Sulfasalazine is a compound molecule of sulfapyridine and 5-aminosalicylate linked in an azo chemical bond. After oral dosing, most of the sulfasalazine is transported unmetabolized to the distal GI tract where cecal and colonic bacteria metabolize the drug to its component parts. Sulfapyridine is largely absorbed by the colonic mucosa but much of the 5-aminosalicylate remains in the colonic lumen where it inhibits mucosal cyclooxygenase and the inflammatory cascade. The appearance of sulfapyridine in plasma therefore reflects the orocecal transit time of sulfasalazine. Acetaminophen and sulfasalazine plasma tracer studies have been validated in the dog,[15,24,25] but there are no published studies comparing animals in health versus disease. Breath tracer studies take advantage of the site-specific absorption of orally administered compounds following gastric emptying (^{13}C-octanoic acid), or of the site-specific fermentation (molecular hydrogen [H_2] generation) of orally ingested food or carbohydrate following orocecal transit. Both can be detected in expired breath, one reflecting gastric emptying time (^{13}C), the other representing orocecal transit time (H_2). The ^{13}C-OBT has been validated as a measure of solid phase gastric emptying in the dog, but there are no published studies comparing animals in health versus disease.[21] The H_2 breath test has been validated as a measure of orocecal transit time in both dogs and cats.[25]

Manometry

Manometry will have limited application in the diagnosis of cricoesophageal and gastroesophageal achalasia, gastroesophageal reflux, and aganglionic megacolon (Hirschsprung disease),[26] but this technique is currently only performed at major referral centers and university teaching hospitals.

Functional Magnetic Resonance Imaging

Functional MRI has been used to quantitate gastric emptying in humans,[27] but this technique has not yet been validated in the dog or cat. Future MRI usage will likely be limited by expense and necessity for access to specialized equipment.

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CHAPTER 27

Endoscopy

ENDOSCOPIC INSTRUMENTATION

Christopher J. Chamness

Overview of Endoscopy Systems

Endoscopy is a medical procedure that permits the clinician to examine internal structure and to perform diagnostic and therapeutic procedures in a minimally invasive manner. The term *endoscope* originally referred to first-generation flexible gastroscopes, which were also used for upper and lower gastrointestinal (GI) endoscopy, as well as bronchoscopy, in larger patients. The term *endoscope* now refers to all sizes and styles of optical instruments used for internal exams, including both rigid and flexible gastroscopes, bronchoscopes, cystoscopes, arthroscopes, laparoscopes, and otoscopes.

A basic endoscope system typically consists of the endoscope, light source, air pump, video camera (or camera processor), and video monitor. Although it is possible to perform endoscopy without a camera and monitor, the current availability, advantages, and superiority of video systems have rendered fiberscopes and their eyepieces much less popular. The endoscope, light source, camera, and monitor comprise the "imaging chain," which is ultimately responsible for creating the image viewed on the monitor. All of the components contribute to the displayed image, whose quality can only be as good as the weakest link in the chain.

Figure 27-1 illustrates a simple gastrointestinal endoscope "tower." A mobile cart improves portability and accessibility, and should be capable of accommodating all of the components of the endoscope system. Much of the equipment (e.g., light source, camera, monitor) can be used for other endoscopic applications including arthroscopy, laparoscopy, cystoscopy, bronchoscopy, and video otoscopy.

In addition to the components of the imaging chain, the following equipment will be required for a state-of-the-art gastrointestinal endoscopy program:

- Suction pump;
- Biopsy devices, foreign-body retrieval devices, cytology brushes, and balloon dilators; and
- An image-capture system or printer for documentation of findings (optional).

Flexible Gastrointestinal Endoscopes

Not all flexible endoscopes are suitable for gastrointestinal endoscopy. The following features of a gastrointestinal endoscope are essential for the successful imaging of the GI tract:

- Four-way tip deflection (up, down, left, and right);
- At least 180° deflection in the up direction;
- Insufflation, to distend the gastrointestinal tract;
- Irrigation, to clean the distal lens or gastrointestinal mucosa; and
- Suction, to remove air and fluid.

A typical gastrointestinal endoscope consists of three main components: the hand piece, the insertion tube, and the umbilical cord (Fig. 27-2).

Endoscope Hand Piece

The hand piece is held in the left hand as shown in Figure 27-3. The index and middle fingers of the left hand control the suction and air/water valves. Fully depressing the suction or air/water valves will activate suction or irrigation (lens cleaning), respectively. Insufflation is activated by simply covering the hole in the top of the air/water valve using either the index or middle finger. The left thumb is used to control one or both deflection control knobs, which cause the bending motion of the insertion tube. The right hand is used to advance the insertion tube and to turn the deflection control knobs when the left thumb cannot easily reach them.

Each of the deflection control knobs has a lock mechanism, which will secure the tip deflection in a fixed position. These locks may be useful when a lesion or structure is located and the examiner wishes to fix the deflected tip position for a period of time while performing the examination or recording images. In the author's experience, most veterinarians rarely use these locks, and it is important to remember not to attempt to deflect the tip while the locks are engaged.

The hand piece also contains the inlet to the instrument channel, which is contiguous with the suction channel. When not in use, the channel inlet is kept closed with an airtight cap, so that air cannot escape or enter under the pressure of insufflation or when applying suction.

Some video endoscope hand pieces also contain buttons to control some of the electronic features such as image capture, white balance, light intensity, freeze frame, picture-in-picture, and electronic zoom.

Figure 27-1 A gastrointestinal endoscope tower including (*top to bottom*) monitor, camera processor, light source, and digital capture system.

Endoscope Insertion Tube

The insertion tube is the portion of the endoscope that goes into the patient. The tube is marked with 10-cm gradations that indicate the depth of penetration of the tube inside the patient. The insertion tube should be handled with care, as it is prone to damage for the following reasons:

- It contains glass fiber bundles and should not be crushed or excessively bent.
- It can be bitten by the patient if an oral speculum is not securely in place.
- Instruments passed through the channel may cause damage with excessive force.

Figure 27-3 Recommended position of video endoscope handle in left hand.

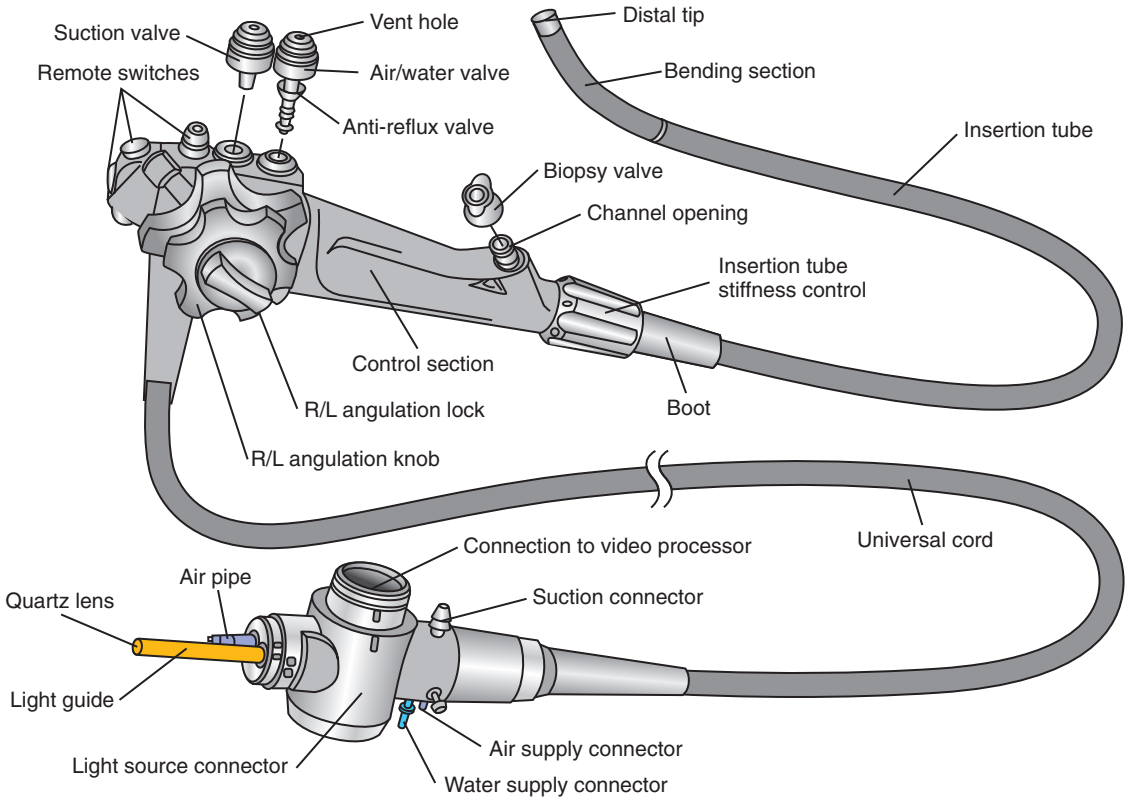


Figure 27-2 External anatomy of an Olympus flexible video endoscope. (Reprinted with permission of Olympus America Inc.)

- It is easy to bang the tip on a hard surface or to close it in a carrying case.
- In the case of video endoscopes (see next section), it contains the sensor chip.

A close examination of the distal tip of the insertion tube reveals the complexity of its array. Three lenses and three channels are located within the tip. The objective lens is the first part of the optical system through which the endoscopic image passes. Light transmitted from the light source passes through two bundles of optical fibers that terminate at two light-guide lenses. The three channels consist of a single large channel for suction and passage of instruments, and two smaller ones for irrigation and insufflation. The irrigation and insufflation channels are covered with small nozzles that direct the flow of air and water across the objective lens.

The nozzles and lenses must be kept meticulously clean for proper functioning and viewing during an endoscopic procedure. Tips and channels are kept free of proteinaceous material and mineral deposits by using (a) an approved enzymatic cleaning solution and (b) demineralized or distilled water during the cleaning process.

The insertion tube also contains the four deflection cables, and many layers of protective materials responsible for keeping the endoscope flexible and watertight.

Endoscope Umbilical Cord

The umbilical cord is the portion of the endoscope that connects to the light source and video processor. The light post and air inlet are inserted into an appropriate light source, which usually contains an integrated air pump for insufflation. Also found in this region are the connectors for a suction pump and the irrigation bottle. A standard suction pump is connected with plastic tubing of appropriate diameter. The irrigation water bottle is an accessory usually supplied by the manufacturer, and it is recommended that only demineralized water be used to prevent the buildup of minerals in the irrigation channel of the endoscope.

The pressure compensation valve found in this part of the endoscope serves two important functions. Before and after every procedure, a simple leakage test should be performed by attaching the manometer provided by the manufacturer (Fig. 27-4) and following factory instructions. Detecting leaks early can minimize costly repairs. The other purpose of the valve is to equalize the pressures between the interior and exterior environment during ethylene oxide gas sterilization or air shipment. The pressure compensation cap should never be left in place when the endoscope is being submerged in fluid, as this will cause fluid to leak into the endoscope.

The video cable connection with tight cap pictured in Figure 27-2 is a feature of true video endoscopes, but not fiberscopes (see next section). It is here that a video cable would be attached to connect the endoscope to a video processor.

Endoscope Dimensions

The key dimensions of an endoscope are its working length, outer diameter, and channel size. The preferred working length depends upon patient size. For example, a working length of 140 cm or more may be required to reach the duodenum of some giant breed dogs, whereas that length would be inconvenient and unnecessary in feline only practice. A small outer diameter (less than 8 mm) is most convenient for traversing the pylorus of cats and small dogs, but a large working channel (2.8 mm) is preferred to maximize the size of biopsy and foreign-body retrieval devices. Because of the diversity in body size and species differences, the desired combination of options may not be available in one model. The most versatile gastrointestinal endoscope for general small animal use will be at least 125 cm in length, no more than 9 mm in outer diameter, with a biopsy channel of at least 2.2 mm. Figure 27-5 shows a gastrointestinal endoscope designed for small animal use with these parameters in mind.

Fiberscopes Versus Video Endoscopes

Before the advent of endoscopic video technology, all flexible endoscopes were dependent upon fiber optics to transmit an image from the tip of the scope to the eyepiece. Thousands of long thin fibers of optical glass are bundled into "coherent image bundles" capable of transmitting images over long distances while curving and bending through tortuous anatomy. Fiberscopes, as they are known, are still very much in use today, especially small-diameter models that are commonly used for respiratory and urinary endoscopy. However, they are most commonly used with a video camera attached to the eyepiece (Fig. 27-6), which enables the endoscopist and other members of the endoscopy team to view an enlarged image on a video monitor.

True video endoscopes were introduced into medical and veterinary practice in the mid-1980s. A video endoscope image is initially

Figure 27-4 Manometer for testing leakage of the endoscope.

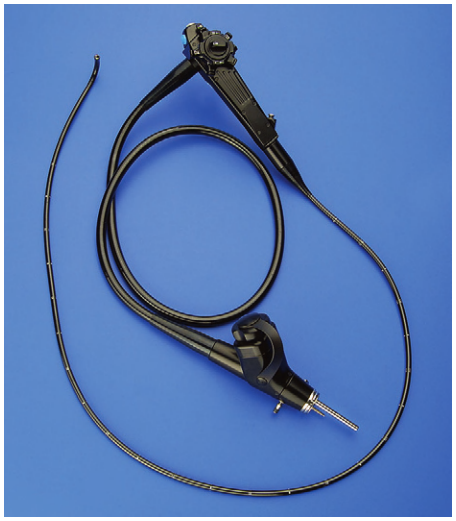


Figure 27-5 A small animal gastrointestinal endoscope with 140-cm working length, 7.8-mm diameter, and 2.8-mm channel.

Figure 27-6 Fiberscope with endoscopic camera attached to the eyepiece.

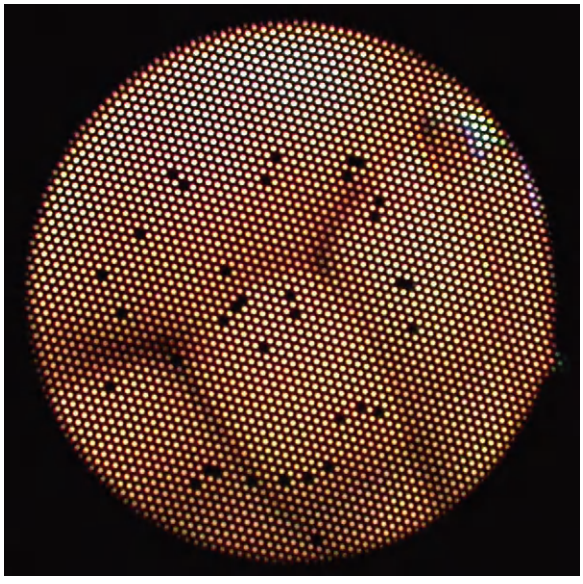


Figure 27-7 Fiberoptic image showing "pixelation" and broken fibers.

sensed by a computer chip (image sensor) in the tip of the endoscope and transmitted electronically to a video processor, and finally onto the viewing monitor. While these endoscopes come at a higher cost, the images are not dependent on fiber technology, consequently they produce images of superior quality. The resolution of fiberoptic images is limited, and they often appear pixelated because of the cladding that surrounds individual glass fibers. Furthermore, it is inevitable that individual fibers in the image bundle will break over time, causing small black spots in the image (Fig. 27-7).

What is often referred to as the "chip in the tip" of a video endoscope is either a charge-coupled device (CCD) or complementary metal oxide semiconductor (CMOS) image sensor. Although both technologies were invented in the late 1960s, the CCD became dominant because it offered superior images with the technology available at the time. These days, both types of image sensors offer excellent performance with proper design. There is renewed interest in CMOS image sensors for endoscopes because of improvements in quality, potential cost savings, and the availability of smaller sensors that could be used to manufacture smaller diameter endoscopes.

It is worth noting that both fiberscopes and video endoscopes contain glass fibers extending the entire length of the umbilical cord and insertion tube. The fiber bundles found in both kinds of scopes are called incoherent because the orientation of the fibers is unimportant. Rather than transmitting images, these fiber bundles transmit light from the light source to the distal tip of the endoscope to illuminate the subject.

Accessories and Instruments for Flexible Endoscopes

A variety of instruments and accessories are available for flexible endoscopes, which may be designed for single or multiple usage (Fig. 27-8). Although single-use instruments have the advantage of being new and sharp, the multiuse instruments tend to be more cost-effective over time. A typical veterinary practice should have at least two biopsy forceps, three or more foreign-body graspers, and two or three balloon dilators available for immediate usage (see Chapter 55). Among the most popular styles of foreign-body retrieval instruments used by veterinarians are two-prong graspers, basket retrievers (dislodgers), and snares. Additionally, a cytology brush with protective tube is useful for both gastrointestinal and respiratory sampling. It is critical that only instruments of the appropriate size, style, and specification are used with any given endoscope. Channel damage by inappropriate instrumentation is a common cause of fluid invasion, which can result in costly repairs. Above all, instruments should never be forced through the channel against obvious resistance. If resistance is met while trying to pass an instrument through a deflected tip, it is recommended to straighten the tip, then pass the instrument before repositioning the tip.

Light Sources and Pumps

Most endoscopic light sources are either halogen or xenon. Halogen is the economical choice, whereas xenon offers a brighter, whiter light at a higher cost. It is important to realize that wattage alone is not necessarily a good indicator of brightness. The wattage simply refers to how much power is being used, but different light source technologies can provide vastly different amounts of light output using the same number of watts of electricity. For example, a 175-watt xenon light source is typically much brighter than a 175-watt halogen light source. Illumination will also depend on the condition and model of endoscope, as well as the light sensitivity of the camera being used. The best way to determine the adequacy of a given light source is to test the complete system in a patient.

Newer light-emitting diode (LED) light sources are becoming more readily available and offer several distinct advantages, including lower cost, longer lamp life (thousands of hours), and improved energy efficiency.

Light sources designed for gastrointestinal endoscopes typically have an integrated air pump and connector that accommodate both the light post and air inlet of an endoscope (Fig. 27-9). The air pump also provides the pressure for irrigation from the water bottle. In some instances the light source and air pump may be separate units, requiring connection by using a special light source adapter and tubing to connect the light source to the air pump.

A suction pump is also required for gastrointestinal endoscopy. A standard unit available in most veterinary practices is sufficient in most cases. It is attached to the connector found on the distal end of the umbilical cord of the endoscope.

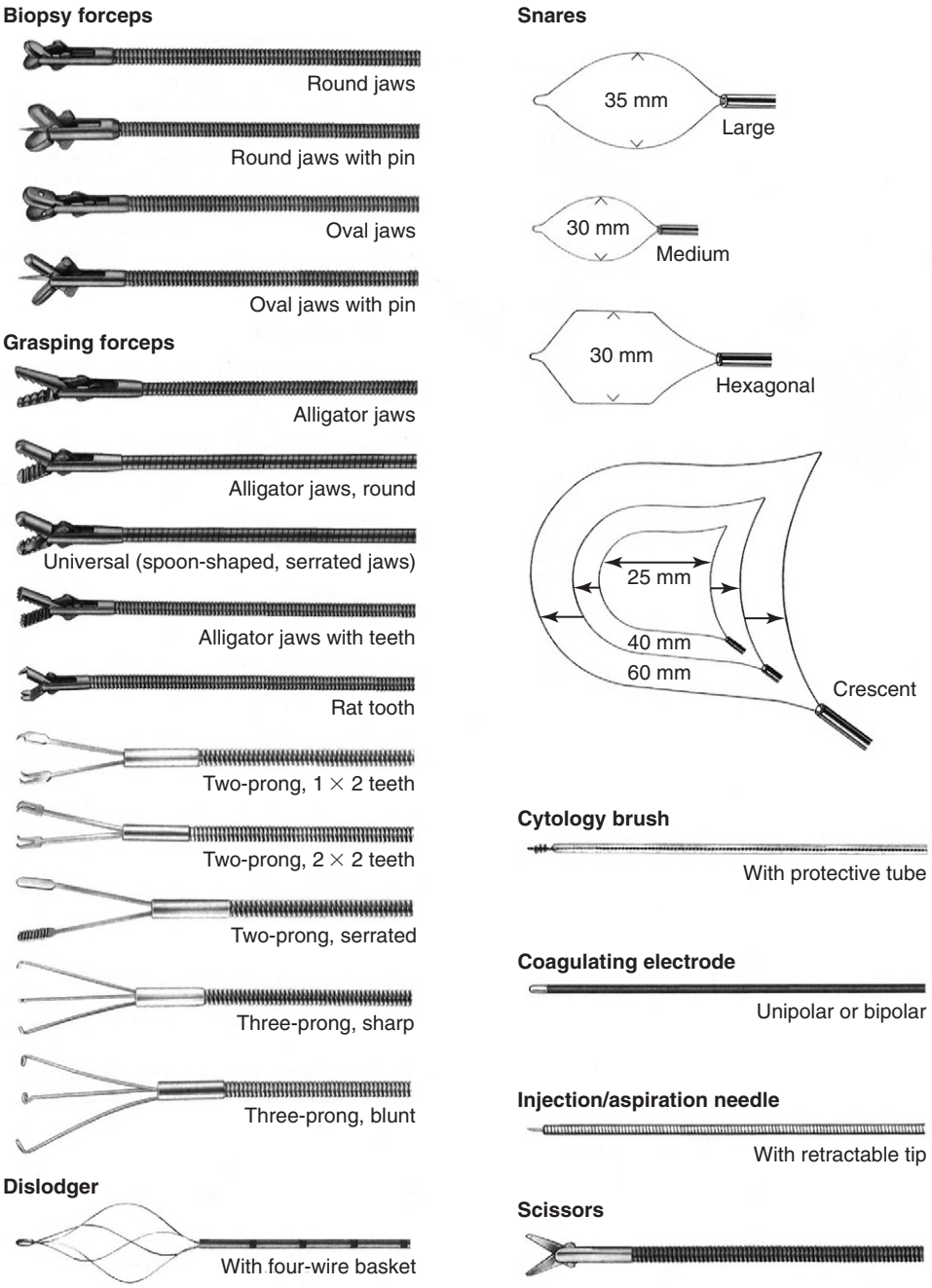


Figure 27-8 Flexible instruments for use through the channel of flexible endoscopes.

Figure 27-9 Endoscope light source with integrated air pump.

Endoscopic Cameras and Monitors

Video cameras and monitors offer the following distinct advantages:

- Enlarged image provides better view of anatomy, pathology, and foreign bodies.
- Ergonomic operation during procedures makes procedures easier to perform.
- Viewing of live video by multiple persons during a procedure facilitates assistance and training.
- Ability to record images or video for medical records, clients, and colleagues.

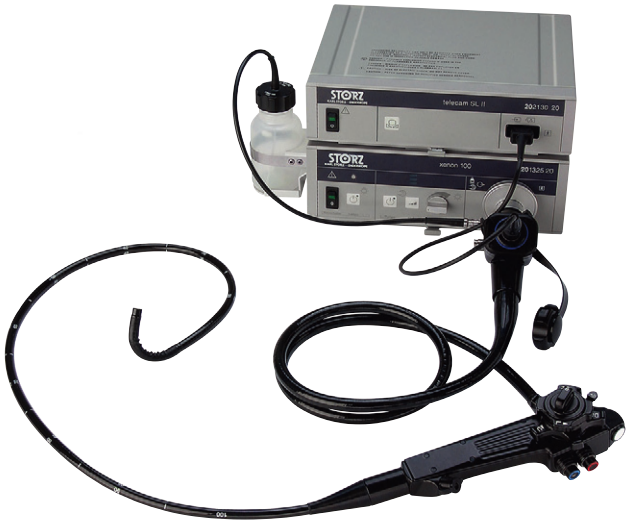


Figure 27-10 Video endoscope attached to camera processor (*top*) and light source (*bottom*)

The basic components of an endoscopic camera system are the processor or "box" and the camera head, which contains an integral cable and connects to the eyepiece of an endoscope (see Fig. 27-6). As camera systems are usually designed to work with specific endoscopes, it is important to consider the compatibility of one with the other before making a purchase. Some camera systems are more versatile than others. The camera head contains a sensor (either CCD or CMOS) similar to the one found in the tip of a video endoscope. A camera head is only necessary, therefore, when using a fiberscope or rigid endoscope with an eyepiece. A video endoscope on the other hand will attach directly to the camera processor (also known as a camera control unit [CCU]) with a cable adapter that is inserted into the same receptacle for a camera head (Fig. 27-10).

Endoscopic cameras are commonly classified as single chip or three chip, and the quality varies widely. Three-chip cameras theoretically provide higher resolution and more accurate color reproduction than single-chip cameras. However, high-quality single-chip video systems currently available may provide excellent image quality suitable for even the most demanding gastroenterologists. High definition (HD) video cameras are a newer technology for the endoscopy industry, fueled by the successes of the consumer electronics industry. It is beyond the scope of this chapter to discuss the intricacies of endoscopic video technology, but the reality is that numerous factors contribute to image quality. The best method of selecting a quality system is to work with a reputable manufacturer who is able to provide a demonstration of various options as well as a warranty. It is also important to take into account the supplier's ability to service the unit over the period of time for which one expects to use it.

Monitor size and style is a matter of preference, but 13- to 20-inch monitors are most commonly used. Because of their size and weight, flat screen monitors are rapidly replacing the standard cathode ray tube (CRT) monitors of the past. The monitor should have the correct input to accept the highest quality video signal (cable) coming from the camera processor, and be of adequate resolution to take full advantage of the camera's capabilities.

Capturing Images and Video

One of the most significant advantages to endoscopic video technology is the capability to capture images during a procedure for review at a later time. This can be achieved in a number of ways, from simply printing images on paper during the procedure to capturing digital images and videos with a dedicated archiving system that can store and manage the data for later retrieval (a searchable database). Some systems also have networking capability, including Digital Imaging and Communications in Medicine (DICOM) compatibility, so that the patient information and image data can be transmitted directly to a hospital's central patient database. Newer digital image capture systems are contained within the same housing as the camera itself, which provides the advantages of space savings and portability (Fig. 27-11).

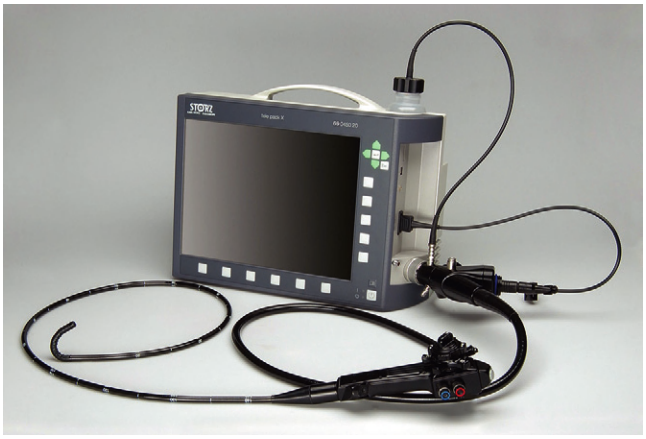


Figure 27-11 Compact unit for veterinary endoscopy includes camera processor, light source, monitor, and digital capture system all in one housing.

ESOPHAGEAL ENDOSCOPY

Michael S. Leib

Indications

Regurgitation is the most important clinical sign associated with esophageal disease in the dog and cat. The initial diagnostic plan usually involves survey thoracic radiographs, barium esophagram, or fluoroscopic evaluation. Endoscopy is often utilized after radiographic studies to obtain supplemental diagnostic information or to provide direct therapy. Esophageal endoscopy with biopsy may assist in the diagnosis of esophagitis, granulomas associated with *Spirocerca lupi* infection, neoplasia, and strictures, as well as to facilitate removal of impacted foreign bodies and stricture dilation.[1-5] A thorough endoscopic examination of the esophagus should also be undertaken whenever gastroduodenoscopy is performed. Chapters 21 and 55 provide more details about the clinical signs related to esophageal disease.

Instrumentation

A flexible endoscope with a working length of at least 100 cm, an outside diameter less than 10 mm, and a 2.8-mm diameter biopsy channel is appropriate for endoscopic examination of the esophagus in most dogs and cats.[6-8] A flexible endoscope should also have four-way distal tip deflection, automatic water–air insufflation, and separate suction pump to evacuate fluid and gas from the gastrointestinal tract. In addition to channel biopsy with a flexible endoscope, rigid biopsy forceps can be passed alongside the endoscope, directly through a rigid endoscope (see the following), or a suction biopsy capsule can be used to obtain samples of the intact esophageal mucosa.

Although not optimal, rigid proctosigmoidoscopes have been used to examine the proximal portions of the esophagus. These instruments are inexpensive and available in a variety of diameters and lengths.[9,10] Rigid biopsy forceps permit sampling of larger pieces of tissue than those obtained with flexible biopsy forceps. Care must be taken during this procedure to grasp only mucosa and submucosa, so as not to perforate the esophageal wall. Rigid endoscopes do have some obvious limitations compared with flexible endoscopies. With rigid endoscopes, the ability to visualize the entire circumference of the esophagus is limited by the rigidity of the scope. Moreover, rigid endoscopes do not have the clarity of mucosal visualization and forceps dexterity associated with flexible endoscopes. Despite these limitations, rigid endoscopes are useful in the removal of foreign bodies lodged in the esophagus.[9,10]

Patient Preparation and Restraint

Endoscopic examination of the esophagus requires the withholding of food, but not water, for at least 12 hours prior to the procedure.[6,11] If esophageal dilation or obstruction is present, endoscopy should be delayed until the esophagus is cleared of ingesta, which may require at least a 24-hour fast. Small amounts of fluid or food within the esophagus can be suctioned or lavaged into the stomach. Larger amounts of food impair visualization and increase the risk of aspiration during extubation and anesthetic recovery. Endoscopic examination of the esophagus requires general anesthesia to restrain the patient and protect the endoscope.[6,12,13]

Diagnostic Procedures

The patient should be positioned in left lateral recumbency.[14] A mouth speculum should be placed between the left upper and lower canine teeth to protect the endoscope from rubbing along the surface of the teeth, and to protect the endoscope if the patient were to awaken during anesthesia. To facilitate passage of the endoscope, the tongue should be grasped and the head and neck slightly extended by an assistant. The insertion tube of the flexible endoscope is passed over the base of the tongue, through the pharynx dorsal to the endotracheal tube, and into the proximal esophagus. The tip of the endoscope should be deflected slightly downward (ventrally) to follow the normal anatomic bend between the mouth and pharynx. The endoscopic tip usually passes easily through the upper esophageal sphincter during the initial insertion, generally making lubrication of the endoscope unnecessary. The proximal esophagus is best examined at the end of the procedure as the endoscope is withdrawn while air is being insufflated (Fig. 27-12).

The esophageal lumen is usually in a state of collapse and when slightly distended has visible longitudinal folds (Fig. 27-13).[6,11,13,15] Constant air insufflation may be necessary to distend the proximal esophagus to allow visualization of the lumen and safe advancement of the endoscope. The endoscopic tip should be centralized within the esophageal lumen by adjusting the inner and outer control deflection knobs. Only minor tip adjustments are necessary, as the esophagus is a relatively straight tube from proximal to distal. By advancing the endoscope only when the lumen is clearly visible, the endoscopist will reduce the risk of esophageal perforation. The endoscope should be advanced until the tip veers away from the center of the lumen. The control knobs should be adjusted slightly to reposition the tip within the center of the lumen, and the endoscope advanced further along the esophagus. In this manner, the endoscope is slowly advanced through the esophagus and into the stomach. Although the entire esophageal mucosa can be visualized as the endoscope is slowly advanced, biopsy and cytologic samples should not be collected until the endoscope is slowly withdrawn at the end of the procedure. Otherwise, hemorrhage could obscure visualization of the esophagus distal to the biopsy site.

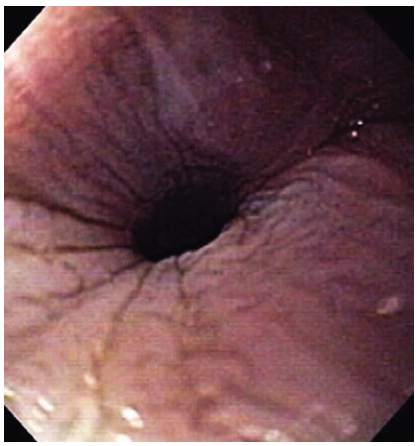


Figure 27-12 Pharyngoesophageal junction. Endoscopic image of the pharyngoesophageal junction of a dog. This view is best obtained as the endoscope is being withdrawn and air is insufflated.

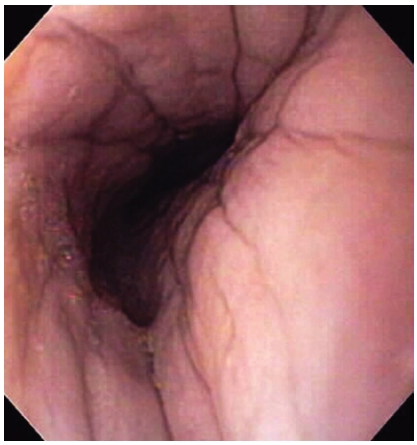


Figure 27-13 Proximal esophagus, dog. Endoscopic image of the proximal esophagus of a dog. The lumen is collapsed and longitudinal folds are visible. Air insufflation will expand the visible lumen and allow the endoscope to be safely advanced while the mucosa is examined.

The normal esophageal mucosa is pale pink, smooth, and glistening. In health, the esophageal lumen is usually devoid of food and fluid. The trachea will indent the distended esophagus, and the tracheal rings should be clearly visible (Fig. 27-14). At the tracheal bifurcation, it is common to see pulsation of the heart and/or aorta. The distal esophageal lumen often remains distended and air insufflation is less necessary. As the esophagus passes through the diaphragm and into the abdomen it may deviate as much as 30° toward the animal's left side.[15] The gastroesophageal junction is normally closed and often assumes a stellate mucosal pattern (Figs. 27-15, 27-16, and 27-17). A small amount of red gastric mucosa can be seen within the distal esophageal lumen.[6]

The normal esophageal mucosa is lined by a stiff stratified squamous epithelium and, because of these properties, it is often difficult to obtain mucosal samples using flexible biopsy forceps. On the other hand, tissue sampling of an intraluminal mass or ulcerated mucosa is relatively easy. To obtain a biopsy sample, the endoscope

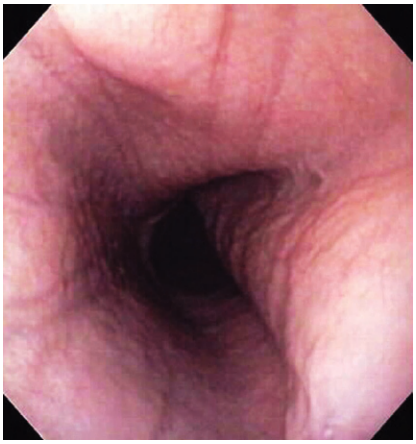


Figure 27-14 Tracheal indentation. Endoscopic image of the tracheal indentation of a dog (seen between the 3 to 4 o'clock position). Air is insufflated to distend the esophageal lumen, which is the dark area at the center of the photograph.

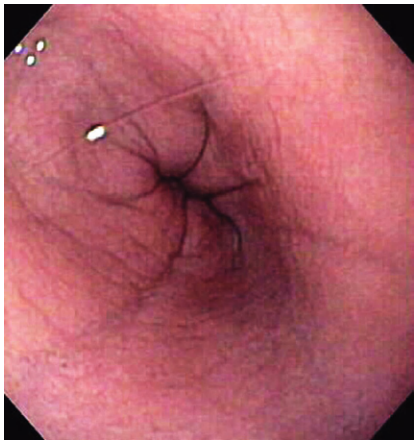


Figure 27-16 Gastroesophageal sphincter. Closeup endoscopic image of the gastroesophageal sphincter of a dog. The sphincter is closed and a stellate mucosal pattern is visible.

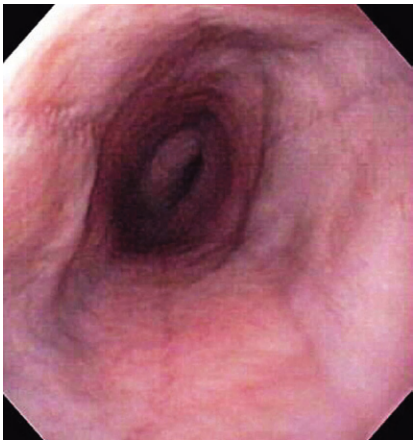


Figure 27-15 Distal esophagus, dog. Endoscopic image of the distal esophagus of a dog. The gastroesophageal sphincter is closed and is visible at the center of the image.

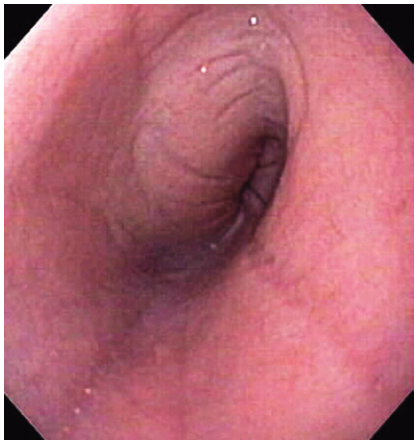


Figure 27-17 Gastroesophageal sphincter. Closeup endoscopic image of the gastroesophageal sphincter of a dog. The directional change of the esophagus, as it passes through the diaphragm into the stomach, is visible as the center of the sphincter is displaced laterally toward the 3 o'clock position of the distal esophageal lumen.

tip should be placed 1 to 2 cm from the area to be sampled and angled toward the esophageal wall. The biopsy forceps are advanced through the biopsy channel until they are visible through the endoscope. The biopsy forceps are opened by an assistant, and the endoscopist advances the forceps until mucosal contact is made. The forceps should be gently advanced until a slight bowing of the forceps can be seen. The assistant closes the forceps and the endoscopist snaps off the tissue sample by withdrawing the closed forceps into the biopsy channel. A small amount of hemorrhage may appear at the biopsy site. For more difficult biopsies, a rigid forceps can be passed alongside a flexible endoscope, or through an accessory rigid endoscope (see next), or a suction biopsy capsule can be used to obtain mucosal samples. As the endoscope is withdrawn, fluid, mucus, and blood should be aspirated through the biopsy channel. After the examination is completed, the area surrounding the endotracheal tube should be examined and any residual fluid should be aspirated to prevent aspiration during recovery.

When passing a rigid endoscope, the head and neck should be fully extended and the endoscope well lubricated. The endoscopic obturator should be placed inside of the rigid scope to facilitate passage into the proximal esophagus. To view the esophagus, the obturator should then be removed, the viewing lens closed, and air manually insufflated with the bulb to distend the esophagus. The endoscope should be slowly advanced as long as the lumen is clearly visible. To obtain a biopsy sample the endoscope should be placed within 1 cm of the lesion, the viewing lens opened, and rigid forceps passed into the endoscope. The esophageal mucosa should be gently grasped and the forceps moved back and forth within the endoscope. If the grasped tissue moves easily, it is safe to completely close the forceps and excise the sample. If the grasped tissue remains fixed to the esophageal wall, the forceps should be opened and the tissue released as a full-thickness tissue sample may have been grasped.

Besides the obvious length and diameter differences between dogs and cats, there are several other differences encountered when performing esophagoscopy in cats.[15,16] First, transverse folds are normally evident in the distal one-third of the feline esophagus as the muscular layer consists entirely of smooth muscle (Fig. 27-18). Second, it is common to visualize superficial blood vessels throughout the length of the feline esophagus (Fig. 27-19).

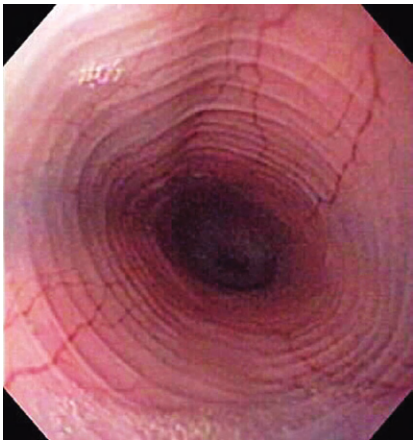


Figure 27-18 Distal esophagus, cat. Endoscopic image of the distal esophagus of a cat. The transverse folds associated with smooth muscle in the distal third of the esophagus are visible. Superficial blood vessels can be seen at 1, 5, and 8 o'clock.

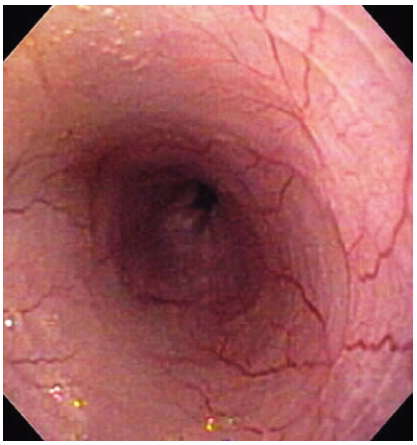


Figure 27-19 Distal esophagus, cat. Closeup endoscopic image of the distal esophagus of a cat. Superficial blood vessels are visible throughout the image. The transverse folds are indistinct because of overdistention of the esophagus with air.

Therapeutic Procedures

Esophageal Stricture Balloon Dilation

Esophageal strictures are best managed with mechanical dilation (Fig. 27-20). Dilation may be achieved with balloon dilation catheters or bougienage tubes.[4,17-19] Esophageal tears have been reported with balloon dilation catheters, but the technology is still thought to be relatively safe in applying radial forces to the stricture site. A greater risk of perforation because of shearing forces applied by the instrument has been attributed to the use of bougienage tubes, although one recent report showed outcomes similar to those reported for balloon dilation.[20] Table 27-1 outlines the parameters needed for a successful balloon dilation. Multiple redilations at 1- to 2-week intervals may be necessary until the stricture is resolved.[3,4,17,21] Esophageal dilation is best performed with direct observation at the time of endoscopy, but it could be performed with videofluoroscopy.

Esophageal Foreign-Body Retrieval

Esophageal foreign bodies should be removed promptly. Prolonged retention increases the likelihood of esophageal mucosal damage, ulceration, and perforation. Rigid or flexible fiberoptic endoscopic retrieval should be the initial approach to treating an esophageal foreign body although fluoroscopic-guided retrieval is also possible.[22]

Figure 27-20 Saline-filled balloon dilation catheter for esophageal dilation. (Courtesy of Cook-Medical.)

Table 27-1 Strategies for Balloon Dilation Treatment of Esophageal Strictures

Intervention	Rationale	Implementation
Barium swallow	Determine location, length, and number of strictures	Barium suspension–30% weight/volume
General anesthesia	High-pressure esophageal dilation stimulates visceral pain	Inhalant anesthesia–e.g., sevoflurane, isoflurane
Patient positioning	Inspection of esophagus and stomach poststricture dilation	Left lateral recumbency for maximal maneuverability
Endoscopes	Direct observation, balloon placement, postdilation trauma	7.5- to 8.5-mm insertion tube, 2.8-mm biopsy channel
Balloon dilation catheters	Multiple catheter lengths and balloon diameters	8 mm × 8 cm to 18 mm × 8 cm balloon catheters*
Procedure	Repeated balloon dilations to achieve increase in luminal diameter	1 to 3 cycles of balloon inflation and deflation/procedure
Manometry	Monitoring of inflation and deflation pressures	Vacuum to 160 psi pressure gauges
Gastrostomy tube placement	Nutritional maintenance during recovery phase with severe strictures	Low-profile gastrostomy tube systems
Recovery phase	Protect esophageal mucosa, inhibit acid secretion, promote healing	Sucralfate, histamine H_2-receptor antagonists
Recurrence/prevention	Most esophageal strictures require 2 to 4 successive balloon dilations	Repeat endoscopy at 13-day intervals as needed

*Sure-Flex Esophageal Balloon Dilation Catheters, Rigiflex Esophageal Balloon Dilation Catheters

A rigid endoscope is most useful in retrieving large foreign bodies, particularly bones or bone fragments.[23] Large grasping forceps are passed through the rigid endoscope to retrieve the foreign body, and in many cases, the foreign body can be pulled into the endoscope for safe removal. Large foreign bodies that cannot be safely removed through the mouth can occasionally be pushed into the stomach and removed by gastrotomy. Smaller foreign bodies are best managed with a flexible fiberoptic endoscope and basket, tripod, or snare retrieval forceps.[24] Flexible endoscopes are particularly useful in retrieving fishhooks.[2]

Esophagostomy Tube Placement

Chapter 33 has a detailed discussion of esophagostomy, gastrostomy, and enterostomy tube placement.

GASTRIC ENDOSCOPY

Albert E. Jergens

Gastric endoscopy (gastroscopy) is a valuable diagnostic tool for evaluating gastric mucosal disease in dogs and cats.[1] The gastric mucosa can be visualized directly and tissue samples can be obtained quickly under endoscopic guidance for histopathologic and/or cytologic evaluation. Gastroscopy is usually performed in conjunction with esophagoscopy and duodenoscopy, and is considered more sensitive than barium-contrast studies for the diagnosis of gastric mucosal disorders.[1] Knowledge of normal versus abnormal appearances, biopsy techniques, and specimen handling are essential to making the correct diagnosis. Therapeutic interventions may also be performed and include foreign-body removal and placement of feeding tubes.

Clinical Indications

Indications for gastroscopy include clinical signs of vomiting, hematemesis, anorexia, nausea, and/or melena. Endoscopically detectable gastric diseases have multiple underlying pathogeneses (Table 27-2). Although gastroscopy is usually performed in animals with chronic signs of gastric disease, it should also be considered in animals with acute vomiting caused by gastric foreign body or gastric ulceration causing hematemesis. Followup gastroscopy may be used to monitor effects of therapy in patients with chronic gastritis or ulcers.[2] Initial diagnostic testing (e.g., complete blood count, serum chemistry, urinalysis, abdominal imaging) serves to eliminate common metabolic disorders (e.g., renal failure, hepatobiliary disease, hypoadrenocorticism, or feline hyperthyroidism) that might mimic primary gastric disease. Endoscopic examination should only be performed after thorough history, physical examination, and diagnostic testing have failed to identify the cause of clinical abnormalities.

Table 27-2 Gastric Diseases or Interventions That Typically Require Gastroscopy

Clinical Problem	Biopsy Recommended
Gastritis (varied causes)	Yes
Gastric neoplasia	Yes
Ulcer erosions	Yes
Chronic hypertrophic gastropathy	Yes
Foreign bodies	No
Physaloptera rara	No
Percutaneous endoscopic gastrostomy (PEG) tube placement	No

Endoscopic Instruments

A flexible endoscope having a working length of at least 100 cm, an outer insertion tube diameter of 9 mm or less, and four-way tip deflection is ideal for most gastroscopic examinations. Endoscopes with an accessory channel diameter of greater than 2.2 mm will accommodate larger biopsy forceps and foreign-body retrieval devices. For inexperienced endoscopists and feline practitioners, an outer insertion tube diameter of 7.9 mm or less will permit easier duodenal intubation when performing esophagogastroduodenoscopy. Video endoscopes are the current gold standard for clinical practice as they provide superior optics with higher resolution when compared to conventional fiberoptic endoscopes. Video endoscopes also permit simultaneous viewing of procedures by multiple personnel (advantageous for training or assistance with interventions such as gastric foreign-body retrieval) and image capture options, such as video recording. The obvious disadvantage of the video endoscopic systems is their cost. Fiberoptic endoscopes are less expensive, and are equally useful for performing a detailed gastroscopy with collection of targeted mucosal biopsies by an experienced endoscopist.[3]

A variety of endoscopic accessories should be on hand for both diagnostic and therapeutic purposes. Multiple biopsy forceps and cytology brushes will be needed for adequate tissue sampling and histologic diagnosis. Both multiple use and "single-use" biopsy forceps are available in a variety of styles for gastroscopic examinations. Similarly, gastric foreign bodies come in all shapes, sizes, and angularities, and will often require specific and sometimes several different types of retrieval instruments to successfully remove the object(s) from the gastric lumen.

Patient Preparation

Dogs and cats requiring gastroscopy should have food withheld for 12 to 18 hours prior to endoscopic examination. This minimizes the amount of residual ingesta in the gastric lumen in most instances. Animals with delayed gastric-emptying disorders may have retained luminal debris, ingesta, or fluids in spite of proper patient preparation. Large-breed dogs (>30 kg bodyweight) undergoing gastroscopy may also have gastric retention of fluids, possibly associated with the stress of hospitalization and handling by strangers. In these instances, careful aspiration of free gastric fluid may still permit adequate visualization of mucosal surfaces for lesion detection and tissue sampling.

Gastroscopy should not be performed for 12 to 24 hours following a barium-contrast study, particularly if gastric retention is suspected. The delay should be sufficient time for gastric emptying of barium to occur and to permit optimal endoscopic viewing of all gastric mucosal regions. Survey abdominal radiography will confirm the presence of retained (gastric) barium if there is a question as to its presence. Suction of liquid barium through the accessory channel should never be performed as residue might adhere to the walls of the biopsy channel.

General anesthesia will be required for gastric endoscopy whether it be for diagnostic or therapeutic purposes. Patients should always be placed in left lateral recumbency as this facilitates passage of the endoscope through the antrum and pylorus. This allows any retained fluid to drain away from these regions into the gastric body and

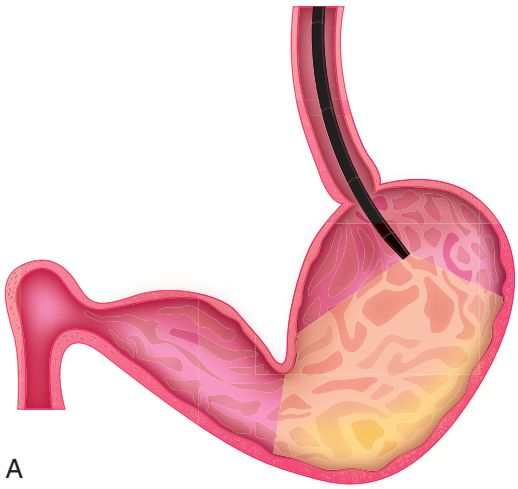
facilitates examination of these structures prior to duodenal intubation. Lastly, a mouth gag or oral speculum should be placed to prevent damage to the endoscope in case the animal should awaken from anesthesia during the procedure.

Performing Gastroscopy

A proper gastroscopic procedure should include direct visual inspection of all areas of the stomach.[1] A working knowledge of the normal gastric mucosal anatomy and anatomic landmarks will help the endoscopist to correctly maneuver the endoscope for viewing the gastric fundus, body (corpus), cardia (retroflexed view), incisura angularis (key anatomic structure), antrum, and the pylorus prior to duodenoscopy. Recognition of the location and appearance of normal gastric landmarks will also help to distinguish morphologic abnormalities of these structures, such as focal ulcers that may occur along the incisura or chronic pyloric mucosal hypertrophy, which might obscure the pyloric orifice.

As the endoscope is advanced along the distal esophagus toward the gastroesophageal sphincter (GES), the endoscopist should note the tone (i.e., open vs. closed) and position of the sphincter orifice. Using gentle forward pressure while insufflating air, the endoscope is directed through the GES and passed with minimum resistance into the gastric lumen. Once the GES is traversed, the endoscope is advanced only a short distance while variable degrees of air are insufflated to gently separate the rugal folds. This allows the endoscopist to achieve spatial orientation within this viscus by visualizing the gastric body (corpus), antrum, and incisura angularis. This "birds-eye" view of the stomach permits a panoramic view of the *gastric body* and greater curvature of the stomach as the insertion tip is moved laterally in a sweeping fashion using both left and right tip deflections (Fig. 27-21). Care is taken to control insufflation such that moderate separation of the rugal folds occurs without overly distending the stomach. A combination of insufflation and aspiration of air optimizes visualization of individual rugal folds and the mucosa along the greater curvature of the gastric body. Once these structures are adequately visualized, the endoscope is advanced through the proximal stomach toward the antrum until the incisura angularis can be identified (Fig. 27-22). This key anatomic landmark appears as a distinct ridge of tissue that serves to separate the body of the stomach from the antrum. The identification of the angularis also allows the endoscopist to orient themselves to the location of the lesser curvature (to the right) and the greater curvature (to the left) when the animal is in left lateral recumbency.

The next endoscopic maneuver performed is the retroversion or J-maneuver, which allows a "head-on" visualization of the angularis and the cardiac and fundic regions of the stomach.[1] This procedure begins as the endoscope tip is positioned at about the level of the angularis or is deflected off the greater curvature proximal to the antrum while the endoscope tip is deflected maximally in an upward direction. With slight forward advancement of the endoscope, the endoscope tip is then rotated laterally until the angularis is visualized "head-on." This view allows the endoscopist to see both the antrum located below this structure and the air-distended gastric body located above it (Fig. 27-23). This "head-on" view of the angularis may not be possible in cats because of anatomic constraints when manipulating the endoscope. To view the cardia and fundus, the endoscope tip is now rotated 180° and retracted toward the esophagus. The endoscope tip is rotated laterally left and right to closely inspect these areas and to view the endoscope as it passes into the stomach through the cardia (Fig. 27-24). Although these regions of the stomach are less



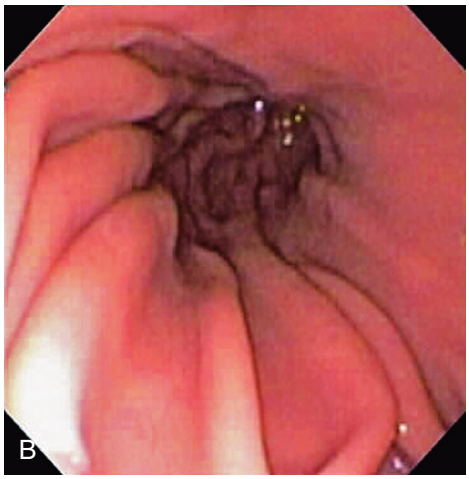


Figure 27-21 "Bird's-eye" view of the proximal stomach as the endoscope is advanced through the gastroesophageal sphincter. **A**, This illustration shows the approximate position of the endoscope. **B**, Endoscopic appearance of the greater curvature of the stomach in a dog photographed from the position of the endoscope shown in **A**.

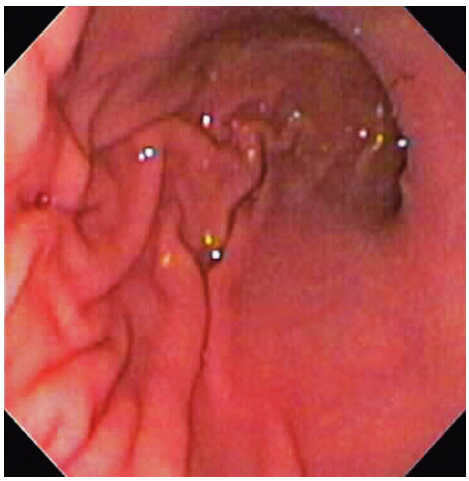
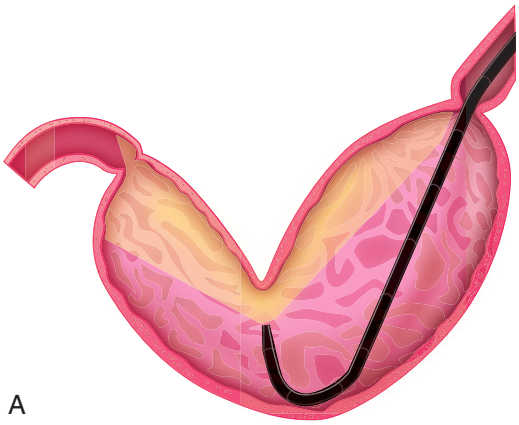


Figure 27-22 Endoscopic appearance of the angularis and antrum in a cat after moderate air insufflation. The antrum is characterized by an absence of rugal folds.



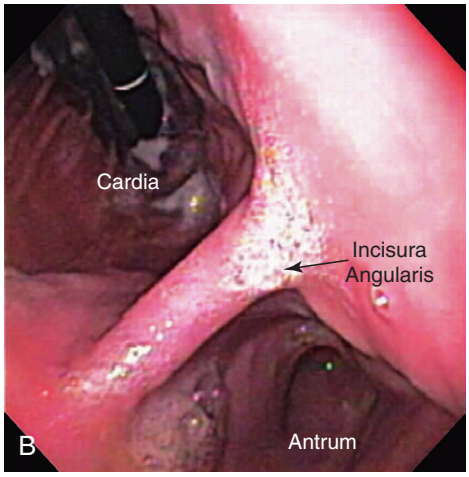
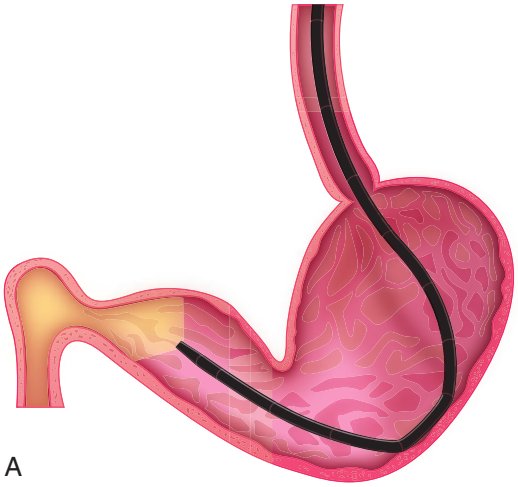


Figure 27-23 Angularis and retroversion (J-maneuver) in a dog. **A**, This illustration shows the approximate location of the endoscope. **B**, Endoscopic appearance of the angularis as viewed "head-on" during the retroversion maneuver. The antral canal is seen at the bottom of the field and the gastric body, fundus, and cardia are viewed at the top. The endoscope is seen in the central background as it enters the esophagus through the gastroesophageal sphincter.



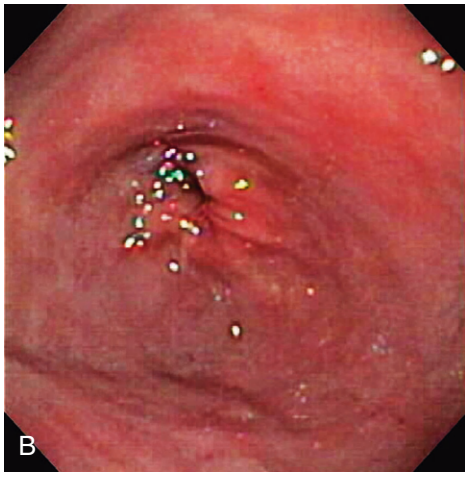


Figure 27-25 Distal antrum and pylorus in a dog. **A**, This illustration shows the approximate position of the endoscope. **B**, Endoscopic appearance of the closed pylorus within a mucosal fold. Only slight changes in tip deflection are required to pass the endoscope through the pylorus.

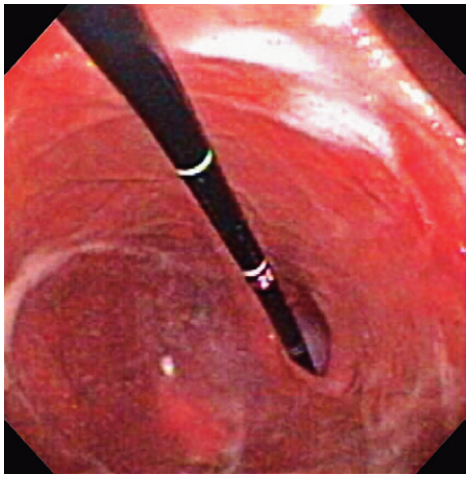


Figure 27-24 Retroversion (J-maneuver) in a dog. Retroflexed view of the endoscope as it passes through the gastroesophageal sphincter.

commonly affected by mucosal disease, this procedure is generally performed quickly and can identify foreign bodies or gastric ulcers, especially in dogs. Retroversion is slowly reversed by advancing the endoscope forward until the proximal antral mucosa and angularis return into view.

The antrum is readily identified by the location of the angularis, the absence of rugal folds, and the observation of peristaltic waves of contraction (usually seen in dogs) that propagate down toward the pylorus. In cats, passage of the endoscope past the angularis and into the proximal antrum may result in a temporary "red out" as the endoscope tip abuts against the antral mucosa. Advancing the endoscope forward with the tip deflected in an upward direction results in observation of the antral canal and pylorus. In most dogs the endoscope can easily be passed around the angularis and through the antral canal. The pylorus is easily visualized in most animals. Exceptions include patients with retained ingesta or accumulated fluids within the pyloric canal. In dogs, the pyloric orifice is often located off center and is partially obscured by fold(s) of mucosa (Fig. 27-25). Cats have a pyloric orifice that is more centrally

located in the pyloric canal. Passage of the endoscope through the pylorus may be easy or difficult. The key to successful passage is keeping the pylorus in the center of the endoscopic field.[1] The position of the pylorus can change as a consequence of antral contractions or breathing patterns by the animal, necessitating slight directional changes of the endoscope tip as it is advanced toward the pylorus. In many dogs, the endoscope is often passed through the pylorus with relative ease. However, in other patients the endoscopist may find it challenging to intubate the duodenum through a closed or "spastic" pylorus. This situation is further complicated by mucosal "red out" as the endoscope tip contacts the pyloric mucosa. Slow gradual directional changes of the endoscope tip will usually be successful in identifying the pyloric orifice in these instances. Steady forward pressure is then applied to advance the endoscope. Excessive force should never be used. Gentle insufflation and careful repositioning of the endoscope tip while advancing will result in eventual success in traversing the pylorus. Pharmacologic manipulation to decrease pyloric tone and facilitate passage of the endoscope through the pylorus has not proven successful in either dogs or cats.[4,5]

Technical Concerns

Gastroscopy can be easily and safely performed in most dogs and cats. Cardiopulmonary complications related to anesthesia or excessive prolonged air insufflation causing gastric distention are uncommon.[6] If respiratory compromise is noted, the stomach should be rapidly deflated to stabilize the patient. The respiratory rate may increase in patients while advancing the endoscope through the pylorus. Passing the endoscope into the antral canal and pylorus of large dogs (>30 kg body weight) may result in inadvertent retroversion (e.g., looping) of the endoscope in the stomach.[1] This situation may occur when excessive air insufflation causes gastric distention and the endoscopist loses orientation within the cavernous lumen. If loop formation occurs, the endoscopist should retract and reposition the endoscope while suctioning off air until the angulus can be viewed. This procedure allows the endoscopist to regain spatial orientation and once again advance the endoscope forward to the pylorus. Small diameter endoscopes (7.9 mm or less) should be used in cats as they are more maneuverable and permit easier duodenal intubation. Gastric perforation is a potential complication of gastroscopy but is rare.

Normal Endoscopic Appearance

The gastric mucosa is normally smooth, pink, and glistening. The rugae appear as linear folds that are uniform in size, shape, and distensibility. Even small amounts of retained gastric or duodenal secretions may obscure portions of the mucosa. Hair can also occasionally be observed within the gastric lumen of cats. The antrum is delineated by the presence of the incisura angularis and is characterized by a paler pink mucosal appearance and an absence of rugal folds. Antral contractions may be observed during gastroscopy in both dogs and cats. The pylorus is easily identified in most animals and may be open or closed.

Abnormal Endoscopic Appearance

Gross mucosal abnormalities are commonly seen in dogs and cats with gastric disease (Fig. 27-26). Lesions may be focal or diffusely distributed throughout the entire gastric mucosa; consequently, careful inspection of all gastric regions will enhance the likelihood that mucosal abnormalities will be detected. Endoscopic lesions of mucosal friability, granularity, and ulcers or erosions are commonly associated with histopathologic abnormalities.[7-10] Friability describes the ease with which the mucosa bleeds upon contact with the endoscope or biopsy instrument (see Fig. 27-26A). An increase in mucosal texture is termed increased granularity (see Fig. 27-26B). Mucosal ulceration-erosion refers to an endoscopically visible breach in the mucosal surface that is often associated with active hemorrhage. Ulcers are focal defects that extend deeply into the adjacent mucosa and often contain hemorrhage and a fibrinonecrotic center (see Fig. 27-26C). Erosions are discrete, superficial mucosal defects that do not have raised margins or necrotic centers (see Fig. 27-26D). Erythema denotes mucosal redness that can be a pathologic or a physiologic response to altered mucosal blood flow, which, in turn, is associated with anesthesia. Mass lesions may be benign (e.g., antral polyp) or malignant (e.g., tumor) and are not readily differentiated based on appearance alone. The presence of food or large volumes of gastric fluids in a properly prepared patient is suggestive of gastric retention. Gastric nematodes (*P. rara*) may also be observed along the gastric body of a dog with a history of chronic vomiting. Finally, alterations in the distensibility of the gastric wall suggest submucosal infiltrative disease or extragastric compression.

Gastric Biopsy

Gastroscopy is usually performed to obtain gastric-tissue biopsies. Tissue samples should be obtained during gastroscopy whether or not endoscopic abnormalities can be identified.[1,3] Histopathologic lesions of the stomach may be present in patients with an endoscopically normal gastric mucosa. Several different styles of biopsy forceps should be available, including those with smooth or serrated cups, with or without a central spike (Fig. 27-27).[11] Personal preference and operator experience are often the main reasons for selection of specific types of forceps. Serrated cup forceps without a central spike are often preferred because they cause fewer biopsy artifacts. The diameter of the endoscope's accessory channel will dictate what size forceps may be used. A channel size of 2.8 to 3 mm facilitates the use of large forceps for mucosal biopsy. The advantage of large forceps is the ability to sample larger and more diagnostic tissue samples. However, the use of forceps that can be passed through smaller diameter endoscopes might still yield excellent quality biopsies for diagnostic purposes.[12]

If gastric lesions are not obvious, the best biopsy samples are obtained from rugal folds along the gastric body. The rugae are prominent and it is easy to grasp large-size tissue samples for diagnostic evaluation. The biopsy forceps are advanced at a 45° to 90° angle into the rugal folds and six to eight mucosal biopsies are collected. Cytologic specimens obtained with a sheathed cytology brush or cytologies made as imprints directly from tissue samples will complement mucosal histopathology.[13] Gross abnormalities of mucosal friability or increased granularity may be biopsied directly. Superficial mucosal erosions should be biopsied at the edge of the lesion. Gastric ulcers require that tissue sampling be performed along the rim of the ulcer at the interface of abnormal and normal tissue. Taking biopsies from the ulcer pit is not advised as the diagnostic yield is minimal and there is some risk of perforation during the procedure. Masses should be biopsied deeply to avoid necrotic surface debris and superficial cells, which may confound the diagnosis. If diffuse neoplasia is suspected, multiple biopsy specimens

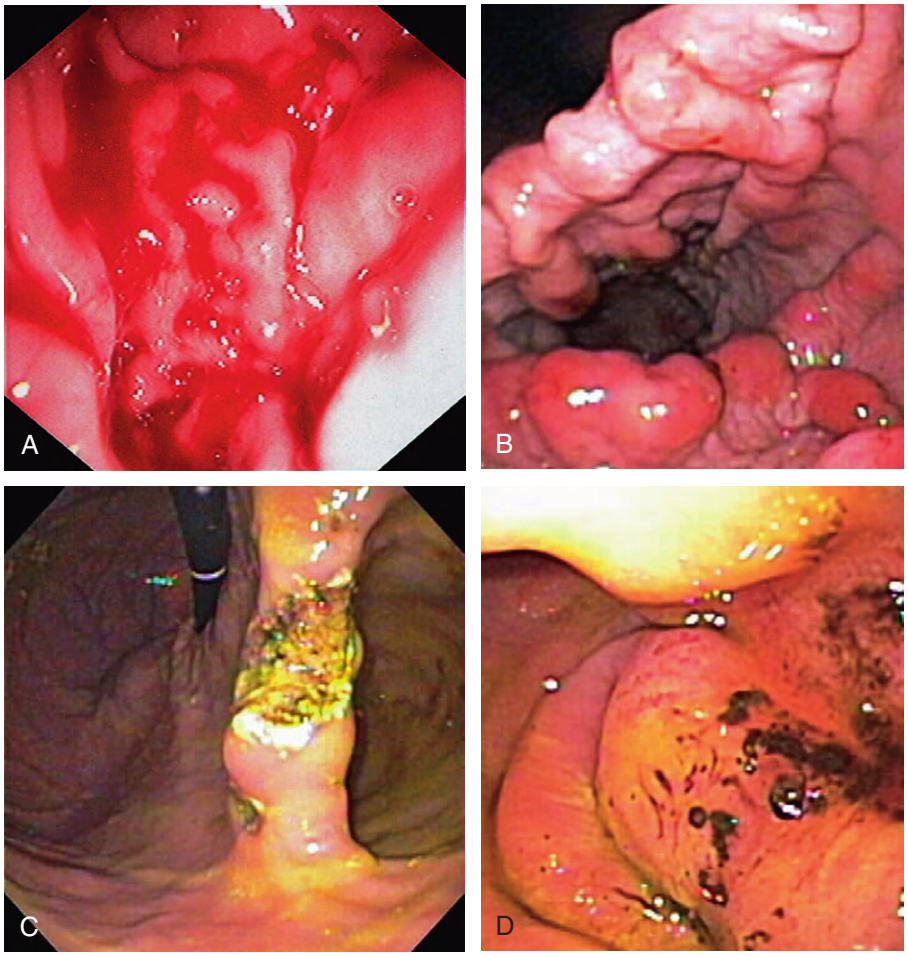


Figure 27-26 Gross mucosal abnormalities seen with gastric diseases. **A**, This image shows mucosal friability of the gastric body. **B**, A severely increased granularity of the gastric rugae. **C**, A focal ulcer along the angularis. **D**, Numerous superficial erosions of the mucosa on the rugal folds. Note that all of these abnormal appearances are commonly associated with infiltrative and inflammatory disorders affecting the gastric mucosa.

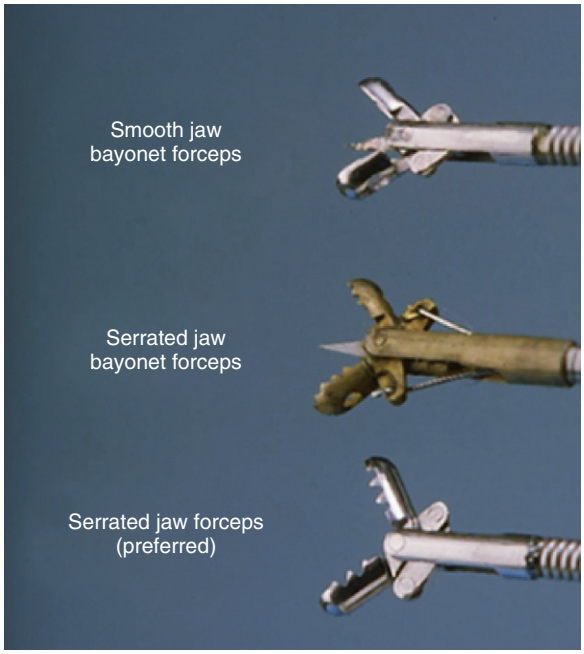


Figure 27-27 A variety of pinch forceps used for acquiring gastric biopsies. The serrated jaw forceps consistently provides the largest tissue samples for histopathologic evaluation and is thus preferred.

collected from deep within the lamina propria should be obtained from both the normal and abnormal appearing mucosa.

Handling of Biopsy Specimens

Endoscopic biopsy specimens are small, fragile pieces of tissue subjected to artifact from handling during the biopsy procedure, mounting, and processing, including microtome sectioning of the paraffin wax–embedded tissue. Biopsy artifacts can be minimized if care is exercised in procuring and handling the specimen. Tissue specimens should be gently teased from the forceps with a needle and placed on lens paper, a cucumber slice, or a specially designed biopsy sponge. Commercial cassettes with precut "sponges" can be used for the submission of endoscopic biopsy specimens (Fig. 27-28). Multiple biopsy specimens can be placed on a sponge, and the sponge is then placed directly into the cassette. The closed cassette is immersed in 10% neutral buffered formalin and submitted to the laboratory.

Cucumber slices can be substituted for plastic sponges and are an excellent medium for the submission of endoscopic biopsy specimens.[11] Mucosal tissue samples are placed on thin slices of cucumber (preserved in alcohol), which are then deposited into formalin containers and submitted for processing. At the laboratory the cucumber slices are removed from the formalin. Then smaller cucumber

Figure 27-28 Endoscopic samples placed in a biopsy cassette for laboratory processing. Samples are aligned in rows on cucumber slices to maintain optimal orientation during tissue sectioning.

sections containing multiple biopsy specimens are arranged in parallel rows and are trimmed away and placed on their side in the processing cassette (e.g., perpendicular to the cassette surface to optimize tissue orientation after sectioning). The tissues are then embedded in paraffin wax. The specimens do not have to be removed from the cucumber slices prior to embedding because the microtome can readily cut through the vegetable material. This technique minimizes specimen handling at the laboratory and consistently yields well-oriented tissues of high diagnostic quality.

Attempts to reorient specimens on biopsy sponges or cucumber slices prior to formalin fixation should be avoided. Specimens should be placed in formalin as soon as possible as tissue dehydration can contribute to artifactual change. Overly dried samples might adhere tightly to the sponge or cucumber and be damaged when removed by the histopathology service. Samples from different sites (e.g., gastric body versus antral mass) should be placed in separate containers and appropriately labeled. The endoscopist should record the number of specimens obtained from each site, relevant endoscopic observations, and salient historical and clinical data on the histopathology form.

Histopathologic Considerations

Taking too few samples during endoscopic examination is generally more problematic than taking too many. Superficial, focal disease generally warrants procurement of fewer samples (e.g., three to four) versus deep focal disease (i.e., a mass that is covered with normal-appearing mucosa) where probably six or more samples should be obtained. If no focal lesions are seen, then the presence of diffuse disease is assumed and multiple specimens should be obtained. A recent study aimed at identifying the minimum number of biopsy specimens to be collected from the stomach suggested a minimum of six marginal or adequate biopsy samples from the feline stomach and six adequate or 10 to 15 marginal samples from the canine stomach.[14] This practice helps ensure that several adequate tissue samples will be available for review by the pathologist, and that focal, patchy lesions will not be missed. The morphologic information obtained from such evaluation depends on the depth of the tissue, total volume of tissue obtained, and orientation of the tissue sample.

Proper orientation of biopsy specimens is an important consideration. Paraffin wax embedding of each biopsy specimen individually within a composite block increases the likelihood that several tissues will be optimally oriented. Serial sections placed in several rows on a single slide are then evaluated. Careful orientation, expert serial sectioning, and the avoidance or recognition of mechanical artifacts typically yields histopathology slides of consistently high quality that allow the pathologist to provide the most accurate evaluation possible.

Interventional Gastroscopy

Percutaneous endoscopic gastrostomy (PEG) tube placement has found wide application in providing enteral nutritional support to small animal patients (see Chapter 33).[15,16] Placement of a PEG tube is useful for feeding dogs and cats when it is necessary to bypass the mouth, pharynx, or esophagus. Common indications for gastrostomy tubes include esophagitis or esophageal trauma, pancreatitis, megaesophagus with aspiration pneumonia, or feline hepatobiliary disease. Gastroscopy is required to assure correct placement of PEG tubes; specifically that the bulb of the feeding catheter is not positioned near the antrum or the cardia. Complications associated with PEG placement are rare. Occasionally, a portion of the feeding catheter breaks away during catheter removal, requiring repeat gastroscopy to remove the retained catheter fragment.

Removal of gastric foreign bodies can often be performed with flexible equipment.[3,17] Endoscopy provides minimally invasive visual assessment of the retained object and permits adept retrieval in comparison to surgical removal. Bones, fishhooks, sewing needles, and linear foreign bodies can all lodge in the stomach. A variety of instruments available for foreign-body retrieval with flexible endoscopes are reviewed elsewhere.[3,17] The diameter of the accessory channel of the endoscope will significantly influence the type and size of grasping instruments that can be used. A working channel diameter of 2.8 mm is ideal for accommodating the most useful retrieval devices.

Sturdy forceps, such as a two-pronged rat-tooth instrument, are essential for removal of large heavy objects (e.g., bones) that create considerable resistance when dragged across the mucosa. A four-wire basket works well for balls and some rocks. One limitation of this instrument is that the wires may be spaced too closely together to fit around some objects. Three-prong wire snares can readily grasp soft pliable foreign bodies (e.g., clothing, tinsel, cellophane) but are insufficiently strong for heavy objects. An "overtube" may be useful in protecting the mucosa during removal of sharp foreign bodies such as bones, glass, and fishooks.[3,17] The endoscope is passed through the larger-diameter overtube. After grasping the foreign body, the endoscope with the attached foreign body is pulled into the overtube thereby protecting the mucosa from further trauma. Some foreign bodies may not be able to be pulled through the lower esophageal sphincter (LES) regardless of the retrieval instrument used. Overall, complications associated with the presence or extraction of gastric foreign bodies are uncommon and long-term prognosis is excellent with successful endoscopic removal.[18]

INTESTINAL ENDOSCOPY

Thomas Spillmann

Intestinal endoscopy has been used primarily in the diagnosis of intestinal inflammation, malignancy, ulcer, and anomalies such as lymphangiectasia. More recently, advanced interventional procedures have been introduced such as endoscopic retrograde cholangiopancreatography and endoscopy-assisted nasojejunal tube placement. More advanced endoscopic methods such as endoscopic ultrasound, double-balloon endoscopy, and wireless capsule endoscopy are now being introduced into clinical veterinary medicine.

Standard Push Enteroscopy of the Small Intestine

Indications

Small intestinal endoscopy (standard push enteroscopy) is indicated in dogs and cats with chronic or recurrent small bowel diarrhea, ill-defined vomiting disorders, recurrent abdominal pain, weight loss of unknown origin, and signs of gastrointestinal bleeding, such as hematemesis, melena, and microcytic, hypochromic anemia.[1-3] The decision to perform endoscopy should be based on the risk of anesthesia, and the likelihood of establishing a definitive diagnosis, prognosis, definitive treatment plan, and positive outcome.

Standard push enteroscopy of the small intestine is limited to the duodenum, proximal jejunum, and terminal ileum, the latter of which can be reached via colonoscopy.[1] Most of the jejunum is inaccessible with standard 100-cm gastrointestinal endoscopes. To diagnose pathologic processes that affect the jejunum in dogs and cats, laparoscopy and laparotomy with full-thickness biopsy are reasonable alternatives to standard push enteroscopy. Endoscopic alternatives such as double-balloon and wireless capsule endoscopy for distal enteroscopy have proven efficacy in humans,[4] and have already been used in dogs. Wireless capsule endoscopy may be more useful in larger-breed dogs in which the intestinal diameter permits passage of the capsule.[5-7] One experimental study in Beagle dogs concluded that wireless capsule endoscopy detected more artificial lesions (sutured plastic beads) in the small intestine than push enteroscopy.[7] More studies will be needed to determine the overall efficacy of wireless capsule endoscopy in the diagnosis of canine and feline gastrointestinal disease. Because double-balloon and capsule endoscopy still have limited distribution in veterinary medicine, most clinical decisions will be based on standard push enteroscopy, laparoscopy, or diagnostic laparotomy.

Chronic or recurrent small bowel diarrhea and weight loss can be caused by either systemic or intestinal diseases. After systemic diseases have been excluded, the decision for or against endoscopy is based on:

- Clinical assessment of disease severity,
- Response to previous empirical treatments,
- Results of laboratory tests, and
- Findings from other noninvasive imaging techniques (e.g., abdominal radiology and ultrasound).

Disease severity in dogs with suspected inflammatory bowel disease (IBD) may be quantified with the canine IBD activity index (CIBDAI), an index representing the sum of six clinical variables, including attitude/activity, appetite, vomiting, stool consistency and frequency, and weight loss.[8] A similar feline IBD (FIBD) index has been developed for use in cats.[9] A definitive relationship between CIBDAI and FIBD index scores and histopathologic findings has not yet been established. In contrast to an initial report that the CIBDAI correlates well with histology,[8] more recent studies have been unable to show any correlation.[10,11] At this time, high CIBDAI (and FIBD) scores should probably be seen as an indication for intensifying the diagnostic workup, especially when the patient does not respond to empirical treatment, laboratory results suggest systemic consequences of an intestinal disease process, or imaging results point to a specific disease process. The role of endoscopy in the monitoring of therapy and CIBDAI scores is also unsettled, because histologic changes might not improve, despite significant clinical improvements.[11,12]

Nonresponse to empirical treatment is another indication for direct endoscopy. In patients that have failed to respond to dietary modification, parasiticides, and antibiotics (with or without modulatory effect),[13,14] it seems reasonable to expect a higher likelihood of endoscopic findings that will influence treatment decisions. It has been shown in one study, for example, that dogs with glucocorticoid-responsive enteropathy have more severe histologic changes in the small intestinal mucosa than dogs with food-responsive enteropathy (60%).[15]

Push enteroscopy is clearly indicated in patients with clinical signs of upper gastrointestinal hemorrhage, that is, melena and hematemesis. It should be remembered however that push enteroscopy has distinct limitation in identifying jejunal sites of hemorrhage. Laparoscopy or laparotomy may be needed to diagnose causes of jejunal bleeding.

Laboratory tests are used in the assessment of systemic involvement and the need for intensified diagnostic workup. Useful laboratory parameters include serum total protein, albumin, cobalamin, folate, and C-reactive protein (CRP). Fecal α_1-antiprotease determinations will confirm protein-losing enteropathy (PLE) but will not differentiate among the various causes of PLE.

Hypoproteinemia is generally associated with a poorer prognosis and the necessity for more intensive medical therapy.[10,15,16] Push enteroscopy is a favorable alternative to laparotomy in PLE patients, especially when it is used to prove lymphangiectasia as the cause of PLE.[17]

Low serum cobalamin (vitamin B_{12}) and folate concentrations may be another indication for endoscopy. Concurrent cobalamin and folate depletion implies longstanding malabsorption when exocrine pancreatic insufficiency and small animal bacterial overgrowth have been excluded as the cause for vitamin B_{12} deficiency.[18,19]

Serum and fecal markers of inflammation may provide useful indicators of the need for small intestinal endoscopy. Canine serum CRP[8] and fecal calprotectin[20-22] have been suggested as noninvasive biomarkers of active inflammation, although the sensitivity and specificity of these assays have not been determined. Increased fecal α_1-antiprotease concentrations are associated with intestinal histopathology more often than not,[23] and may signal the need to perform gastrointestinal biopsies.[24]

Abdominal ultrasound is helpful in determining whether endoscopy, laparoscopy, or laparotomy should be chosen as the next diagnostic step. Laparotomy with full-thickness biopsy of the intestinal wall is indicated when ultrasound reveals marked thickening, irregularity, and loss of structure of the intestinal wall. These sonographic findings are strongly associated with neoplastic processes.[25-27] Endoscopy is indicated when abdominal ultrasound reveals intestinal hyperechoic mucosal striations in a hypoproteinemic patient. The finding is associated with lacteal dilation in patients with intestinal lymphangiectasia.[28] However, mucosal striations are neither specific enough to differentiate lymphangiectasia from other intestinal disorders nor predictive of the histopathologic severity.[29] Consequently,

ultrasound cannot replace endoscopic and histologic examination of the small intestinal mucosa. This is particularly true for IBD.[30]

In cats, because standard push enteroscopy may not have the same diagnostic value as in dogs, laparoscopy or laparotomy may be the preferred diagnostic method. In cats with IBD, ultrasonographic findings appear to have a better association with the histologic grade than endoscopy.[31] It has also been reported that full-thickness biopsy specimens are more useful in differentiating lymphoma from IBD in the small intestine.[32,33] In another important species difference, chronic FIBD may be complicated by concurrent pancreatitis and cholangitis (so-called triaditis). If these conditions are to be considered, laparotomy or laparoscopy with biopsies from all three sites may be more appropriate.[34]

Contraindications, Complications, and Limitations

Hypoproteinemia, hypovolemia, hypotension, coagulopathy, and excessive anesthetic risk are the most important contraindications for intestinal endoscopy. Intestinal distention and perforation are the most important (and life-threatening) complications of intestinal endoscopy. The most important limitations of intestinal endoscopy are the inability to differentiate lymphoma from severe IBD in some cases,[32,33,35] and the inability to safely retrieve many intestinal foreign bodies

Technical Requirements

Standard push enteroscopy of the small intestine requires the same flexible endoscopy equipment as described for gastroscopy. The diameter of the outer insertion tube should not exceed 9 mm. A 9-mm–diameter endoscope can be used in all cats and dogs weighing 4 or more kg. For cats and dogs weighing less than 4 kg, an endoscope with smaller diameter (e.g., 7.8 mm) would be more appropriate. In large-breed dogs, to achieve duodenal intubation and examination, the length of the endoscope should be at least 130 cm. In humans, four tissue biopsies are usually sufficient to characterize the disease and its severity.[36-38] In companion animals, it has been recommended that at least eight individual tissue pieces should be taken.[39] The best tissue sampling is performed with a biopsy forceps of 2.8-mm diameter. For biopsies of the small intestinal mucosa, side-opening cup forceps provide the best mucosal biopsies. With this approach the intestinal villi are sampled in the longitudinal rather than the transverse orientation. This allows better processing of the samples for histopathologic evaluation Spike forceps may be used but it should be recognized that they induce puncture artifacts.

Patient Preparation

Standard patient preparation for push enteroscopy includes a 12- to 18-hour fast, preoperative medications (e.g., dexmedetomidine and butorphanol), propofol induction, and isoflurane/oxygen or sevoflurane inhalant anesthesia. Atropine or glycopyrrolate should be given 30 minutes before dexmedetomidine to diminish the undesirable side effects of dexmedetomidine.[40] Duodenal intubation is technically more difficult in animals premedicated with atropine, butylscopolamine, atropine/opioid combinations, L-methadone, metoclopramide, or glucagon.[41,42]

Procedure

The patient is initially placed in left lateral recumbency to facilitate passage of the endoscope into the pylorus and duodenum. Following intubation of the esophagus and stomach, the endoscope is advanced into the distal antrum, and the endoscopic tip is pressed gently against the pylorus while maintaining it in the center of the pyloric lumen. The distal end of the endoscope is advanced slowly downward while maintaining pressure against the pylorus, which eventually opens to permit passage into the duodenum.

The small intestinal mucosa and villi are assessed while pushing the endoscope under visual control as far as possible into the duodenum. In cats and small dogs, it is often possible to reach the proximal jejunum. The World Small Animal Veterinary Association (WSAVA) Gastrointestinal Standardization Group has developed a standard protocol for the assessment of endoscopic findings (see Figs. 27-46 and 27-47). The report should contain general macroscopic findings such as mucosal appearance, masses, polyps, foreign bodies, parasites, and other luminal abnormalities. A grading system (normal, mild, moderate, severe) should be used to describe lesions such as failure to inflate the lumen, hyperemia/vascularity, edema, discoloration, friability, texture, hemorrhage, erosion/ulcer, and lacteal dilation.[43]

Findings

The normal duodenal and jejunal mucosa has a velvet appearance caused by the villi of the small intestine. The color of the canine intestinal mucosa is reddish pink (Fig. 27-29), while the feline intestinal mucosa has a lighter color, varying from cream to slightly reddish (Fig. 27-30). Peyer's patches represent the lymphatic tissue

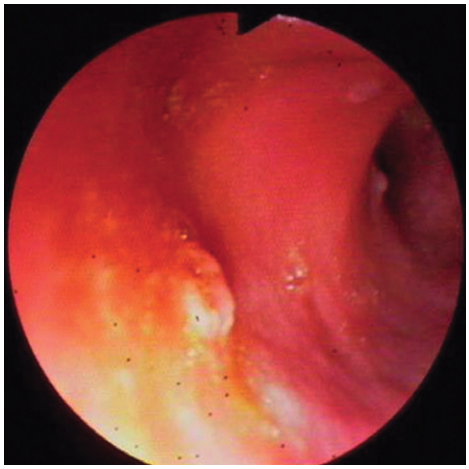


Figure 27-29 Endoscopic picture of normal small intestinal mucosa in the duodenum of a healthy Beagle, showing also the major, minor, and accessory papillae.[54]

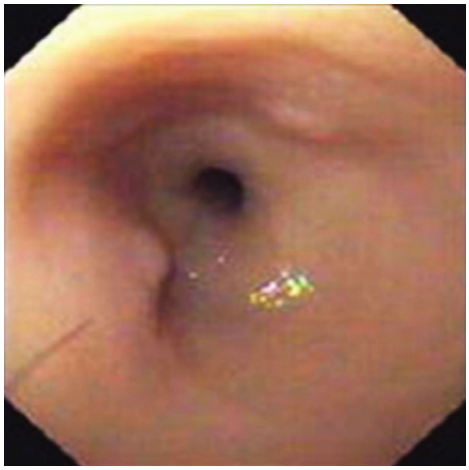


Figure 27-30 Endoscopic picture of normal small intestinal mucosa in the duodenum of a European Shorthair cat showing also the rare occurrence of major and minor papillae.

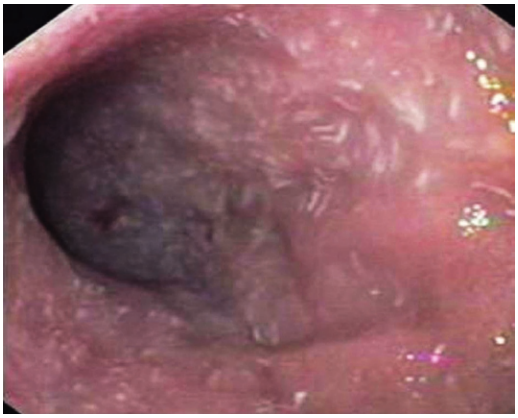


Figure 27-31 Endoscopic picture of the small intestine of a Yorkshire Terrier with protein-losing enteropathy, showing multiple white villi with histologically confirmed severe lymphangiectasia.[17]

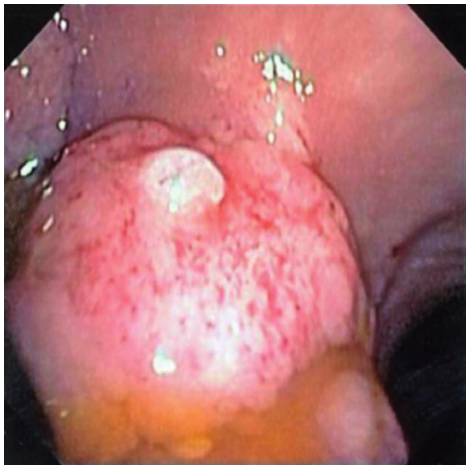


Figure 27-32 Endoscopic picture of the cranial duodenum of a German Shepherd dog, showing a histologically confirmed duodenal carcinoma involving the major papilla.

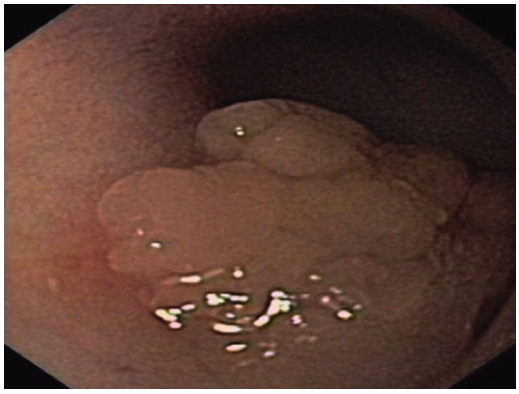


Figure 27-33 Endoscopic picture of the cranial duodenum of a Domestic Shorthair cat, showing a histologically confirmed papillary adenocarcinoma.

associated with the intestine. They appear as shallow, 2- × 1.5-cm craters and can nearly always be visualized in dogs on the lateral wall of the small intestine, starting from the descending duodenum distally. The major duodenal papilla, representing the opening of the common bile duct and the pancreatic duct, can be found in both cats and dogs. Dogs usually also have a minor duodenal papilla, which is the opening of the accessory pancreatic duct of the exocrine pancreas. Dogs can have up to two accessory papillae corresponding with pancreatic ducts (Fig. 27-31). In cats, a minor papilla is rare but possible (Fig. 27-30).

When ileal endoscopy is performed (see "Colonic Endoscopy" section), the patient must be prepared as for colonoscopy to successfully intubate the ileocolic sphincter. Biopsies of the ileal mucosa can be sampled directly or taken blindly by gently passing the biopsy forceps through the ileocolic sphincter if passage through the sphincter is impossible.[1]

Macroscopic findings in the duodenum include intraluminal contents such as bile, food, foreign material (e.g., trichobezoars in cats), blood, and occasionally helminths. Abnormalities affecting the intestinal wall include edema, discoloration, friability, hemorrhage, erosion/ulcer, lymphangiectasia (see Fig. 27-31), and masses (Fig. 27-32 and 27-33). The absence of macroscopic abnormalities does not exclude severe histologic changes in the mucosa and submucosa. Furthermore, macroscopic changes are never pathognomonic for one disease process; for example, endoscopic findings of alimentary lymphoma can resemble lymphoplasmacytic enteritis.[44] Therefore, endoscopy of the small intestine should always be accompanied by mucosal biopsies for histologic interpretation.

Biopsies should be taken with a standard biopsy forceps or forceps with side-opening cups to preserve the longitudinal orientation of the intestinal villi. The best biopsy results are achieved when the cups of the biopsy forceps can be attached at a 90° angle to the intestinal wall. If this is not possible, sampling can be improved by air suction applied during the biopsy. Tissue samples are taken out of the forceps without squeezing, by using a blunt probe instead of a sharp needle to avoid damaging the forceps cups. The biopsies should be placed on a small wooden plate, plastic platform, or cassette in the same direction as they were in the cups of the biopsy forceps. This will facilitate the positioning of the intestinal villi (by the pathologist) in the longitudinal orientation. Tissue dehydration, for example, under a strong light source, should be avoided. The tissue platform is placed in a transport tube containing 10% formalin solution. The number and quality of the tissue samples plays an important role in the sensitivity of histologic findings.[43] A minimum of eight biopsies should be taken per site or gastrointestinal lesion.[39]

Endoscopic aspiration of the intestinal contents has been recommended for protozoal diagnosis, but is probably of limited diagnostic value. In one study, only six of 394 endoscopic aspiration samples from dogs and cats were diagnostic for *Giardia*, of which three cases were also positive in fecal flotation.[45] Duodenal fluid culture has been recommended for the diagnosis of small intestinal bacterial overgrowth (SIBO), but it, too, has limitations in sensitivity and specificity.[46,47]

Endoscopic Retrograde Cholangiopancreatography

Endoscopic retrograde cholangiopancreatography (ERCP) is a combination of endoscopy and fluoroscopy that is used to perform radiographic imaging of the biliary and pancreatic ductal systems.[48-55]

Indications

Endoscopic retrograde cholangiography (ERC) has had most of its applications in human medicine and is indicated in the diagnosis of extrahepatic cholestatic disorders caused by biliary tract stones, papillary stenosis, biliary tract inflammation, and acute (obstructive) pancreatitis, and in the control of postsurgical bile duct pathology.

Endoscopic retrograde pancreatography (ERP) is mainly used to differentiate pancreatic carcinoma from chronic pancreatitis.[48,56] Therapeutic applications for ERCP include extraction of bile stones, placement of drainage tubes or biliary stents, and performance of endoscope-guided sphincterotomy or papillectomy for the treatment of papillary stenosis.[48]

Contraindications, Complications, and Limitations

ERCP is contraindicated in patients with complete extrahepatic biliary obstruction when diagnostic endoscopy cannot be followed immediately by therapeutic intervention. Another contraindication is a pancreatic pseudocyst when the cyst cannot be drained immediately. Bacterial contamination of a pancreatic pseudocyst or of dilated bile ducts above a stenosis can cause life-threatening complications. Therefore, pseudocysts should be ruled out with abdominal ultrasound before performing ERCP.[49]

Complication rates of 0.7% to 1.38% for diagnostic ERCP have been reported in human studies.[57,58] Complications include acute pancreatitis (0.2%), purulent cholangitis (0.16%), sepsis (0.12%), injury of the common bile duct (0.08%), misinterpretation of artifacts (0.08%), and sedative-induced adverse effects (0.08%).[57] ERCP studies performed in healthy beagle dogs and dogs with chronic gastrointestinal disturbances have not revealed any important clinical complications,[54,55] although ERCP may be followed by a transient increase in serum amylase, lipase, and trypsin that returns to reference range within 1 to 2 days.[53]

In veterinary medicine, most uses of ERCP are limited by the size of the duodenoscope. Using a standard duodenoscope with a distal end outer diameter of 11 mm (JF 1T10; Olympus Medical Systems Corp., Tokyo, Japan), ERC was successful in 20 of 30 dogs (67%) and ERP in 21 of 30 dogs (70%). Successful intubation was impacted by intraduodenal food, mucus, or blood, problems in papillary cannulation, stomach overdistention, changes in duodenal mucosa, and body size. Because of size differences, ERCP is impossible to perform with a standard duodenoscope in dogs weighing less than 10 kg.[55] However, own investigations have shown that ERCP is also possible in cats with a body weight of 4 kg when using a pediatric side view duodenoscope (e.g., PJF 160, Olympus Medical Systems Corp., Tokyo, Japan).[56]

Technical Requirements

In contrast to standard push enteroscopy, ERCP requires a duodenoscope with a 90° side viewing optic (Fig. 27-34). For dogs larger than 10 kg body weight, a standard duodenoscope with a distal end outer diameter of 11 to 12 mm can be used.[53-55] For smaller dogs and cats, a pediatric duodenoscope (e.g., PJF 160; Olympus) with a distal end outer diameter of 7.5 mm is a viable option (Fig. 27-35).[56,59]

ERCP guidewires and catheters are necessary for intubation of the duodenal papilla and for injection of an iodine contrast medium into the biliary and pancreatic duct system (see Fig. 27-34). Additionally, fluoroscopy equipment is needed to monitor the filling of the biliary and pancreatic ducts and to obtain still or dynamic images. The contrast medium used for radiographic imaging of the pancreatic and extrahepatic biliary ducts by ERCP are iomeprol (Imeron 300; Bracco Byk Gulden, Konstanz, Germany)[53-55] and iohexol (Omnipaque 350; Schering, Berlin, Germany).

Patient Preparation

Patient preparation and anesthesia are similar to those for standard push enteroscopy of the upper gastrointestinal tract. The anesthetic regimes reported consisted of premedication with dexmedetomidine and butorphanol, followed by induction with propofol, and maintenance with isoflurane/oxygen inhalation.[53-55] Dogs should be treated with either enrofloxacin (5 mg/kg body weight)[53-55,60] or gentamicin and ampicillin 1 hour before ERCP.[48] Management of postoperative pain should always be considered.[54]

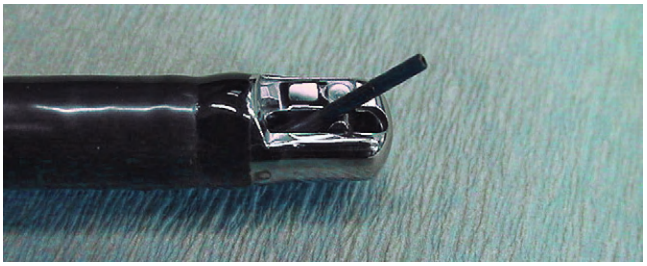


Figure 27-34 Distal end of a pediatric duodenoscope with 90° side view optic (PJF 160, Olympus). The inserted standard ERCP catheter is lifted up by the forceps elevator integrated into the tip of the endoscope.

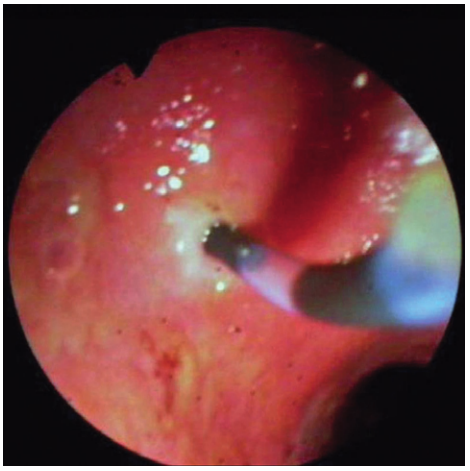


Figure 27-35 Endoscopic picture of the cranial duodenum of a dog. A contrast-filled ERCP catheter is placed into the minor papilla.

Procedure

As with push enteroscopy, the patient is placed in left lateral recumbency. Once the intestine has been intubated, the endoscope is pushed into the distal duodenum for safe placement prior to positioning the patient in dorsal recumbency. The duodenoscope is then gently pulled back into the proximal duodenum. In dogs, the distance between the pylorus and major papilla is approximately 5 cm (range, 3 to 7 cm). The proximal major papilla is observed at the 7 o'clock position and the distal minor papilla at the 11 o'clock position (see Fig. 27-29). When pancreatography is indicated, the minor (more distal) papilla should be cannulated first for contrast filling of the pancreatic ducts prior to cannulating the major papilla for cholangiography.

For radiographic imaging of the pancreatic and extrahepatic bile ducts, an ERCP catheter (e.g., standard CAN2 reusable ERCP catheter; Medwork Medical Products, Neuss, Germany) is filled with the contrast medium and pushed through the working channel of the duodenoscope. To insert the catheter into one of the papillae, it is necessary that the papilla is visible in the center of the image. For contrast filling of the common bile duct, gallbladder, and hepatic

bile ducts, 20 to 40 mL of iodine contrast medium is administered through the major papilla. A smaller volume of 1 to 2 mL iodine contrast medium is administered via the minor papilla (see Fig. 27-35) into the accessory pancreatic duct system.[54,55] Contrast filling is stopped when the main pancreatic ducts are clearly visible by fluoroscopy.[61] Overfilling of the pancreatic parenchyma should be avoided because of the high risk of inducing acute pancreatitis.[48,49,57,58]

Findings

The common bile duct in healthy Beagle dogs has a straight craniomedial course when assessed with ventrodorsal radiographs (Fig. 27-36). The duct diameter is 3.04 ± 1.89 mm at the proximal end, and tapers gradually to 2.11 ± 0.84 mm at the distal end. The right and left branches of the accessory pancreatic duct unite in the pancreatic body. The mean diameter of the two branches is 0.88 ± 0.14 mm at their junction, and 0.61 ± 0.11 mm at their distal ends. The mean length of the right and left branches was 81.6 ± 14.3 mm and 107.0 ± 24.9 mm, respectively (Fig. 27-37).[54]

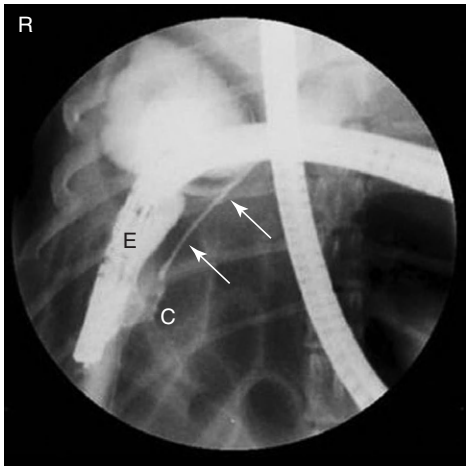


Figure 27-36 Endoscopic retrograde cholangiography of a healthy Beagle (dorsal recumbency). Marked structures from left to right are side view endoscope (*E*), catheter (C), and common bile duct (*arrows*).[54]

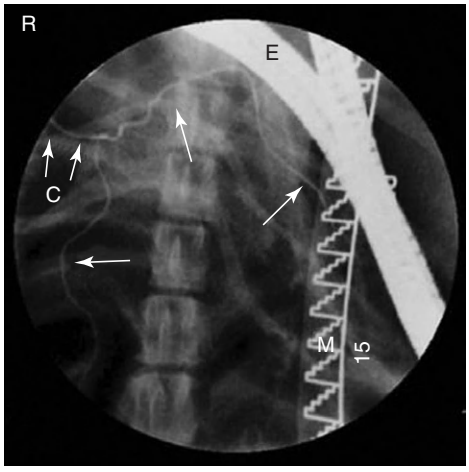


Figure 27-37 Endoscopic retrograde pancreatography of a healthy Beagle (dorsal recumbency). Marked structures from left to right are catheter (C, *open arrows*), right and left branches of the accessory pancreatic duct (*closed arrows*), side view endoscope (*E*), and radiopaque measure (M).[54]

Abnormal findings on endoscopic retrograde cholangiography (ERC) in dogs with chronic gastrointestinal problems have included enlarged common bile duct, intraductal filling defects (Fig. 27-38), deviated course of the common bile duct, and major papilla stenosis (Fig. 27-39). In one dog with stenosis of the major papilla and intraductal filling defects, endoscopic-guided sphincterotomy was successfully performed and led to improvement in the clinical signs of recurrent diarrhea, abdominal pain, and weight loss.[55]

Abnormal ERP findings in clinical patients have included accessory ductal deviation and end-stage pancreatic acinar atrophy (Fig. 27-40).[55] Experimental studies in dogs have revealed severe changes in pancreatograms after induction of chronic pancreatitis or pancreatic carcinoma.[62,63] ERP can probably be used in canine patients to differentiate pancreatic carcinoma from chronic pancreatitis, and to

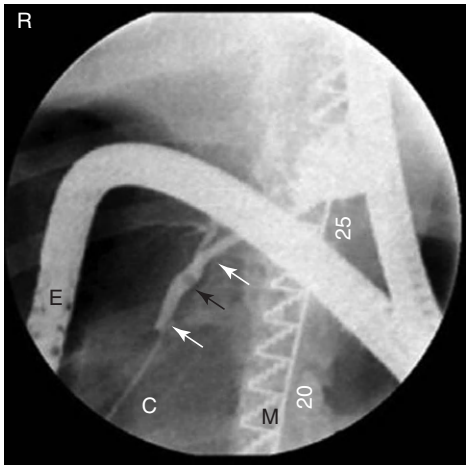


Figure 27-38 Endoscopic retrograde cholangiography (dorsal recumbency) of a crossbreed dog with chronic recurrent abdominal pain for about 4 months: marked structures are endoscope (*E*), catheter (C), enlarged common bile duct (*white arrows*, maximum diameter 4.7 mm), and radiolucent filling defect (*black arrow*).[55]

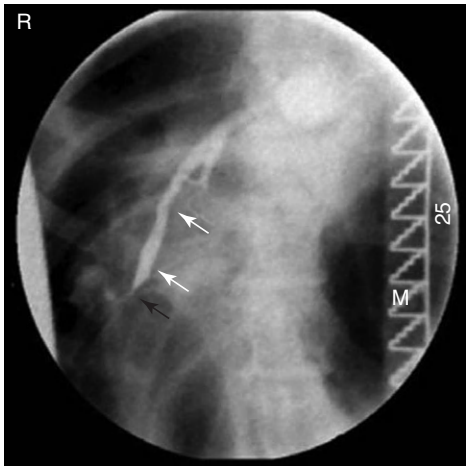


Figure 27-39 Endoscopic retrograde cholangiography (dorsal recumbency) of a Great Munsterland dog, with recurrent vomiting, diarrhea, and abdominal pain for about 9 months. Marked structures are dilated common bile duct (*white arrows*, maximum diameter 4.5 mm) and stenotic major papilla during excretion of contrast medium into duodenum after stimulation of gallbladder contraction with the cholecystokinin analogue ceruletide (*black arrow*).[55]

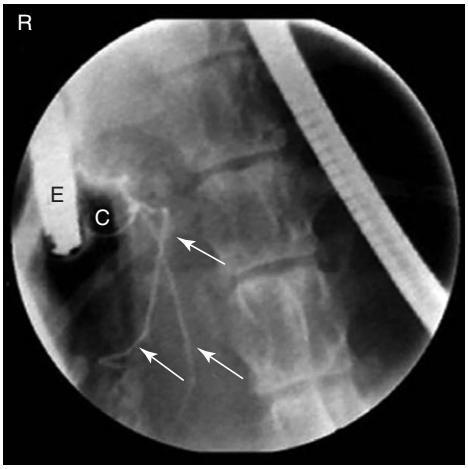


Figure 27-40 Endoscopic retrograde pancreatography (dorsal recumbency) of a German Shepherd dog with end-stage pancreatic acinar atrophy. Marked structures are endoscope (*E*), catheter (C), and the parallel left and right branches of the accessory pancreatic duct.[55]

grade chronic pancreatitis by the shape and degree of pancreatic duct dilation or stricture formation.[48,49]

Endoscopically Assisted Nasojejunal Tube Placement

Indications

Nasojejunal tube placement is indicated for postduodenal feeding of patients with uncontrollable gastric-origin vomiting, gastroparesis, biliary tract disease, and increased risk of aspiration secondary to impaired mentation, prolonged recumbency, or unprotected airways.[64,65] Another indication may be acute pancreatitis, because intrajejunal nutrition does not stimulate enterohormones, pancreatic secretion, or enzyme–protein synthesis and release. Although somewhat controversial in light of more recent ideas about the underlying pathogenesis of acute pancreatic necrosis, intrajejunal feeding may permit the inflamed pancreas to remain in a state of physiologic rest.[66,67] An experimental study in healthy dogs proved the feasibility of using nasojejunal tubes for short-term postduodenal feeding (3 to 5 days) without complications.

Procedure

A nasojejunal tube is placed under general anesthesia according to standard protocols for enteroscopy of the upper gastrointestinal tract. According to a placement protocol developed by Papa and colleagues,[63] the distal end of a standard gastroscope with a working channel diameter of 2.8 mm (e.g., GIF-100; Olympus) is inserted into the proximal duodenum and a Seldinger guidewire (350-cm long) is advanced through the working channel of the endoscope deep into the jejunum. The distal end of a polyvinyl chloride (PVC) tube (diameter 2.6 mm, length 250 mm) is marked with waterproof ink, using the following marking scheme: 20 cm = one ring, 40 cm = two rings, and 60 cm = three rings. The tube is placed over the Seldinger guidewire via the working channel into the duodenum until the three-ring mark is visible. Thereafter, the endoscope is removed while keeping the wire-stabilized tube in place. The endoscope is then reinserted into the stomach to ensure that the three-ring mark is within the duodenum. To avoid looping of the tube in the gastric lumen, it is necessary to pull the tube orally to place it close to the angulus fold after removal of the Seldinger guide wire. For nasal placement of the tube, a lidocaine-lubricated red rubber urinary catheter of similar diameter as the tube is inserted through one nostril into the nasopharynx and oral cavity. The proximal end of the feeding tube located in the oral cavity is firmly attached to the rubber catheter and pulled retrograde through the nasopharynx until it comes out of the nostril and straightens in the naso- and oropharynx. The tube is sutured to the skin lateral to the external nares, to the dorsal nasal midline, and to the forehead. To prevent self-removal of the feeding tube, an Elizabethan collar should be used. The appropriate placement of the tube in the jejunum is ensured by radiography. The tube can remain in place for up to 5 days.[64] One complication is the hardening of the PVC tube if it is maintained for several days in the stomach and small intestine. For guidelines and more details on how to perform nasojejunal intubation and feeding, see Chapter 33 and additional reference material.[68]

COLONIC ENDOSCOPY

Patrick LeCoindre

Colonoscopy refers to the endoscopic examination of the large bowel—the ileocolic sphincter, cecum, ascending colon, transverse colon, descending colon, and anorectal canal. Endoscopy of the distal ileum (ileoscopy) is often performed during the same procedure. Patient preparation is more cumbersome for colonoscopy, but the technique has become the method of choice for investigating clinical signs of colonic disease in dogs and cats. The inexperienced endoscopist will undoubtedly find this procedure technically challenging, but, the canine and feline large intestines are anatomically simple compared with other species and therefore are more readily accessible for direct examination. Furthermore, this technique will usually provide a definitive diagnosis of common colonic conditions, especially in the dog. Colonoscopy should not be regarded as a procedure that replaces complete history-taking, physical examination (including rectal examination), or laboratory-based investigations. Endoscopy should instead be seen as complementary to other parts of the medical investigation.

Instrumentation

Standard colonoscopes differ from most gastroduodenoscopes in their outer tube diameter (10 to 13 mm), working tube length (150 mm), and biopsy channel diameter (2.8 mm). For clinical practices unable to make the investment in two endoscopes, gastroduodenoscopes have also been used to perform colonic examination. Their major limitation will be in small-breed dogs and cats in which it may be more difficult to traverse the splenic flexure to reach the transverse and ascending colon.[1]

Ileocolic sphincter intubation is impossible to perform safely in small dogs and cats (weighing <10 kg).[2] Standard gastroscopes (9.0 to 9.8 mm) in dogs weighing more than 20 kg and pediatric gastroscopes (7.9-mm diameter) in dogs weighing 12 to 20 kg can be used to safely intubate the ileocolic sphincter and ileum.

Many practitioners have used rigid proctoscopes and sigmoidoscopes designed for human studies, but these devices are solely limited to visualization of the rectum and descending colon. They should instead be used to obtain deeper and larger biopsy samples, especially in the rectum which is most commonly involved in locally invasive neoplastic processes in dogs.[2]

Useful endoscopy accessories include multiple biopsy forceps, polyethylene catheters, and diathermy probes. There are several types of biopsy forceps, but the author favors the use of flexible biopsy forceps with fenestrated, ellipsoid jaws without needle. Some endoscopists will prefer using a central needle point to facilitate biopsy sampling of tubular organs, but it should be remembered that these devices produce puncture artifacts.[2,3]

Indications

Colonoscopy

Colonoscopy is indicated for patients exhibiting signs of large bowel diarrhea—tenesmus, dyschezia, fecal mucus, and hematochezia—that do not respond to dietary, antibiotic, and other empirical therapeutic trials.[3,4] Weight loss, hypoalbuminemia, and anemia are secondary but important indications for colonoscopy and biopsy.[3]

Hematochezia with normal or diarrheic stools is an important indication for colonoscopy. This sign is frequently observed in cats with chronic colitis and is the first and often the only clinical sign associated with rectal tumors in dogs.[4]

Although vomiting is reported more often with proximal digestive tract disorders, it may be observed in 30% of cases of large bowel disease. In fact, it may be the only clinical sign reported in cats with colonic disease. Because of the greater difficulty in using clinical signs to localize gastrointestinal disease in this species, it is generally advisable to perform a complete endoscopic screening including upper and lower digestive tract endoscopy.

Dyschezia, tenesmus, and constipation are another indication for coloscopy, particularly when anal and perineal examination have not yielded a definitive diagnosis. Colonoscopy is not necessary for the diagnosis of prostatomegaly, rectal diverticula with perineal herniation, or common diseases such as anal sac disease or perianal fistulae (anal furunculosis). It is most useful to diagnose infiltrative disorders, such as inflammatory bowel disease, neoplastic disease, fungal infections, and other anatomic abnormalities such as strictures. Ileocolic intussusceptions are readily diagnosed by colonoscopy, but ultrasound has a high sensitivity and specificity without the need for anesthesia.[5]

Finally, colonoscopy is indicated in cases of diarrhea of unknown origin to confirm functional disorders, for example, irritable bowel syndrome.[5,6]

Ileoscopy

Ileoscopy has several important clinical indications. It should be performed in conjunction with duodenoscopy when a severe, diffuse infiltrative disease of the small intestine, for example, lymphoma, IBD, protein-losing enteropathy, and lymphangitis, are suspected.[4,7,8] Ileoscopy may yield a diagnosis in some focal intestinal disorders such as regional granulomatous enteritis and focal lymphoma. Ileoscopy should also be considered when colonic disease is associated with systemic signs such as unexplained weight loss and chronic anemia.[2]

Ileoscopy can be performed on a more routine basis as part of the investigation of colonic inflammatory disorders as the disease process may extend into the distal ileum. Ileoscopy also permits the assessment of ileal sphincter incontinence and colorectal reflux, which are not uncommon complications of chronic colonic disease. Nevertheless, these observations should be confirmed on a large-scale study. As with more proximal GI disorders, histopathology may not correlate very well with endoscopic appearance, and therefore the endoscopist must be prepared to take serial biopsy samples from the area under investigation.[9]

Patient Preparation

Preparation of the Colon

The aim of patient preparation is to completely evacuate the colon of feces from the cecum to the rectum, for adequate visualization of the mucosa and enhanced biopsy quality.

Three days of fasting prior to colonoscopy would be ideal, but is rarely practical. As a compromise, 24 to 48 hours of (food) fasting is usually adequate. A low-residue diet (e.g., chicken, cheese, and water) may be fed prior to fasting to decrease the fecal load.

Oral laxatives should be administered on the day before the procedure. Laxative solutions containing polyethylene glycol with electrolytes (sodium chloride, potassium chloride, sodium bicarbonate, and sodium sulphate) (GoLYTELY; Seward) generally result in most reliable colonic cleansing. The electrolytes prevent dehydration and there is limited net fluid exchange in the small intestine.[10] Contraindications for administration of laxatives include patients who are already severely dehydrated, patients with intestinal obstruction, and those with severe colonic pathology that might be placed at increased risk for perforation.[11]

Polyethylene glycol solutions are recommended at a dose of 20 to 30 mL/kg body weight, for a total volume of 400 to 600 mL for a 20-kg dog. Administering such volumes often necessitates the use of nasogastric or orogastric intubation and is best performed in the hospital environment.[2,4]

Warm-water enemas can be used to augment oral laxatives, but are no substitute for them.[12] Large volumes are required (500 mL for a 10 kg dog, and up to 1.5 L for a 30-kg dog). Enemas can be given repeatedly on the day prior to colonoscopy and again a few hours before the procedure.

Enemas are less effective in cats because of the adherence of the feces to the feline colonic mucosa. They are necessary, however, because the administration of oral laxatives is not well tolerated in many cats. Moderate volumes are used (50 to 75 mL per cat) and are introduced slowly as brisk and excessive dilation of the colon can lead to vomiting and even cardiovascular shock.

Careful examination of the anal and perineal area by palpation is warranted prior to colonoscopy in order to rule out obstructive rectal conditions and rectal diverticula that could perforate during colonoscopy.

Restraint, Neuroleptanalgesia, and Anesthesia

In most cases of colonoscopy, moderate neuroleptanalgesia may be sufficient. Anesthesia is recommended, however, whenever ileoscopy or deep biopsies in the anal or rectal area are to be performed.[2,11] General anesthesia will be also needed, particularly in cats, when colonoscopy is performed as part of a full endoscopic evaluation of the lower and upper digestive tract.

Specific Procedures

Endoscopic Technique

Endoscopy of the colon is performed with the animal placed in left lateral recumbency to avoid the accumulation of fluid in the transverse colon and to facilitate passage of the colonoscope at the splenic flexure. In the dog and cat, there is no sigmoid flexure and the colon is fairly easily intubated. After a digital rectal examination has been performed, the endoscope is lubricated with a local anesthetic gel and the endoscope is advanced into the rectum using moderate insufflation to lift the rectal mucosa off of the endoscope.

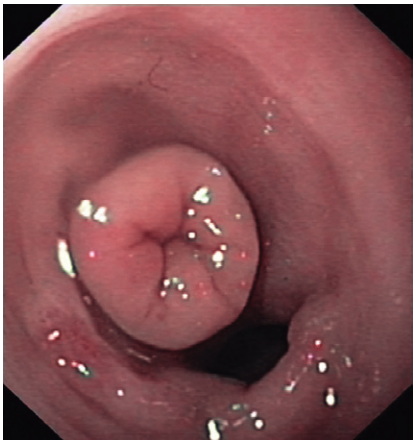


Figure 27-41 Endoscopic view of the cecocolic opening and the ileocolic sphincter in a normal dog. In dogs, the latter structure appears as a round cuff of mucosa membrane which is often very congested.

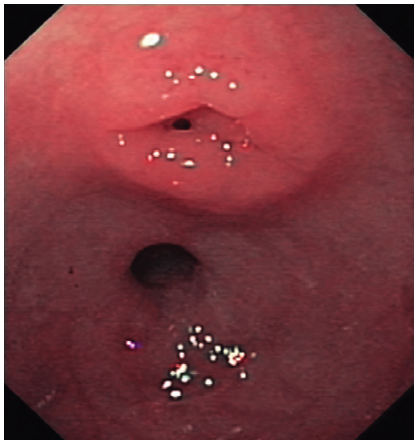


Figure 27-42 Endoscopic view of the ileocecocolic sphincter area of the cat. The ileocolic sphincter appears as a small mucosal fold.

Occlusion of the anal orifice improves insufflation by preventing air leakage.

Once the colon has been adequately distended, the endoscope is advanced into the descending colon up to the splenic flexure (i.e., the junction between the descending and transverse colon). The transverse colon is entered by directing the end of the endoscope dorsally at the splenic flexure. The transverse colon is short in the dog (on the order of 5 to 8 cm) and is delimited proximally by the hepatic flexure.[1,4]

Passing the endoscope beyond the hepatic flexure permits visualization of the ascending colon.

For inexperienced endoscopists, it may be difficult to pass the endoscope through these two flexures, especially in small-breed dogs and cats.[1] In the cat, the transverse and ascending colon are very short segments and form a single curvature that links the descending colon to the ileocecocolic sphincter. Care must be taken not to exert too much physical pressure on the endoscope when passing through these flexures. In some patients, it may be necessary to alternately move the endoscope forward and backward while maintaining insufflation.[1]

Despite the best of planning and patient preparation, residual fecal fluids and adherent fecal material may make it necessary to irrigate the colon to achieve adequate visualization.

In dogs, the ileocolic sphincter appears as a round cuff of mucosa membrane, which is often very congested (Fig. 27-41). The ileocolic sphincter is different in the cat in which it appears as a small mucosal fold (Fig. 27-42). It is not always possible to intubate the ileocolic valve, particularly in small dogs and cats, but biopsy samples can be obtained by passing the biopsy forceps from the ascending colon into the distal ileum to obtain blind ileal tissue biopsy samples (Fig. 27-43).

The entrance to the cecum is located to the side of the ileocolic sphincter. It is often folded upon itself and contains chyme, such that irrigation and insufflation may be necessary before the mucosa can be examined. Examination of the cecum can reveal whipworms or inflammatory lesions that can easily be biopsied.[2]

Endoscopic examination of the descending colon is carried out as the instrument is withdrawn at the end of the procedure. During endoscopic retraction, the tip of the endoscope should always be positioned in the center of the lumen.[4] The normal mucous membrane is pale pink, smooth and shiny. Submucosal blood vessels and

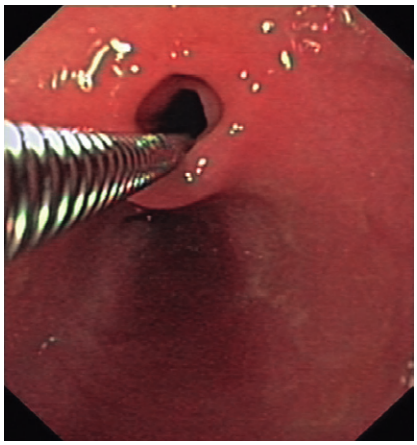


Figure 27-43 It is not always possible to advance the endoscope through the ileocolic sphincter, particularly in small dogs and cats, but biopsy samples can be obtained by passing the biopsy forceps into the distal ileum to obtain blind ileal tissue biopsy samples.

lymphoid patches (2 to 3 mm in diameter) are readily observed. Hyperemia of the mucosa is frequently seen but this change can be physiological, as a consequence of water enemas or of endoscopic passage. Varying amounts of mucus may be observed.

The anorectal canal is easily distended to permit retroflexion of the endoscope and examination of the anal margin from the rectal side. This procedure is possible only in dogs more than 20 kg of bodyweight, because retroflexion and rotation of the endoscope require a minimal luminal diameter. This latter procedure should be performed whenever possible as lesions are common in this part of the alimentary tract (Fig. 27-44).[2]

Colonic Biopsies

Most colonic diseases are associated with mucosal pathology and occasionally with submucosal pathology at some time during their development. Endoscopy enables the clinician to detect small lesions at an early stage, and, as with the small intestine, histologic examination of biopsies is the only means of determining the exact nature of the lesion. Biopsies should be acquired in a systematic way at every level of the colon, even if the mucosa membrane appears normal, because endoscopic changes and histopathologic findings are not always well correlated.

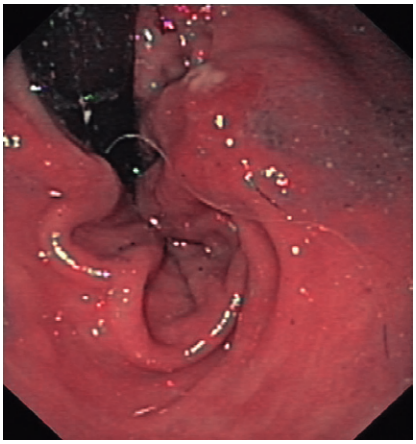


Figure 27-44 Retroflexed view of the rectum of a dog with granulomatous and ulcerative lesions of the rectal mucosa.

Endoscopic biopsy forceps take small pieces (rarely larger than 2 mm) of the mucosa and occasionally the submucosa. As with the esophagus and intestine, endoscopic biopsy in a tubular organ like the colon is more difficult than biopsy procedures in a hollow viscus like the stomach. Using the control mechanism at the handle, the end of the endoscope should be deflected until it is at an angle of 70° to the gut wall, at which time the jaws of the forceps can grasp the colonic mucosa. Applying concurrent suction will decrease tension in the colonic wall so that larger and deeper samples may be obtained. The associated risk of perforating the wall is negligible.[11]

Collection of brush samples for cytological examination may be useful in the diagnosis of certain conditions, such as histoplasmosis, protothecosis, and neoplasia.

BIOPSY GUIDELINES

Michael Willard and Joanne Mansell

Endoscopy has been called "minimally invasive surgery." If endoscopy can be done well enough that it replaces the need for invasive surgery, then it is usually worth doing. If endoscopy cannot be done well enough to avoid the need for invasive surgery, then it is often a waste of time and money. In particular, obtaining good quality diagnostic endoscopic biopsies can be difficult,[1] and consistent success requires practice, constructive criticism, and attention to detail.

Laboratory Testing

Complete blood count and serum biochemistry are routinely indicated prior to flexible endoscopic biopsy, and the same tests plus at least a mucosal bleeding time are important when performing rigid laparoscopy to collect biopsy samples from the liver. These tests are important not only to prepare for anesthesia, but also to alert the endoscopist to risks (e.g., hemorrhagic tendencies) or lesions that may require special consideration (e.g., lymphangiectasia).

Diagnostic Imaging

Abdominal ultrasound is routinely indicated before endoscopic biopsy of almost any abdominal organ. Finding a mass or infiltrate may allow percutaneous aspiration that diagnoses lymphoma, carcinoma, histoplasmosis, and so on. Ultrasound may also reveal localized lesions that are outside the range of the endoscope (e.g., a mass in the mid-jejunum) or that cannot be detected endoscopically (e.g., mass in the middle of a lung lobe), thus alerting the clinician that a surgical rather than an endoscopic biopsy is necessary.

Flexible Endoscopic Biopsies

An important advantage of endoscopy is its ability to reveal focal mucosal lesions that cannot be identified from examination of the serosal surface of the intestine, thus allowing the endoscopist to direct the biopsy forceps to the lesions.[2] Mucosal lesions can be very localized (Fig. 27-45A to C), and there may be more normal-appearing mucosa than abnormal mucosa, even in severely ill patients. Sampling the gross lesions may be crucial to obtaining a diagnosis as nonaffected tissue millimeters away may be nearly normal (Fig. 27-45D to F). Detailed endoscopy reporting forms were developed by the WSAVA Gastrointestinal Standardization Group in an attempt to promote complete endoscopic examinations (Figs. 27-46 and 27-47) that will hopefully result in fewer missed lesions.

It is crucial to provide the pathologist with the best possible tissue samples. Tissue samples should be as large as possible, free from artifact, and include the full thickness of the mucosa (with or without submucosa; Fig. 27-48). It is often easier to obtain high-quality tissue samples from smaller animals and from the ileum, probably because the mucosa is thinner. Taking multiple, high-quality samples from one site may be necessary to find certain lesions. Recent work shows that the quality of the endoscopic biopsy is inversely proportional to the number of samples that are required to find specific lesions. For example, to have 95% confidence in finding intestinal crypt lesions or lymphangiectasia with inadequate samples requires 28 or 62 pieces, respectively. If the tissue samples are adequate, those numbers fall to four and nine, respectively. In general, a minimum of eight to 10 good-quality duodenal tissue samples are recommended.[3]

There are numerous techniques and types of forceps.[2,4-6] The authors prefer reusable forceps with elongated, fenestrated jaws having serrations on the sides. To obtain the best possible tissue samples, the biopsy forceps are typically pushed into the intestinal mucosa at as close to a 90° angle as possible. The authors' technique (sometimes described as the "turn-and-suction" technique) is as follows[2]: (a) advance the biopsy forceps several millimeters in front of the tip of the endoscope; (b) open and then retract the jaws until they rest against the tip of the endoscope; (c) maximally deflect the tip of the endoscope so as to come as close as possible to looking at the adjacent intestinal mucosa at a 90° angle, typically causing a "red out"; (d) apply suction and advance the opened biopsy instrument 3 to 5 mm into the mucosa. There should be substantial resistance while advancing the biopsy forceps, in this way you are pushing the forceps deep enough into the mucosa to obtain full-thickness of mucosa (and maybe submucosa); (e) the jaws of the biopsy forceps are closed, the tip of the scope straightened out, and the biopsy instrument is withdrawn. Pushing too hard may cause the tip of the biopsy forceps to turn and start sliding along the mucosal surface. If substantial resistance is not encountered, the tip of the biopsy forceps is sliding along the mucosal surface. Good tissue samples obtained should have a consistency that is relatively "solid" as opposed to the "jelly-like" consistency seen when more superficial samples are obtained.

Text continued on page 296

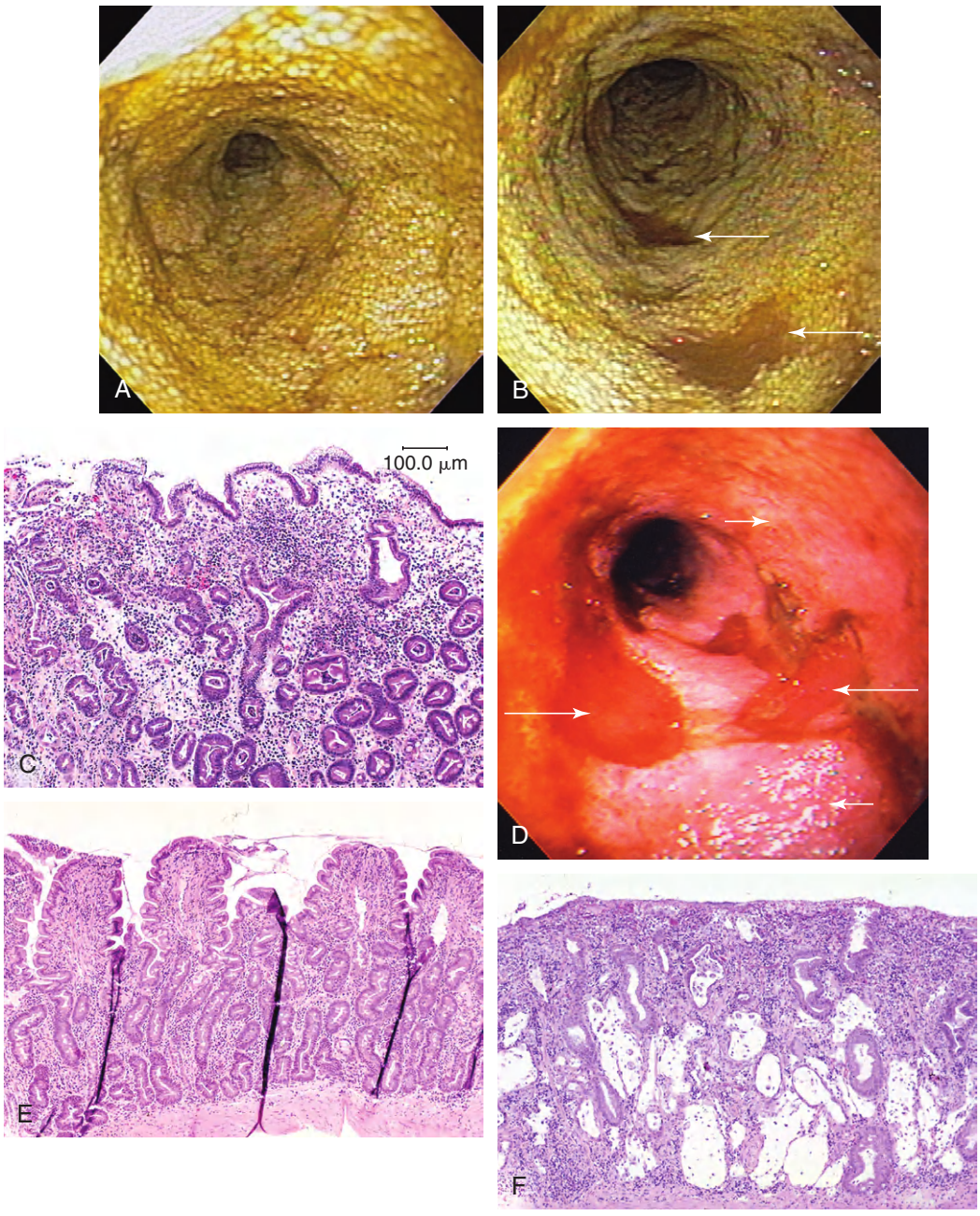


Figure 27-45 **A**, Endoscopic view of the duodenal mucosa of a Pug with a severe protein-losing enteropathy (serum albumin 1.4 g/dL). The mucosa appears uniformly normal throughout this image. **B**, Endoscopic view of the same duodenum. This image was taken several centimeters further aborad. Now focal areas that appear to have loss of villi (i.e., the surface is depressed relative to the rest of the mucosa and is smooth, *arrows*) can be seen. However, there is still more normal-appearing mucosa than abnormal-appearing mucosa. **C**, Photomicrograph of a tissue sample from the depressed, smooth areas seen in **(B)**. Note that there is an intact epithelial surface but a complete loss of villi plus a marked inflammatory cell infiltrate. **D**, Endoscopic view of the duodenum of a Bedlington Terrier with severe diarrhea and protein-losing enteropathy. Note that there are areas of the mucosa that are relatively light colored (*small arrows*) and other areas that are darker red in color (*larger arrows*). Also note that the darker red areas comprise a much smaller portion of the surface area of the duodenal mucosa. **E**, Photomicrograph of the light-colored duodenal mucosa seen in **(D)**. Note that this is relatively normal except for some villus blunting. **F**, Photomicrograph of the darker-colored duodenal mucosa seen in **(D)**. Note that there is fusion of villi (despite an intact but damaged and attenuated epithelial surface) and severe distortion of mucosal crypts. This is severe mucosal disease.

Endoscopic Examination Report: Upper Gastrointestinal Endoscopy

Date of procedure: _____ Case number: _____

Patient and client information:
(card or stamp)

Procedure(s): _____
Indication(s) for procedure: _____
Endoscope(s) used: _____
Forceps/retrieval device(s) used: _____

Problems/complications: None ☐
Perforation ☐ Excessive bleeding ☐ Anesthetic complications ☐ Excessive time ☐ Other ☐
Comments: _____
☐ Unable to complete full examination: why? _____
☐ Unable to obtain adequate biopsies: why? _____
☐ Unable to retrieve foreign object: why? _____
☐ Visualization obscurred: why? _____

Sampling: Biopsy ☐ Brush cytology ☐ Washing ☐ Aspiration ☐ Foreign body retrieved ☐

Documentation: Video ☐ Photographs ☐
Esophagus Normal ☐ Foreign body ☐ Mass ☐ Stricture ☐ Hiatal hernia ☐

Lesion	Code	Comments (include location)
Hyperemia/vascularity		
Discoloration		
Friability		
Hemorrhage		
Erosion/ulcer		
Contents (mucus/bile/food)		
Dilation		
Gastroesophageal sphincter		
Other		

Code: Normal = 0 Mild = 1 Moderate = 2 Severe = 3

Figure 27-46 A sample endoscopy form for the upper GI tract that includes tick boxes for all areas that should be viewed as well as tick boxes for lesions that the endoscopist should specifically look for. The development of this form was sponsored by the World Small Animal Veterinary Association (http://www.wsava.org/StandardizationGroup.htm). (Reprinted with permission from the WSAVA Gastrointestinal Standardization Group.)

Stomach Normal ☐ Foreign body ☐ Mass ☐ Polyp(s) ☐ Parasite(s) ☐
Site(s) of lesions: Fundus ☐ Body ☐ Incisura ☐ Antrum ☐ Pylorus ☐
Site(s) of biopsies: Fundus ☐ Body ☐ Incisura ☐ Antrum ☐ Pylorus ☐

Lesion	Code	Comments (include location)
Can't inflate lumen		
Hyperemia/vascularity		
Edema		
Discoloration		
Friability		
Hemorrhage		
Erosion/ulcer		
Contents (mucus/bile/food)		
Gastroesophageal sphincter		
Passing scope through pylorus		
Other		

Duodenum/jejunum Normal ☐ Foreign body ☐ Mass ☐ Polyp ☐ Parasite(s) ☐
How far was the tip of the scope advanced? _____
Was/were the papilla(e) seen? Yes ☐ (which? _____) No ☐

Lesion	Code	Comments (include location)
Can't inflate lumen		
Hyperemia/vascularity		
Edema		
Discoloration		
Friability		
Texture		
Hemorrhage		
Erosion/ulcer		
Lacteal dilatation		
Contents (mucus/bile/food)		
Other		

Code: Normal = 0 Mild = 1 Moderate = 2 Severe = 3

Comments and Recommendations: _____

Endoscopist signature _____

This standard form was developed by the WSAVA Gastrointestinal Standardization Group (Drs. Washabau, Willard, Hall, Jergens, Day, Mansell, Wilcox, Minami, Guilford, and Biltzer) with sponsorship from Hill's Pet Nutrition.

Figure 27-46, cont'd

Endoscopic Examination Report: Lower Gastrointestinal Endoscopy

Date of procedure: _____ Case number: _____

Patient and client information:
(card or stamp)

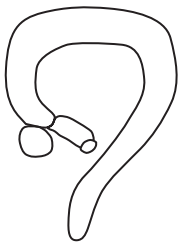
Procedure(s): _____
Indication(s) for procedure: _____
Endoscope(s) used: _____
Forceps used: _____
Method of preparing colon:

Problems/complications: None ☐ Colonic preparation inadequate ☐
Perforation ☐ Excessive bleeding ☐ Anesthetic complications ☐ Excessive time ☐ Other ☐
Comments: _____
☐ Unable to complete full examination: why? _____
☐ Unable to obtain adequate biopsies: why? _____
☐ Visualization obscurred: why? _____

Sampling: Biopsy ☐ Brush cytology ☐ Washing ☐ Aspiration ☐

Documentation: Video ☐ Photographs ☐
Colon: Normal ☐ Foreign body ☐ Parasite(s) ☐ Mass ☐ Polyp ☐
Visualized: Ileocolic valve ☐ Cecocolic valve (dog) ☐ Cecum (cat) ☐
If did not see ileocolic valve area, how far was the scope advanced? _____

Lesion	Code	Comments (include location)
Hyperemia/vascularity		
Discoloration		
Friability/hemorrhage		
Erosion/ulcer		
Intussusception		
Stricture		
Artifact		
Other		



Code: Normal = 0 Mild = 1 Moderate = 2 Severe = 3

Figure 27-47 A similar form developed for the lower GI tract and sponsored by the World Small Animal Veterinary Association (http://www.wsava.org/StandardizationGroup.htm). (Reprinted with permission from the WSAVA Gastrointestinal Standardization Group.)

Ileum **Not examined** ☐

☐ Tried to pass scope through ileocolic valve: Successful ☐ Unsuccessful ☐

☐ Tried to biopsy the ileum: Successful ☐ Unsuccessful ☐

Biopsies taken by: Direct visualization ☐ Blindly passing forceps through ileocolic valve ☐

Normal ☐ Foreign body ☐ Parasite(s) ☐ Mass ☐

Lesion	Code	Comments (include location)
Can't inflate lumen		
Hyperemia/vascularity		
Edema		
Discoloration		
Friability/hemorrhage		
Erosion/ulcer		
Lacteal dilatation		
Texture of mucosa		
Mass		
Other		

Cecum **Not examined** ☐

☐ Tried to intubate the cecum (dog): Successful ☐ Unsuccessful ☐

Normal ☐ Foreign body ☐ Parasite(s) ☐ Mass ☐

Lesion	Code	Comments (include location)
Can't inflate lumen		
Hyperemia/vascularity		
Edema		
Discoloration		
Friability/hemorrhage		
Texture		
Erosion/ulcer		
Other		

Code: Normal = 0 Mild = 1 Moderate = 2 Severe = 3

Comments and recommendations: _____

_____

_____

Endoscopist signature _____

This standard form was developed by the WSAVA Gastrointestinal Standardization Group (Drs. Washabau, Willard, Hall, Jergens, Day, Mansell, Wilcox, Minami, Guilford, and Biltzer) with sponsorship from Hill's Pet Nutrition.

Figure 27-47, cont'd

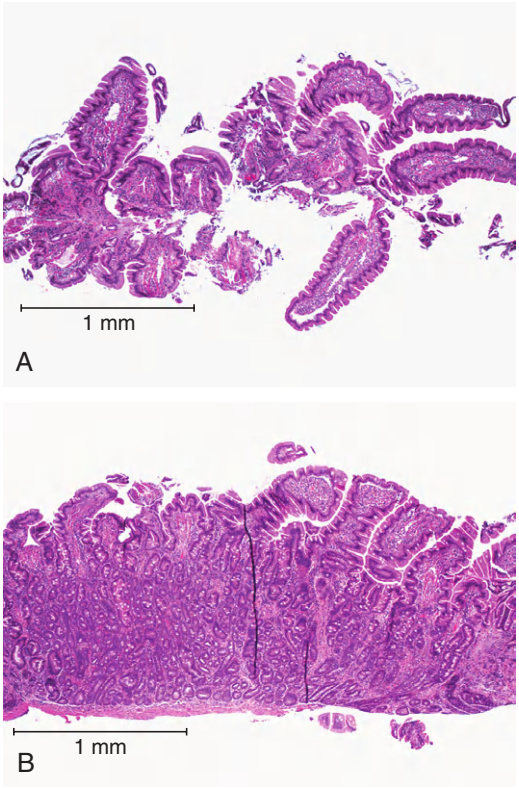


Figure 27-48 **A**, Photomicrograph of duodenal tissue taken endoscopically from a dog. Note that there are several villi but the subvillus mucosa is severely distorted and largely absent. **B**, Photomicrograph of duodenal tissue taken endoscopically from same dog shown in **A**. One can see the full thickness of the duodenal tissue, including a little submucosa. The orientation is not optimal as evidenced by the fact that the crypts are not perpendicular and are cross-sectioned, and accurately judging villus length would be impossible in this section.

Ileal biopsies can sometimes provide a diagnosis not available from duodenal biopsies, especially in cats.[2,7-9] If the endoscope can be inserted into the ileum, then the technique for obtaining ileal biopsies is essentially as described previously. If the endoscope cannot be inserted into the ileum, then the biopsy forceps are blindly passed through the ileocolic valve, the forceps jaws opened, and the forceps advanced until resistance is felt. Then the jaws are closed and the sample retrieved.

Gastric biopsies are relatively easy to obtain because it is usually easy to have a near–right-angle approach to the gastric mucosa. Antral and pyloric mucosa is typically much "tougher" than other parts of the gastrointestinal tract; therefore, one must typically close the endoscopic forceps very tightly, straighten the tip of the endoscope and vigorously "jerk" the forceps back through the endoscope.[2]

Colonic mucosa is sampled much as described for duodenal mucosa.[2,7,8] The flat surface and thin nature of the mucosa make it relatively easy to obtain excellent tissue samples. Rigid colonoscopic biopsies are now performed infrequently, but they typically retrieve tissue samples far superior to anything a flexible endoscope can produce. Using rigid as opposed to flexible endoscopic biopsy forceps is often necessary to diagnose submucosal rectal and colonic lesions (e.g., scirrhous carcinomas). For submucosal rectal lesions, it is often easier to sample "blindly," digitally guiding the biopsy forceps instead of visualizing the lesion with an endoscope.

Laparoscopy

As for flexible endoscopy of the gastrointestinal tract, rigid endoscopic procedures must be done accurately to ensure that focal lesions are identified.[10] Laparoscopic biopsies should generally be obtained with rigid forceps as opposed to core biopsy needles; otherwise one might just as well take the biopsies with ultrasound guidance instead of laparoscopy. "Double-spoon"–type forceps are preferred for hepatic biopsies, whereas pancreatic biopsies generally require a "punch"-type forceps. It is reasonable to obtain at least one and preferably two samples from each hepatic lobe that is accessible, unless there is one lesion that is obviously the problem (e.g., tumor) or there are marked bleeding tendencies. Hepatic samples are generally obtained from the margins of the liver lobes, but one can thrust one side of the double spoon forceps into the surface of the hepatic lobe to obtain samples from the middle of the lobe. Laparoscopy can also be used to sample the pancreas, kidney, and intestines.[11]

Submission for Histopathology

Flexible endoscopic samples of the duodenum and ileum are fragile and must be handled carefully to minimize artifact and allow the laboratory to orient the tissues properly. It is important to traumatize the villi as little as possible so that the pathologist may accurately determine if villus atrophy is present.

Submission of the tissue samples is equally important.[2,4] In the authors' practice the tissue is first examined while still in the biopsy forceps to see if it is folded. Once it is unfolded, it is carefully lifted out of the jaws with the tip of a needle and laid on a histopathology sponge (commercially available sponges precut to fit a histology cassette) with the submucosal side down and the villi up. After all the samples are obtained, the sponge is gently placed in formalin with the specimen side down. The histopathology laboratory knows to embed these samples at a right angle relative to how they are placed on the sponge. In this way, most of the samples will hopefully be sectioned longitudinally (i.e., parallel to crypts and villi). If the laboratory does not know (or care) how the tissues are oriented when sectioned, then you may need to consider whether this laboratory is providing the information you need for your patients.

Gastric and colonic mucosal samples are relatively easy to handle; they have no villi making it irrelevant whether the mucosal surface or submucosa is placed down on the sponge. The most important aspect of handling these samples is to ensure that they are not folded; but it is critical not to "stretch" the samples when unfolding them and placing them on the sponge.

Laparoscopic hepatic and pancreatic biopsies are relatively easy to handle compared with endoscopic biopsies of the intestines and they can be placed directly into formalin. The major artifact to avoid is drying of the tissue before it is placed in formalin. Orientation is not important.

Histopathology Reports

It is important for the clinician to understand what information an endoscopic biopsy can provide and not have unrealistic expectations of how much information can be obtained from biopsies (endoscopic or full-thickness). It is essential that the clinician provide a full clinical history. In addition, it is important for clinicians to state what they need to know from the biopsy because this information can affect how the pathologist asks the laboratory to process or stain the specimens. Without a clinical history, it is often impossible for the pathologist to know what information is desired. Clinicians

should understand that distinguishing between some diseases with histopathology may not be possible because the intestine responds to many stimuli in a general way (e.g., lymphocytic and plasmacytic infiltrates). Currently it is difficult (perhaps impossible) to distinguish between canine IBD, antibiotic-responsive enteropathy, and diet-responsive enteropathy, or between severe feline lymphocytic enteritis and well-differentiated mucosal lymphoma.

Use a laboratory and pathologist with whom you feel comfortable communicating. The interaction of clinician and pathologist is essential to producing informative results.[12] Endoscopic biopsies of the gastrointestinal tract are relatively difficult to evaluate histologically, and this process is not made easier if inadequate specimens are submitted or inadequate clinical history is supplied. Conscientious pathologists typically feel pressure to find a pathologic change in tissues, and there can be a tendency to overread endoscopic biopsies, assuming that a disease process must be present because the area was sampled. Feel comfortable in calling the pathologist if you have queries about the diagnosis and feel comfortable if the pathologist calls you with queries about the specimens or history. Communication is essential in jointly forming the correct diagnosis.

It is important that the pathology report include the number of pieces of tissue submitted, the presence/absence and severity of collection or processing artifacts, general quality of the samples in terms of the depth of the mucosa that can be examined (e.g., full mucosal thickness, partial mucosal thickness, mostly villus fragments), orientation on the glass slide, a description of the severity of the lesions found, and a diagnosis when appropriate. A conscientious endoscopist will want to know if the samples submitted were adequate or inadequate, and will typically ask the pathologist to comment on this in the report. Without this information, it becomes very difficult for the clinician to know how much faith to place in the histologic diagnosis.

Interpretation of Biopsy Results

There are two questions that must always be asked when evaluating a diagnosis (histologic or otherwise). First, does the diagnosis fit the patient (i.e., does the diagnosis seem reasonable)? Although it is possible that any particular patient may have some strange, unexpected disease, these are not common. Second, does the response to treatment fit the diagnosis (i.e., do the drugs, diets, etc. that the books say should work actually help this patient)? If the answer to either of these questions is "no," then it is appropriate to reconsider whether the histologic diagnosis was correct.

INTERVENTIONAL ENDOSCOPY

Massimo Gualtieri

Flexible endoscopy has a fundamental role in the treatment of specific diseases of the GI tract. The most common therapeutic indication of endoscopy in small animals is the removal of GI foreign bodies. Gastric and esophageal foreign bodies are frequently encountered in dogs and cats and endoscopic retrieval is currently considered the therapeutic procedure of choice for this condition. Endoscopic treatment is critical also for other less-common lesions of the digestive tract, such as esophageal strictures and GI polyps, for which surgery represents an invasive option, often associated with a high rate of failure (e.g., thoracic esophageal strictures, rectal polyps). A further possible therapeutic indication of endoscopy is the excision of preneoplastic mucosal lesions such as gastric intestinal metaplasia and mucosal dysplasia.

Treatment of Esophageal Strictures

Esophageal strictures may be classified as congenital or acquired, benign or malignant, and, based on their origin, as intramural or extramural. Endoscopic treatment of esophageal strictures finds its best indication in acquired benign intramural forms. Congenital forms are extremely rare and may appear as fibrous rings or membranes rings at different levels in the esophagus.[1-4]

An esophageal stricture may develop secondary to severe mucosal lesions or esophagitis of different origin extending to the submucosal or muscle layer of the esophagus.[5-12] The reparative process by intramural fibrosis leads to the stricture formation. Malignant strictures (squamous cell carcinoma and primitive or secondary esophageal sarcoma) are very rare in small animals and, unlike in people where palliative dilation is performed, are usually not treated because of their advanced clinical stage when clinical signs appear.[13-16]

Treatment options for benign esophageal strictures include conservative and surgical procedures. Conservative treatment is based on mechanical dilation of the narrowing (bougienage, balloon catheter dilation),[6,7,9-11,17-21] endoscopic electrocautery incision of the fibrous tissue,[6,11,22] and stent placement[9] (Fig. 27-49). Surgery includes resection and anastomosis, esophagoplasty or reconstructive procedures (patch grafting), and is indicated when conservative treatment fails or in case of neoplastic or large strictures.[23-28] Conservative endoscopic dilation of esophageal strictures by bougienage or balloon catheter is preferred over surgical treatment. In veterinary literature, a success rate of 50% to 75% for bougienage and as high as 85% for balloon catheter dilation is reported, whereas surgery is successful in less than 50% of cases.[6,18,20] Similar success rates for conservative and surgical treatment have also been obtained by the author,[29] who did not experience major success differences between bougienage and balloon catheter technique, as reported in humans.[30-32] The main consideration in choosing between the two procedures appears to be financial, as balloon catheter instrumentation is far more expensive than bougienage; furthermore, the pneumatic material of a balloon catheter is far less durable than the rigid material of bougies.

Esophageal surgery is usually technically demanding and associated with a high frequency of complication such as stricture formation and/or leakage at the anastomosis site.[17,23,26,29]

Bougienage

Bougienage involves the passage of progressively larger instruments through the stricture. Several bougienage techniques are available but the most widely used are semiflexible polyvinyl bougies with conic tips (Savary-Gillard, Stark, Celestin, etc.) and metallic olives (Eder-Puestow), both with progressively larger diameter and driven

Figure 27-49 Nitinol stent for stabilization of esophageal stricture. (Courtesy of Christopher J. Chamness.)

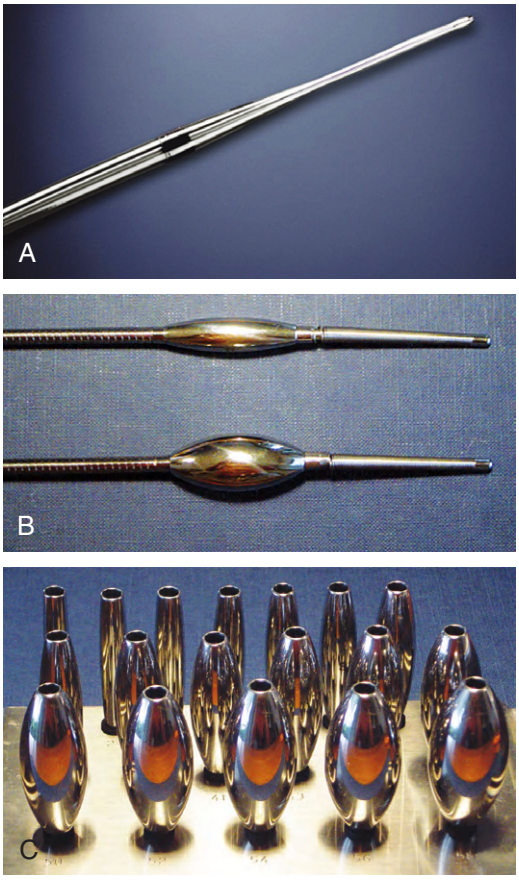


Figure 27-50 Bougienage. **A**, Savary-Gillard dilator. These dilators consist of a range of polyvinyl tubes (5- to 20-mm diameter), each with a 20-cm tapered tip. A radiopaque band at the widest point of the dilator aids radiologic localization. **B**, Eder-Puestow dilator. Metal olives are mounted on a flexible shaft and moved on a guidewire. **C**, Series of graduated metal olives (6.6- to 19.3-mm diameter). (**A** is courtesy of Cook-Medical.)

on a guidewire (Fig. 27-50). With bougienage, the longitudinal forces applied are transformed into radial forces that dilate the stenotic tract.

The dilation is performed with the patient under general anesthesia and after a complete assessment of the stricture site has been done. Probes are driven on a metallic guidewire to prevent the risk of perforation as a result of the blind introduction of the dilator through the stricture. The tip of the endoscope is advanced to the stricture; then the guidewire with flexible tip is introduced in the instrument's operative channel. It is advanced through the stricture, at least 20 to 30 cm below the lowest point of the stricture, usually in the gastric antrum. In the gastric cavity, the harmonic steel guidewire winds in coils assuring its stability in the stomach. When retrieving the endoscope, the guidewire is left in situ and fixed externally to minimize the risk of internal displacement.

When flexible bougies are used, a well-lubricated bougie is introduced on the guidewire and is advanced to the stricture, which is passed by applying a gentle pulsion until a lower resistance of the fibrous tissue is felt (Fig. 27-51). It is crucial in this phase to avoid excessive forces so as to prevent the severe complication of esophageal laceration. The bougie is passed forward and backward through the dilated tract; then it is retrieved and the procedure is repeated with a larger bougie. Between dilations, repeated endoscopies should be done to assess the evolution of the blind procedure (Fig. 27-52). The introduction of progressively larger probes causes the distention

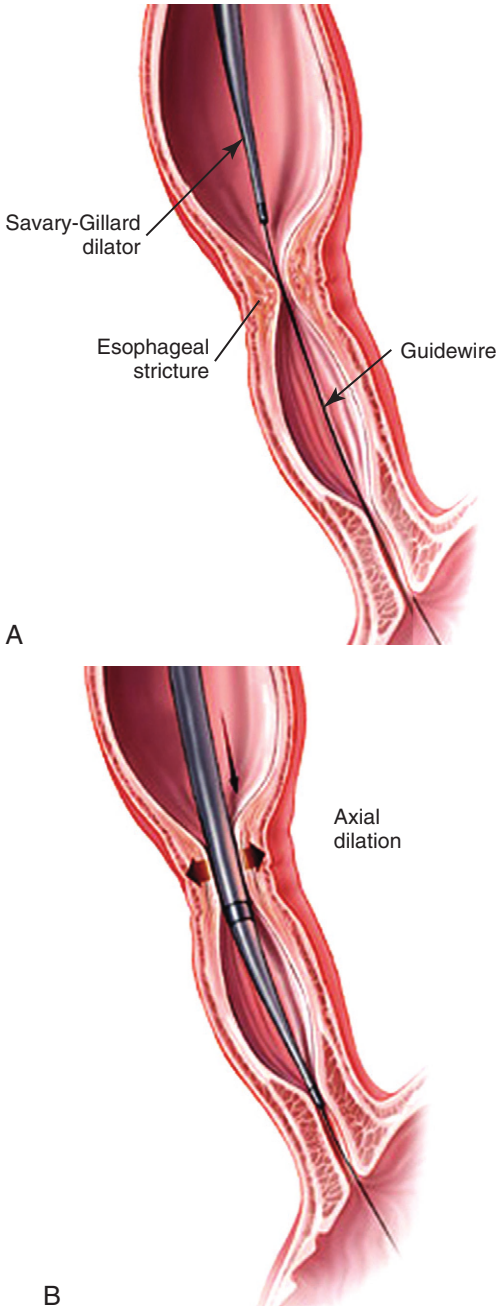


Figure 27-51 **A**, Esophageal dilation with Savary-Gillard device. The dilator is introduced on the guidewire and advanced until the stricture. **B**, The dilator is gently advanced through the stricture. Wire-guided dilation gives greater assurance that the dilator is following the line of the esophageal lumen, thus reducing the risk of perforation.

and subsequent dilation of the stricture; the procedure should be repeated until an improved lumen diameter is obtained. A 1-cm diameter is usually appropriate for cats and small-size dogs (≤10 kg). In larger dogs, a 1.5- to 2-cm diameter may be required.

The Eder-Puestow device includes metallic olives with graduated diameter that are assembled on a flexible supporting pole. The metallic supporting pole with progressively larger olives is assembled on the guidewire and passed through the stricture repeatedly until an improved lumen diameter is obtained, as seen for semiflexible bougies.

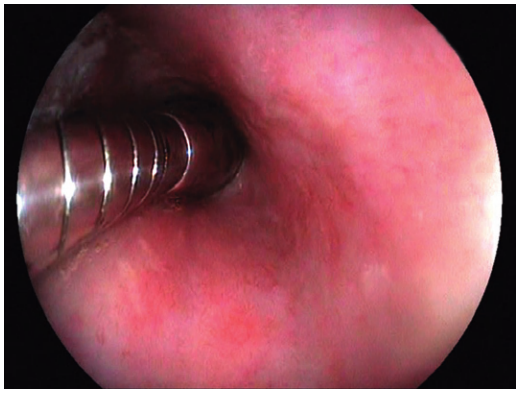


Figure 27-52 Esophageal dilation with Eder-Puestow device. A metal olive, a few millimeters larger than the stricture, is mounted on a flexible shaft and advanced through the lesion.

Figure 27-53 Inflation device used to inflate, deflate, and monitor pressure of the line of balloon dilators during esophageal stricture balloon dilation. (Courtesy of Cook-Medical.)

Key to a successful outcome of the procedure is the accurate endoscopic assessment of the esophageal mucosa of the prestenotic and stenotic tract before dilation. Prestenotic mucosa may show inflammation, erosion, and even ulceration, while the fibrous tissue may be limited to the stenotic ring. A similar condition means that the lesion is still evolving as the inflammatory process underlying the condition and/or the healing–scarring process has not completed ("active stricture"). Any dilation procedure attempted in this phase induces an adjunctive trauma on an already altered and inflamed substrate (the esophageal wall). The consequence is a strong inflammatory response of this tissue increasing the scarring process. When instead the scarring process has ultimate ("stable stricture"), the prestenotic mucosa appears whitish with an irregular surface, sometimes cribrous and markedly thickened. The endoscopic assessment of these aspects is of great importance for therapeutic and prognostic purposes. Treatment of "stable" strictures results, in the author's experience,[9,29] in a lower rate of early relapse compared with active lesions. For this reason, treatment of these forms should be delayed, if appropriate, for 2 to 3 weeks, during which the patient can be fed by a gastrostomy tube and treated for the underlying disease (e.g., gastroesophageal reflux disease). Regardless of the dilation device used, the procedure may be repeated at 7- to 15-day intervals until a lumen diameter large enough to allow adequate feeding is achieved. The total number of dilation procedures may vary from one to seven and may be dictated by the severity of the stricture and the clinical answer to treatment (clinical signs of obstruction).

Balloon Catheter Dilation

In this procedure, stationary radial forces dilate the stricture in a centrifugal manner. Polyethylene balloon catheters (Wilson-Cook, Rigiflex Dilator; Microvasive Inc., Milford, MA) are available with different inflated diameters up to a maximum of 20 mm (see Figs. 27-20 and 27-53). Balloon catheters can be passed through a 2.8-mm accessory channel of the endoscope, or alongside the scope under direct endoscopic or fluoroscopic vision. The catheter of appropriate diameter (i.e., based on the lumen diameter desired) is advanced until the lumen of the stricture is reached (Fig. 27-54A). Once positioned, the balloon is distended with air or filled with water (or contrast medium for fluoroscopy) to the pressure recommended by the manufacturer (usually 45 to 50 psi) (Fig. 27-54B). Balloon catheter dilation may be achieved by suitable devices. A dilation time of approximately 60 seconds seems to be adequate and the procedure is immediately repeated with progressively larger catheters. The choice of using water or air for distending the balloon catheter

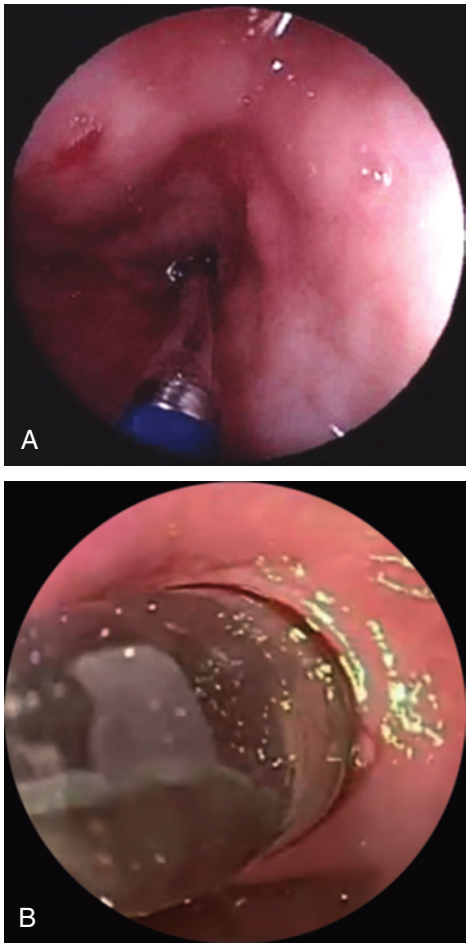


Figure 27-54 Balloon (hydropneumatic) esophageal dilation in a cat. **A,** The deflated catheter is positioned in the stenotic lumen. **B,** The inflated balloon catheter dilates the stricture. Recommended inflation times range from 20 to 60 seconds but the optimum is unknown.

depends on the stricture resistance and the fragility of the esophageal wall. Owing to the physical principle of liquid incompressibility, water distention of the catheter induces an even pressure at any site of the balloon surface, being particularly suitable for the dilation of strong strictures. Catheters distended with air are characterized by higher deformability and are better indicated for cats or young

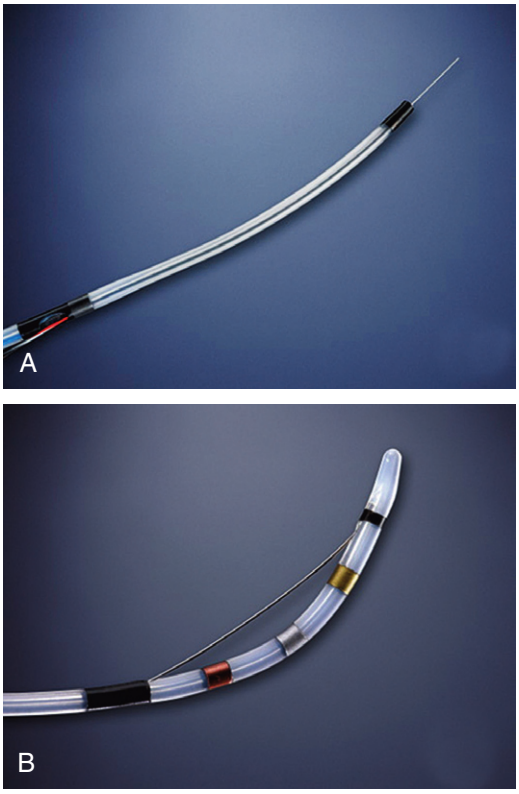


Figure 27-55 Electrocautery incision instruments. **A,** Needle knife. **B,** Sphincterotome. Both instruments are connected to an electrosurgical unit. (Courtesy of Cook-Medical.)

animals whose esophageal wall is thin and fragile. Balloon dilation technique and frequency of application is similar to that of bougienage, but it is easier and faster and can be done under direct vision and without a guidewire.

Endoscopic Electrocautery Incision

Dilation of certain types of resistant annular stricture or tortuous strictures may be done by electrocautery incision of the fibrous tissue followed by dilation,[33,34] a technique first developed in veterinary medicine by the author.[22] It requires a flexible endoscope, an electrosurgical unit, a needle knife, and a dilation device (radial or axial) (Fig. 27-55). Before electrocautery, a 360° gentle palpation of the stenotic ring (annular strictures) is performed with an open biopsy forceps, assessing sites of greater resistance characterized by a deeper infiltration of fibrous tissue into the esophageal wall ("traction sites"). During stenotic ring development, traction induced by the developing fibrous tissue on the esophageal wall is not homogeneous. In fact, the healing response is influenced by the severity and deepness of the insult. As a result, traction will be higher in some areas (traction sites) and lower in others, even without changes in the circumferential morphology of the stricture. "Traction sites" are areas offering a greater resistance to the dilation procedure. After retrieving the biopsy forceps, a needle knife connected to the electrosurgical unit is introduced into the biopsy channel of the endoscope and three equidistant electrocautery incisions are made around the circumference of the stricture (Fig. 27-56). Alternatively to the needle knife, a polypectomy snare partially extracted from the Teflon sheath or a standard papillotome can be used. The electrocautery incisions should be initially superficial and then deepened until an almost complete cut of the fibrous tissue is achieved. This procedure should be made cautiously to avoid esophageal perforation. After electrocautery, dilation by bougienage or balloon catheter is conventionally done.[35] Electrocautery incisions alone without dilation are particularly useful for treating semilunar and mucous branches strictures (Fig. 27-57). When this technique is performed by an expert endoscopist, encouraging results may be obtained both as long-term control of clinical signs and as definitive cure.[6,9,11,22,29,33-35] Dogs treated by the author with electrocautery did not require further procedures.

Strictures in the cervical tract of the esophagus may also be incised using standard or diathermic laparoscopy scissors. Best results are obtained with a 360° rotating shaft control scissors (Fig. 27-58). This instrument is introduced alongside the endoscope and allows

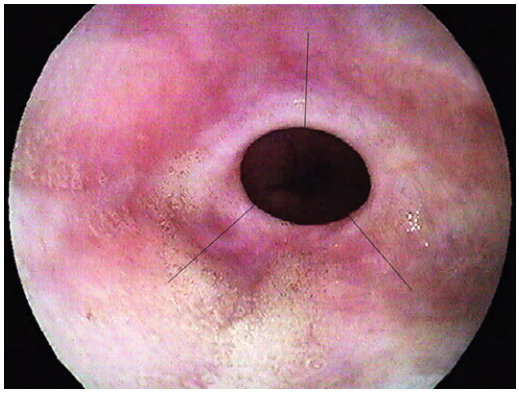


Figure 27-56 Esophageal annular stricture. The *black lines* indicate the sites of incision of the fibrous tissue of the stricture.

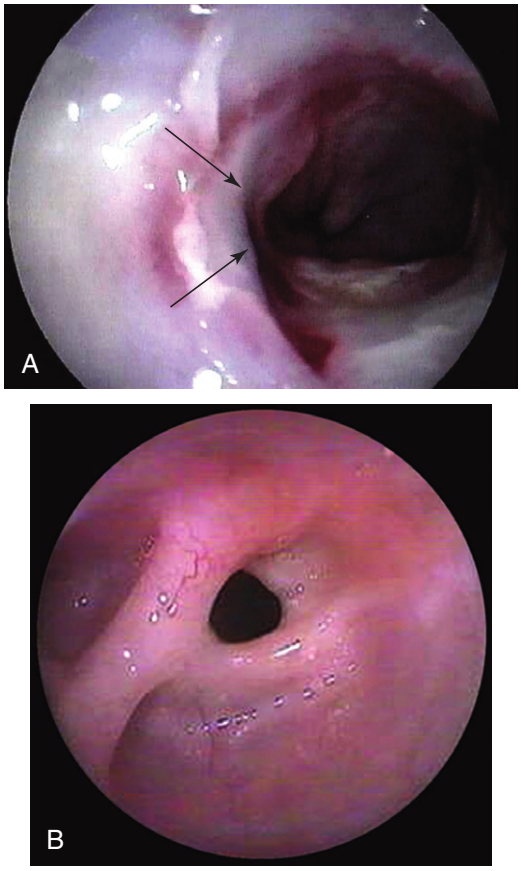


Figure 27-57 **A,** Semilunar esophageal stricture (dog). A white flap of fibrous tissue (*arrows*) occludes partially the lumen. **B,** Mucous branches stricture. The esophageal lumen is narrowed by a mesh of fibrous tissue occluding the organ.

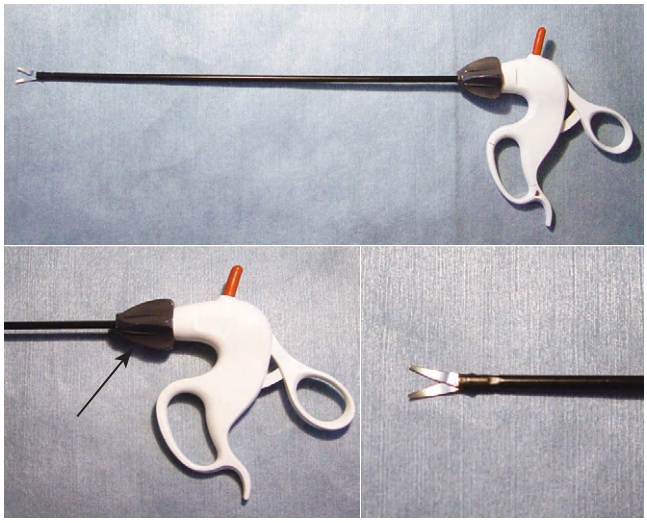


Figure 27-58 Laparoscopy scissors. The distal end can be rotated 360° on scissors' long axis by the nut ring on the handle (*arrow*), making the procedure easier and safer.

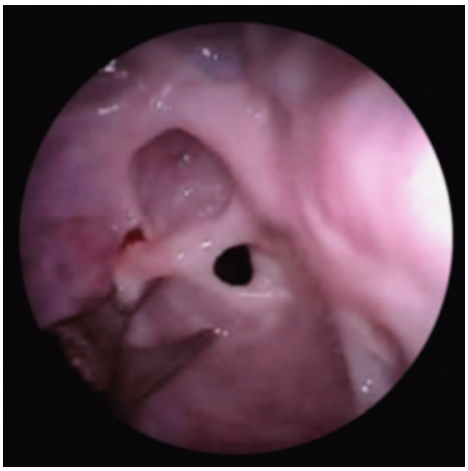


Figure 27-59 Incision of a mucous branches stricture (dog, cervical tract). Laparoscopy scissors are introduced alongside the endoscope to cut the fibrous tissue, allowing the spontaneous relaxation and dilation of the stenotic tract.

accurate incision of the fibrous tissue under direct vision (Fig. 27-59). Strictures located more than 35 cm distant from the scissors are not suitable for this technique as laparoscopy forceps are usually less than 40 cm long.

Postoperative Care

Whatever the dilation technique used, medical treatment should be instituted as adjunctive therapy to dilation. A broad-spectrum antibiotic (e.g., ampicillin, 20 to 40 mg/kg TID) and prednisolone (0.5 to 1 mg/kg BID, IM, SC, or PO) should be administered for 10 to 14 days. Prednisolone is used to diminish fibroblastic activity and fibrous connective tissue formation. Regardless of the dilation technique used, oral feeding may be initiated after 6 hours, starting with single bites of raw meat of a size similar to the lumen diameter achieved by dilation, every 2 to 3 hours. The food bolus will help to maintain the dilation, together with standard nutrition that should be initiated within 24 hours. Key for the positive outcome of the dilation procedure is the diagnosis and treatment of the underlying disease (gastroesophageal reflux, hiatal hernia, etc.).

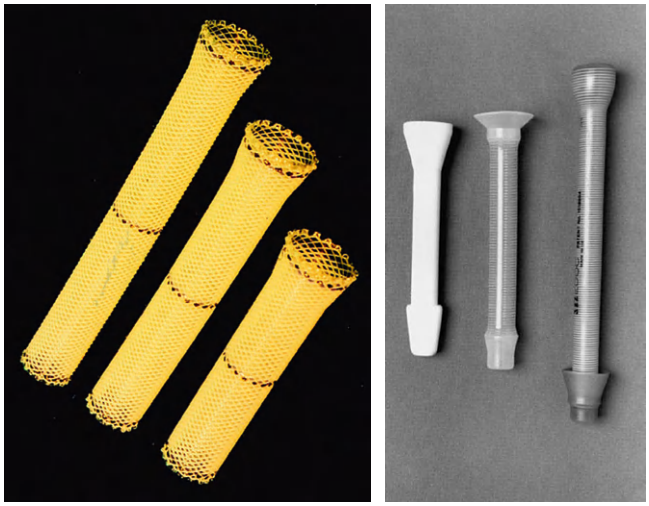


Figure 27-60 Esophageal plastic stents. These prostheses are radiodense tubes of different length and diameter, with a tapered proximal end. *Left to right*: Wilson-Cook, Tygart, Atkinson, polyvinyl homemade, Buess. (Courtesy of Medscape.)

Esophageal Stents

For strictures that fail to respond to repeated dilation procedures, because they are too extended or not surgically treatable, palliative endoscopic stent placement to permit oral feeding and diminish the risk of aspiration may be considered. Esophageal stents are rarely used in veterinary medicine because of the high rate of complication and elevated cost.

Esophageal stents can be plastic or self-expanding.[9,36,37] Plastic stents (Wilson-Cook, Atkinson, Tygart, etc.) are radiodense tubes of different length and diameter, with a tapered proximal end (Fig. 27-60). Before placement, the stricture must be dilated to the same diameter as the stent. Stent placement can be accomplished by an appropriate device (pusher) or by endoscopy (Fig. 27-61A). Owing to the space occupied by the endoscope and the pusher, placement is better done under fluoroscopic than endoscopic guidance. With the pusher, a mild force is applied to the stricture and the stent is released. The healing response of the esophagus will help maintaining the stent in situ. After placement, a semiliquid diet should be exclusively fed to avoid stent obstruction.

Self-expanding stents (Z-stent, EsophaCoil, Wallstent, InStent, Ultraflex, etc.) are metallic tubes characterized by strong radial forces (see Fig. 27-49). Once placed, the stent expands until a predetermined diameter (up to 22 mm). They differ in their design (coils, mesh), material (stainless steel, nitinol) and physical properties. Metallic stents are mainly used in human medicine for the palliative treatment of malignant strictures (Fig. 27-61B). This type of stent has never been used by the author because of the elevated cost and the difficult removal in case of wrong positioning or complications.

Complications

Iatrogenic gastric overdistention can be a common complication of endoscopy in animals with strictures, since air inflated with the endoscope cannot be aspirated if the stricture precludes passage of the instrument in the stomach. During stricture assessment and dilation, air inflation should be careful and moderate. If not promptly recognized, gastric distention can cause severe circulatory (caudal vena cava compression, hypotension, and bradycardia as a result of vagal stimulation), respiratory (respiratory failure), and gastric (wall ischemia) problems. Stomach decompression should be done with an 18-gauge needle.

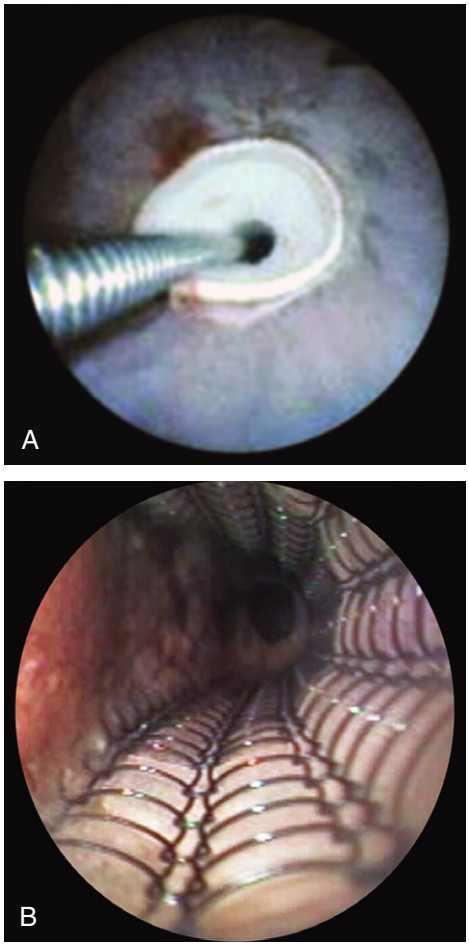


Figure 27-61 **A,** Positioning of a plastic stent (Atkinson) with a pusher in an esophageal stricture of a dog. **B,** A self-expanding metallic stent used to palliate an esophageal cancer in man.

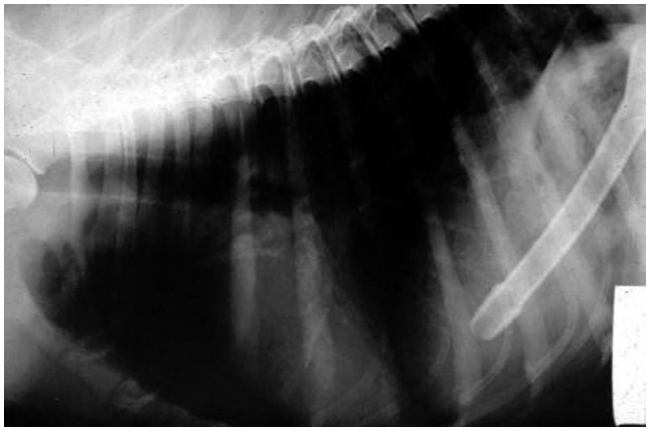


Figure 27-62 Complication after placement of an esophageal plastic stent (Atkinson) in a dog with cervicothoracic stricture. The stent has dislocated into the stomach.

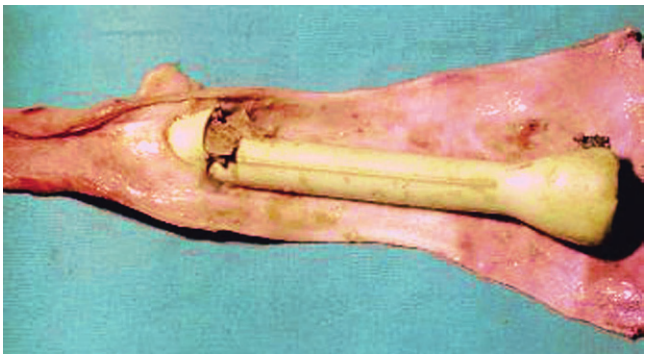


Figure 27-63 Gross aspect of the cervicothoracic tract of the esophagus of a dog with a stricture. The distal part of the esophageal plastic stent (Atkinson) caused compression and trauma to the point of passage between the cervical and the thoracic portion of the esophagus, causing proliferation of the esophageal wall and impingement of the stent.

The most severe complication of stricture dilation and stent placement is esophageal laceration/perforation. Regardless of the technique used, during the dilation procedure the esophageal wall may suddenly rupture, especially if the stricture is in active phase or in cats, where the organ wall is thin and fragile. An inadequate assessment of the lumen diameter to achieve dilation or excessively powerful procedures are often responsible for this complication.

Electrosurgical instruments (polypectomy snare, sphincterotome, needle knife) can also induce complications such as perforation or cardiac interference (arrhythmias, cardiocirculatory arrest).

A esophageal stent may be occluded by coarse food, dislocate in the stomach (Fig. 27-62), or cause mechanical compression (Fig. 27-63) and/or fistulization of the esophageal wall.

Treatment of Gastrointestinal Polyps

Although uncommon, polyps of the gastrointestinal tract have been diagnosed more frequently in dogs and cats, probably because of the increased use of endoscopy in approaching gastrointestinal disease. Unlike small incidental lesions, large polyps or polyps located close to sphincters can cause severe clinical signs such as vomiting, diarrhea, and hemorrhage, depending on level of the GI tract involved. Treatment is mandatory in these cases and current options are endoscopy or surgical polypectomy. Because of the possible malignant nature of polyps, small and clinically silent polyps should also be removed. The preneoplastic nature of some benign polyps in men stimulate a deeper knowledge of these lesions also in animals. The fact that some benign polyps may be preneoplastic lesions, justifies more attention being paid to these changes in dogs and cats.

The term *polyp* describes any circumscribed lesion protruding from the GI mucosa without specifying the nature of the lesion. Used alone, polyp is a purely descriptive term, while the specific nature of the lesion is defined by histopathology.[38,39] Most commonly, polyp refers to a process involving the mucosa (epithelial polyps), but it also indicates submucosal lesions.[40,41] Polyps of the GI tract are rarely observed in small animals, although their incidence is probably higher, as they can be clinically silent and often incidentally diagnosed (particularly in the esophagus, stomach, and duodenum) during endoscopy or necropsy.[42,43,45] Polyps can be pedunculated, sessile, or have a large base (intermediate form). The most common histologic types encountered in dogs and cats are adenoma–adenocarcinoma and hyperplastic polyp.[43,44] Inflammatory and hamartomatous polyps have been also reported in dogs.[15,38,45] Canine GI polyps are mainly located in the rectum,[41-51] rarely in the stomach,[40,45,52-55] and exceedingly rarely the duodenum, esophagus, colon, and ileum.[45,56-58] The occasional reports of GI polyps in cats include mainly duodenal adenomatous polyps.[45,58,59]

Endoscopic Polypectomy

Endoscopic polypectomy can be considered the procedure of choice for GI polyps; features that influence the choice of the therapeutic procedure are the size and location of the lesion and the presence or absence of a stalk. A coagulation panel should be done before polypectomy to determine the risk of bleeding. The technique differs based on the presence or absence of a stalk. Endoscopic polypectomy of pedunculated polyps requires a flexible endoscope, a polypectomy snare, and an electrocoagulation unit. With the patient under general anesthesia, the polyp is visualized, the polypectomy snare (standard or asymmetrical) (Fig. 27-64) is advanced through the operative channel of the endoscope and connected at the handle to the electrocoagulation unit. The snare is opened and the polyp surrounded at the base. Before closing the snare, its correct position should be assessed to make sure that the GI wall has not been included in the snare and avoid the risk of perforation. The snare is then gently closed around the base of the polyp until a mild color change in the polyp head is observed, indicating a degree of ischemia. The snare is now tightly closed. Before activating the current, the polyps is pulled toward the center of the organ lumen to avoid contact with the wall and secondary energy dispersion or burns (Fig. 27-65). The current is now activated and the polyp excised. The site of excision is assessed to exclude hemorrhage; then the polyp is retrieved with grasping forceps and submitted in toto for histopathology to characterize the histologic nature and the completeness of excision. In experienced hands, this technique is usually followed by recovery and a low incidence of complication[45]; it is best used with 3-cm or smaller polyps. For larger polyps (3 to 6 cm in diameter), the lesion can be excised in smaller multiple pieces (piecemeal resection), lowering the risk of burn and hemorrhage (Fig. 27-66). This technique is useful when the large size of a pedunculated or sessile polyps hinders assessment of the correct positioning of the snare around the base of the lesion. Partial portions of the head of the polyp are repeatedly removed until the base of the lesion can be completely excised with the snare.

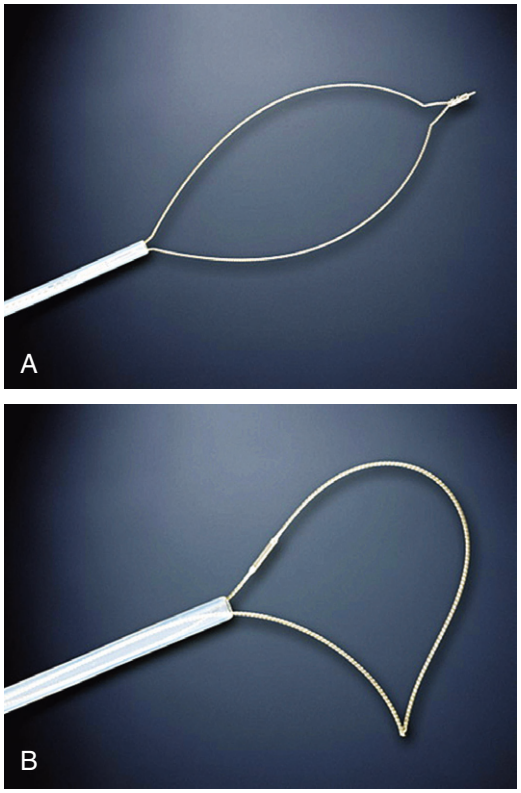


Figure 27-64 Polypectomy snares. **A,** Standard polypectomy snare and (**B**) asymmetrical polypectomy snare. (Courtesy of Cook-Medical.)

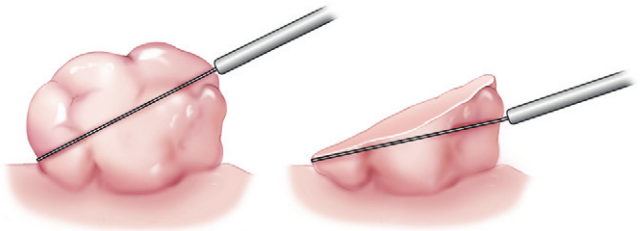


Figure 27-66 Polypectomy, piecemeal technique. Partial portions of the head of the polyp are repeatedly removed until the base of the lesion can be completely excised with the snare.

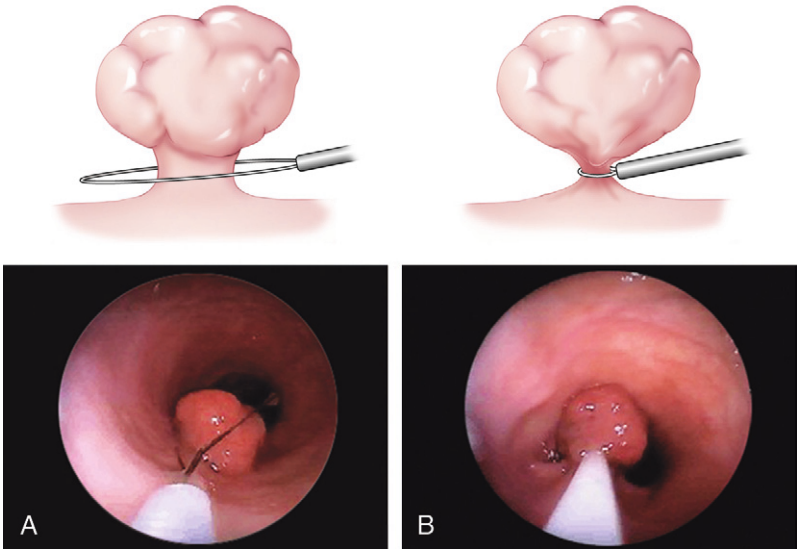


Figure 27-65 Standard procedure for polypectomy of pedunculated polyps. **A**, The snare is opened and the polyp surrounded at the base. **B**, The snare is tightly closed around the base of the lesion. The head of the polyp is pulled toward the center of the organ lumen to avoid energy dispersion and burns.

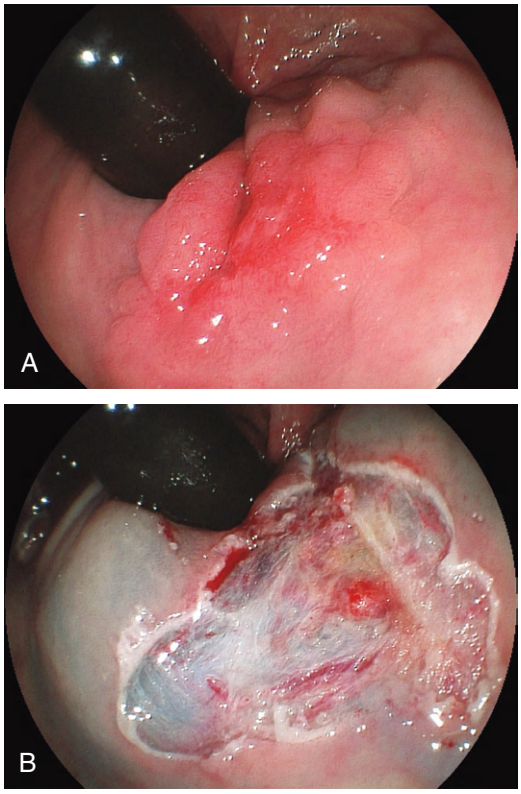


Figure 27-67 Endoscopic view of a raised, bleeding lesion near the anal sphincter in an 8-year-old, male dog before (**A**) and after (**B**) mucosectomy. Histopathology revealed an adenomatous polyp.

Surgical excision is instead indicated when the polyp is close to "difficult" sphincters (pylorus), when too large (>6 cm in diameter), or when the malignant invasion of the stalk or a previous incomplete excision is histologically demonstrated.

Complications

Complications of endoscopic polypectomy are usually a result of improper technique, inexperience, and nonobservance of contraindications. Possible complications are mainly bleeding and perforation.

Bleeding after endoscopic polypectomy may originate from incomplete coagulation of blood vessels of the stalk or of the base of the polyp. If bleeding is not severe, a systemic hemostatic treatment and, when necessary, blood transfusion may be curative. If bleeding does not stop, surgery is recommended.

Perforation during polypectomy is not common and can be due to the operator's hazardous maneuver or inexperience. Not including the organ wall in the polypectomy snare is key to minimize the risk of perforation. Consequences of perforation depend on the organ involved.

Endoscopic Mucosectomy

Endoscopic mucosectomy is a well-described procedure in humans[60-63] that, in the author's experience, also can be useful to treat some pathologic conditions in dogs and cats. Mucosectomy involves the removal of a portion of the gastrointestinal wall including the mucosa, muscularis mucosae, and submucosa. It is a therapeutic procedure that may be useful for the excision of benign sessile or pedunculated polyps difficult to excise with a polypectomy snare (Fig. 27-67) or of metaplastic/dysplastic areas of the mucosa that could become neoplastic. The multiple technical variants used in human medicine require specific and expensive instruments (dual-channel endoscope, elastic ligature unit, plastic hood, etc.) that are currently not justified in veterinary medicine because of the different clinical significances of the lesions. A simple and inexpensive technique that can be used in animals is the saline lift technique,[64] which is useful for the excision of sessile polyps that are difficult to remove with a snare because of their localization (sphincters, gastric angulus, tubular organs), morphology (villous polyps), or size (small polyps); another indication to use this technique is for excision of an epithelial lesion.[65] Besides a standard endoscopic polypectomy set, instruments needed are a sclerosing needle (Fig. 27-68), saline solution, and methylene blue solution. The needle is introduced into the operative channel of the endoscope and the lesion-bearing mucosa is submucosally injected with saline in multiple sites, so that the lesion is lifted on the organ wall. The amount of saline used depends on the degree of lifting desired and on the size of the lesion (5 to 30 mL). Epinephrine (1:10,000) to minimize bleeding and methylene blue to better delineate the lifted area from the healthy tissue may be diluted in the saline. With a polypectomy snare, it is possible to grasp all the lifted tissue and excise the lesion with standard polypectomy technique or other techniques (Fig. 27-69).

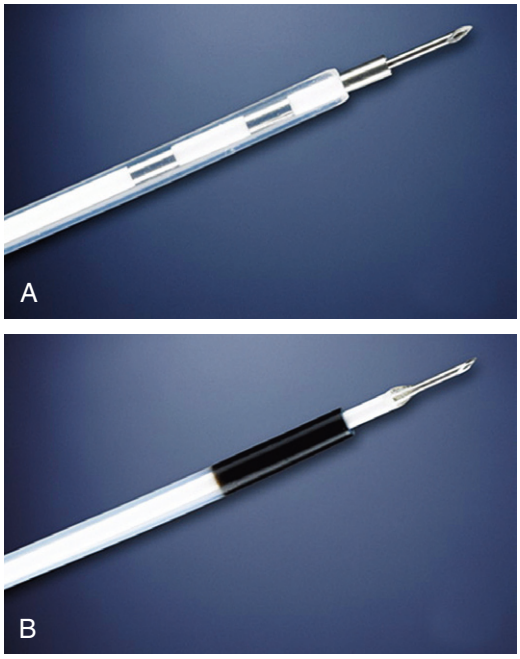


Figure 27-68 **A** and **B**, Devices used for endoscopic injection into gastrointestinal mucosa. (Courtesy of Cook-Medical.)

Endoscopic mucosectomy can be used also to obtain large biopsies for diagnosis. This technique is, however, indicated only for biopsy of intraepithelial lesions as the submucosal injection of saline modifies the normal anatomy of the submucosal layer, hindering histopathologic examination.

Complications

The complications of endoscopic mucosectomy are similar to those for endoscopic polypectomy.

Endoscopic Removal of Gastrointestinal Foreign Bodies

GI foreign bodies are common in small animals and are more frequent in the stomach than in the esophagus or in other

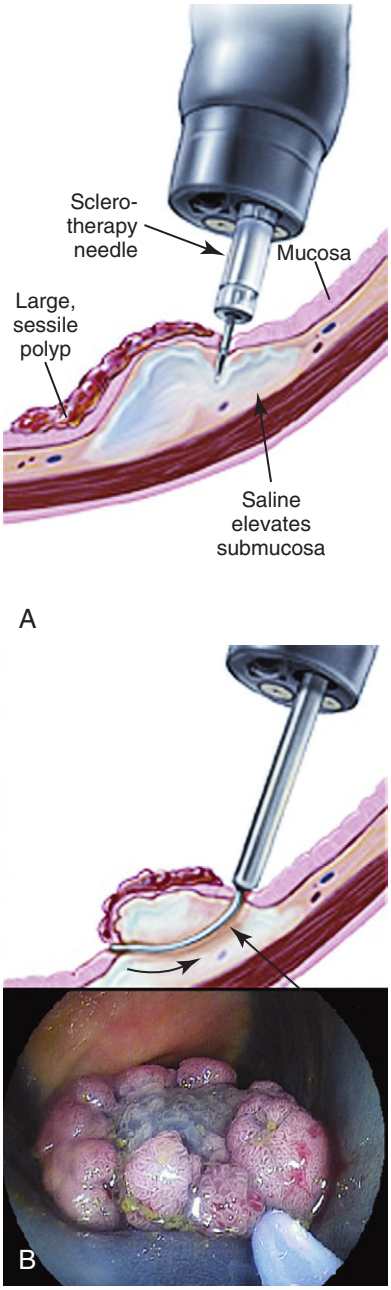


Figure 27-69 Saline lift technique. **A**, The needle is introduced in the operative channel of the endoscope and the lesion-bearing mucosa is submucosally injected with saline in multiple sites so that the lesion is lifted on the organ wall. **B**, With a polypectomy snare it is now possible to grasp all the lifted tissue and excise the lesion.

intestines.[9,66,67] They are more common in the dog than in the cat, as a result of the different feeding behavior of the two species. The variety of foreign bodies that can be encountered in the digestive tract is infinite, but they may be distinguished as sharp, pointed, smooth, linear, or toxic. Retrieval technique could be surgical or endoscopic and depends on the anatomic site and type of the foreign body.[66-68] Endoscopic retrieval should be considered the elective procedure for treatment of most esophageal and gastric foreign bodies, either symptomatic or clinically silent. A number of ancillary instruments exists for removal of different objects (Fig. 27-70).[67] In most cases endoscopy allows a nontraumatic retrieval of foreign bodies, except when the extended contact time with the gastric fluid modifies the physical state (from soft to rigid) of the foreign body, or for linear objects (ropes, wires, clothes, etc.) that extend into the duodenum.

Esophageal Foreign Bodies

An esophageal foreign body should always be promptly removed because the likelihood of complication depends on the duration of the foreign body's contact with the mucosa. Foreign bodies in the cervical esophagus can also cause dyspnea secondary to tracheal compression. Because it is usually successful, endoscopic removal should be considered as the first approach to esophageal foreign bodies.[7,9,67-70] Surgery should be considered when endoscopic removal fails or when there is evidence of esophageal perforation.[68]

The technique used for removing a foreign body varies with the type and size of the object ingested. Rigid or flexible grasping forceps can be used based on the foreign body's location (proximal or distal, respectively) and the size of the patient. A laparoscopy rigid instrument is passed alongside the endoscope to firmly grasp large proximal and well-anchored objects (Fig. 27-71). The length of rigid instruments (40 cm maximum) limits their use, as foreign bodies in the thoracic esophagus of medium- or large-size dogs cannot be reached in this way. Flexible forceps are instead inserted into the working channel of the endoscope. Once the object has been grasped, if no resistance is felt, both the endoscope and the forceps are withdrawn simultaneously, paying particular attention to the passage through the upper esophageal sphincter. To facilitate this passage, the endotracheal tube cuff is deflated. The removal of pointed or sharp bones should be done with particular care and gentleness.

Pointed objects that have been embedded in the esophageal wall for long periods can be gently pushed–pulled and rotated to grasp the object on its distal side (Fig. 27-72). If the object does not move by these attempts, a flexible overtube with a smooth end and a diameter slightly larger than the foreign body may be introduced into the esophagus. The endoscope is passed inside the tube. The tube will mildly dilate the esophageal lumen, facilitating the dislodgment of the foreign body under direct endoscopic visualization. Preanesthetic administration of high-dose atropine (0.04 mg/kg IM) to prevent or reduce the vagal stimulation induced by the manipulation during retrieval is important. Cardiac-circulatory arrest is possible during this procedure, especially for foreign bodies located at the cardial region**.** When an esophageal foreign body cannot be retrieved, it can be pushed into the stomach and removed by gastrotomy. Bone foreign bodies can be left in the stomach as they dissolve rapidly in the gastric cavity, but abdominal radiographs should be taken to confirm the dissolution. Pointed objects such as fishhooks should be first dislodged from the esophageal wall and then turned with the pointed end toward the cardia so as to avoid further anchoring to the wall during retrieval (Fig. 27-73). An overtube should be used to remove sharp objects such as razor blades or bone fragments to protect the esophageal mucosa and the larynx (Fig. 27-74). The residual foreign body's site and the proximal esophageal mucosa (e.g., iatrogenic lesions) should always be assessed after removal. Esophageal perforation should be radiographically ruled out in case of pointed and sharp objects or long-standing foreign bodies; sometimes the foreign body plugs the perforation and clinical signs manifest only after its retrieval. Postoperative treatment is based on the administration of a broad-spectrum antibiotic (e.g., ampicillin, amoxicillin-clavulanic acid, cefazolin) and treatment of possible complications.

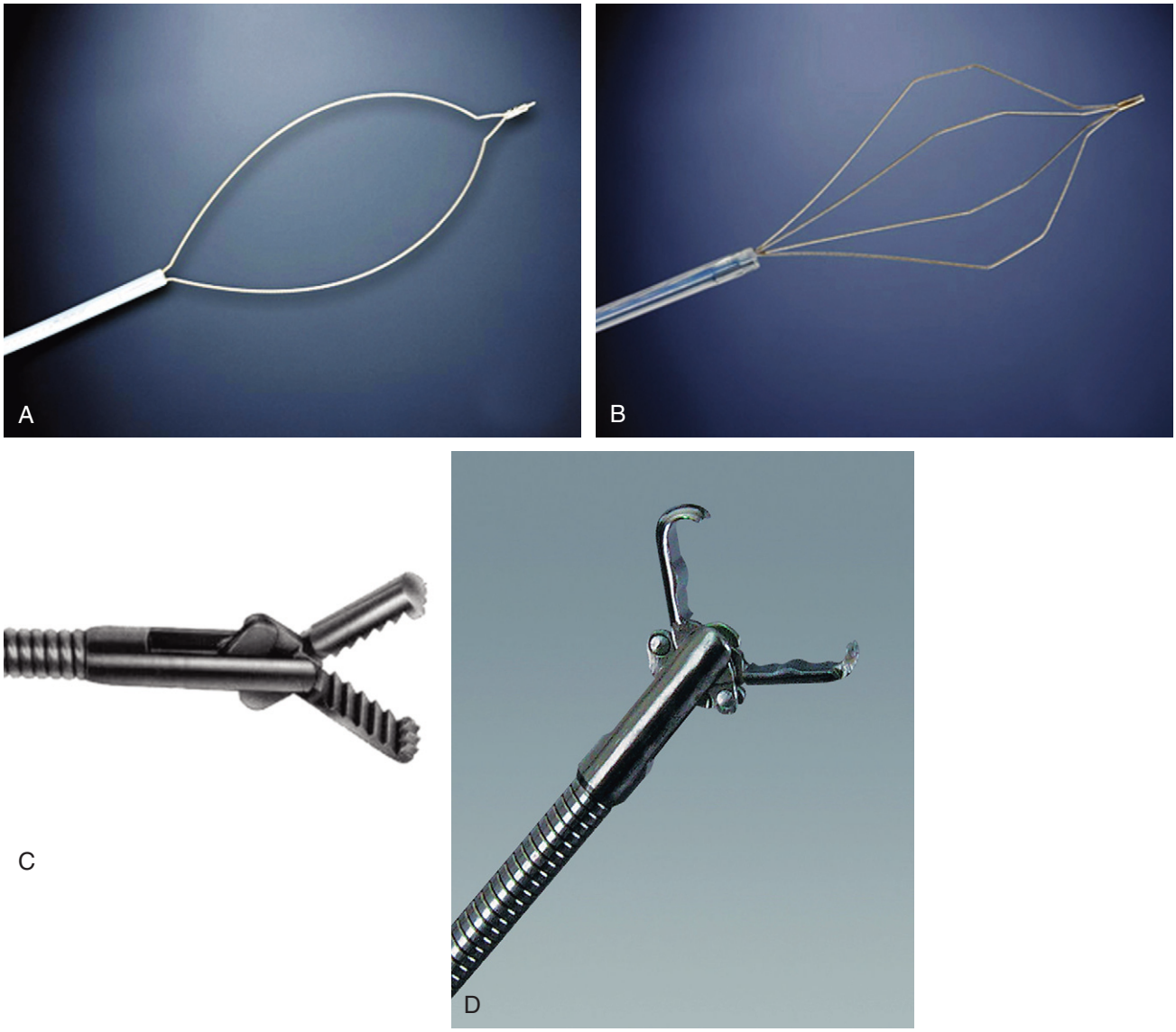


Figure 27-70 The most commonly used flexible grasping instruments for foreign-body removal. **A**, Oval grasping snare. **B**, Four-wire basket. **C**, Alligator-jaw grasping forceps. **D**, Rat-tooth grasping forceps. (B is courtesy of Cook-Medical.)

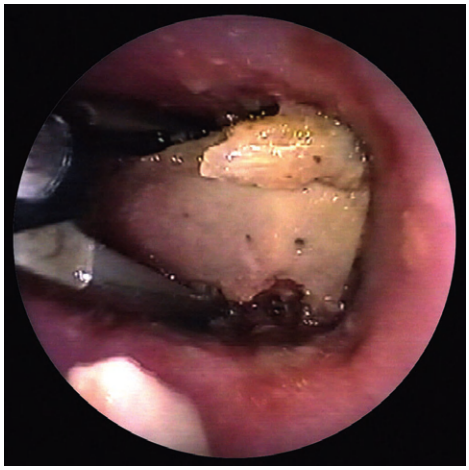


Figure 27-71 Endoscopic removal of an esophageal foreign body (bone fragment occluding the lumen) in a dog. The object is removed using a laparoscopic grasping forceps introduced alongside the endoscope.

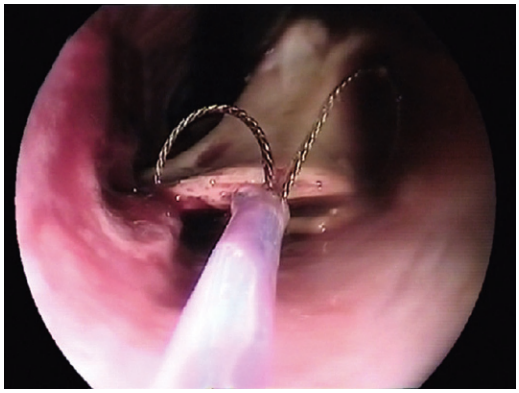


Figure 27-72 Endoscopic removal of an esophageal foreign body (bone fragment) in a dog. The object is firmly grasped with a snare. The snare is gently pushed–pulled and rotated on its long axis to free the bone from its site and retrieve it through the mouth.

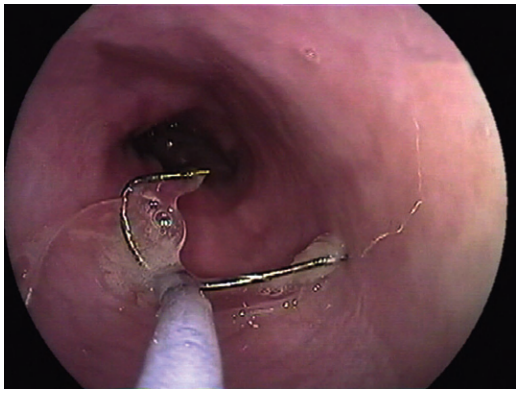


Figure 27-73 Removal of a fishhook from the esophagus of a dog. A flexible grasping forceps is used to unhook the object from the esophageal wall and to orient the pointed end distally. Keeping the pointed end close to the endoscope tip, the object is retrieved with no risk of sticking.

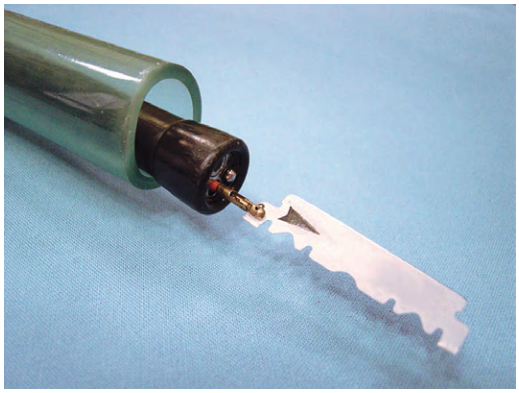


Figure 27-74 Technique for removing a sharp foreign body (razor blade). A plastic overtube is introduced in the esophagus and the endoscope is inserted in the tube until the object is reached. The grasped foreign body can now be pulled inside the plastic tube and retrieved together with the tube, avoiding lesions to the esophagus and larynx.

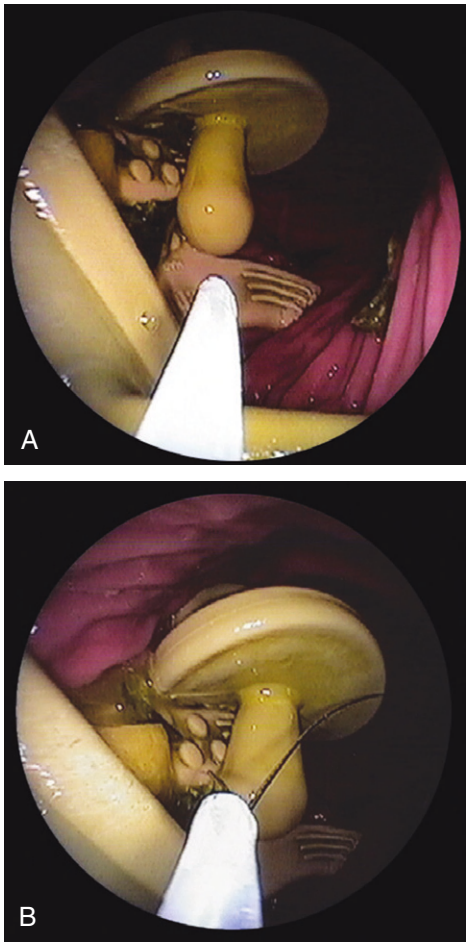


Figure 27-75 **A**, Multiple foreign bodies (three rubber dummies) in the stomach of a dog. **B**, The objects are singularly grasped with a flexible snare and retrieved. When present for a long time, rubber objects can become fragile and break down during removal, requiring time and patience for complete retrieval.

Gastric Foreign Bodies

The best strategy for removing a foreign body from the stomach is to grasp the object as firmly as possible so that it can be moved retrograde through the LES, the esophagus, and the upper esophageal sphincter (UES). Passage of the object through the LES is the most difficult phase of this procedure (Fig. 27-75).[67,68,70,71] Long foreign bodies (long bones, skewers, etc.) should be grasped by the distal end to minimize resistance to the passage of the LES. Removal of blunt objects (stones, small balls, toys, etc.) may benefit from a reduction of gastric distention (air deflation) so that the Hiss angle (angle formed by the entrance of the esophagus in the stomach) becomes less acute. Simultaneously the tip of the endoscope should be slightly deflected to the left to align it with the gastric cardia.

Foreign bodies in other portions of the GI tract are not often removeable by endoscopic procedures. Linear foreign bodies (ropes, socks, clothes) can be found in the duodenum, but they are better removed surgically to avoid the risk of intestinal invagination. A gentle attempt to remove endoscopically a duodenal foreign body is justifiable.

Rare, foreign bodies that successfully traverse the upper GI tract can be encountered in the distal intestinal tract and the rectum (e.g., pointed bone fragments, glass fragments, needle). Because of anal spasm induced by pain and trauma, these objects may not be passed out with normal defecation and removal with a rigid or flexible endoscope can be attempted.

Complications

Complications of foreign body removal are infrequent and endoscopy can be safely used in most cases. Possible complications are laceration/perforation, gastric overdistention, and sphincter neurologic dysfunction.

COMPLICATIONS

Olivier Dossin

Although well documented in human medicine, complications of GI endoscopy are rarely reported in dogs and cats. Complications, as defined in human gastroenterology, have the following characteristics: (a) they are a result of the procedure; (b) they are deviations from the expected course and tend to delay or impair recovery; (c) they cause changes in the management of the patient; and (d) they lead to morbidity or even mortality.[1]

A major advantage of GI endoscopy is the minimal morbidity and mortality associated with this procedure,[2] implying that complications are rare. In human gastroenterology, the overall rate of GI endoscopy-associated complications is reported to vary between 0.1% and 1.9%.[3,4] Most of these complications are minor, but some, such as perforation, can be life-threatening.

Complications of Diagnostic Endoscopy

Preprocedural Complications

Contraindications

Contraindications to endoscopy are always important to consider. The risks of general anesthesia must be considered as GI endoscopy is almost always performed under general anesthesia in dogs and cats. The only absolute contraindication for endoscopy is the presence of, or risk for, digestive tract perforation. Air insufflation, which is a prerequisite for GI endoscopy, may cause further perforation along a plane of tissue devitalization, the consequence of which will be bacterial and GI fluid effusion into the thoracic or abdominal cavity.[5] In patients with uncontrolled coagulation disorders, GI biopsies and other procedures, such as tube placements, should be postponed until the coagulation disorder can be controlled.[5]

Patient Preparation

Large volumes of oral lavage solutions can be associated with vomiting, aspiration pneumonia, hypovolemia, and electrolyte disturbances,[3,6,7] and even with gastric dilation and volvulus in the dog.[8] Enema-associated complications are related to the volume or to the method of administration, but can also be metabolic in cases of hypocalcemia secondary to phosphate enemas,[9] especially in small dogs and cats. Such patients may develop acute dehydration associated with hypernatremia and hyperphosphatemia with secondary decreases in serum calcium concentrations and life-threatening hypocalcemia.[10] In the author's experience, bowel perforation during preparation for colonoscopy is a rare complication and only occurs when the colon is severely damaged (e.g., necrosis or neoplasia) or when inappropriately stiff catheters are used for enema procedures. Inadequate bowel preparation may predispose to missed lesions as well as bowel perforations.[3] In human medicine, 6% to 17% of colonic adenomas may be missed during colonoscopy, some of which are attributable to poor bowel preparation.[7] Poor bowel preparation is a frequent problem in veterinary medicine, but can be avoided by following an appropriate procedure (see "Colonic Endoscopy" section). Cats are very sensitive to rapid and voluminous colonic distention, which can induce vomiting or even shock. Consequently, enema volume should not exceed 50 to 75 mL in this species.[8]

Barium contrast agents and mucosal-adherent medications such as sucralfate should be discontinued for at least 8 to 12 hours prior to endoscopy,[11,12] as they may mask mucosal lesions.[7] Animals that are severely anemic should receive component transfusion therapy before anesthesia and endoscopy.[2]

Anesthesia

General anesthesia complications are the same as for other procedures and include hypotension, reduced cardiac output, hypoventilation, and airway aspiration. Lidocaine jelly or benzocaine sprays used for local anesthesia in human patients are infrequently used in veterinary medicine as the patient is usually under general anesthesia. Some complications, such as methemoglobinemia with benzocaine[13] and reduced pharyngeal motor function with increased risk for aspiration, may occur.[3] This is especially true for veterinary patients because vomiting is sometimes associated with the recovery phase of anesthesia following GI endoscopy.[6]

Procedural and Postprocedural Complications

Endoscopy and Biopsy

Gastric overdistention is probably the most frequent and important complication of endoscopy. In extreme cases it can be associated with respiratory depression because of decreased respiratory tidal volume, caudal vena cava compression, and a secondary drop in cardiac venous return and blood pressure.[14] Gastric overdistention may occur not only during gastroscopy, but also during esophagoscopy and duodenoscopy. During esophagoscopy for very small strictures, insufflated air can be trapped as the stricture may prevent gastric air from being spontaneously expelled or aspirated by the endoscope from the esophagus.[5,11] Extreme cases may require gastric trocarization.[14] Overinflation of the stomach may also induce difficulties in pyloric intubation because of decreased endoscopic maneuverability and reflex antral and pyloric contractions.[14] This is especially true of large-breed dogs in which the endoscope may be too short to even reach the pylorus. Gastric overdistention has also been reported as a rare complication of colonoscopy in dogs.[6] Laceration of major organs or vessels adjacent to the GI tract can also occur because of overdistention, stretching, or perforation.[15,16]

Cats and small dogs are especially sensitive to stretching and displacement of the gastric body and pylorus.[5,17] This may induce bradycardia and significant respiratory depression, which should prompt the operator to deflate the stomach and withdraw the endoscope until the patient stabilizes.[5,16]

Gastroesophageal reflux or retching may occur, especially when attempting to advance the endoscope through the pylorus. It usually subsides after a short period of time and the endoscope can be advanced after fluid and air aspiration.[17] Fluids refluxed into the esophagus should be aspirated at the end of the procedure as they may induce esophagitis and secondary esophageal stricture. Esophageal entrapment of an endoscopic tip deflection has been described in human medicine as a consequence of belching during gastroscopy,[18] but this is an unlikely scenario with veterinary patients as they are maintained under general anesthesia. Entrapment could theoretically occur in hernia pouches.[7]

Gastric perforation may occur when excessive force is applied and occurs mostly in the hands of an inexperienced operator.[17] Keeping the lumen within the field of vision at all times is one way to avoid perforation associated with excessive pressure or stretching.[5] Perforation rates associated with colonoscopy have been estimated to be less than 0.2% in human medicine.[7] A similar rate was reported in a retrospective study of colonoscopy-associated complications in dogs[6] in which only one case of perforation was reported in more than 355 total colonoscopies (0.28%). The dog that suffered the perforation had a colonic stricture associated with pyogranulomatous colitis and recovered after surgical treatment of the perforation.[6] Perforation can be a result of any of four different causes: (a) direct force applied by the tip of the endoscope against the bowel wall, (b) biopsy, (c) lateral pressure of the endoscope tube during tip deflection, or (d) pneumatic distention.[3] Perforations associated with the last two causes are the most difficult to diagnose as they may not occur under direct endoscopic visualization. No attempts should be made to push the endoscope forward while in the cecum, as its thin wall can easily be perforated.[12] Perforation of blind pouches is also possible, especially when a perineal hernia is present and the endoscope is advanced against excessive resistance.[8] The best way to avoid such complications is to systematically perform a digital rectal examination before inserting the endoscope.[12] Perforation of the intestinal wall with flexible biopsy forceps is unlikely to occur unless the biopsy is made in the middle of a necrotic lesion. Special precaution is advised when using rigid biopsy forceps to obtain biopsies in the rectum or the

descending colon.[8] Blind biopsies of the duodenum may be dangerous, too, because of the sharp angulation of the cranial duodenal flexure. A biopsy forceps that is blindly advanced through the pylorus may sample deep into the mucosa at the same location without bending downstream, increasing the risk for duodenal perforation. The author had this experience in one dog in which the technique resulted in biopsies of the serosa. The dog recovered uneventfully and no postendoscopic complication occurred, but perforation and peritonitis are possible complications in such a situation. Another risk of blind biopsy in the duodenum is the slight possibility of damaging the duodenal papilla,[19] which may induce scarring and secondary cholestasis or pancreatitis. If there is no alternative to blind biopsy through the pylorus, it is recommended to perform no more than three to four superficial mucosal biopsies. Perforation may occur when the endoscopist attempts deeper biopsies in the attempt to sample the submucosa.[14] The risk of perforation increases when the tissue is very friable or necrotic. Hemorrhage associated with biopsies is usually mild, but can be severe when dealing with necrotic neoplastic tissue.[6] Bleeding may persist in this instance,[6] in which case severe hemorrhage may require blood transfusion and emergency endoscopic cauterization or celiotomy.

When moving the patient from left lateral to dorsal recumbency to facilitate endoscopic intubation of the pylorus,[16] gastric torsion may be induced, particularly if the stomach is dilated. Gastric dilation and volvulus may also occur after the endoscopic procedure.[5] The best way to avoid this complication is to carefully assess gastric distention during the procedure and to aspirate all gastric gas and fluids before the endoscope is removed, and by closely monitoring the patient during the recovery phase of the procedure.

Glutaraldehyde-induced colitis has been reported in human medicine and reproduced in a rodent model.[3,20] It is characterized by an acute ischemic, ulceronecrotic colitis.[20] This complication can be avoided by proper endoscope cleaning after glutaraldehyde disinfection.[3,21]

The endoscope can be a source of transmission of various infectious agents, including bacteria, fungi, viruses, and parasites.[22] If current guidelines for endoscopic management are followed (see "Care and Cleaning of Instruments" section) the risk of disease transmission is greatly reduced.[3,7] The water bottle or irrigation tubes may also be colonized by pathogens, such as *Pseudomonas* spp.,[22,23] and can act as a source of endoscope-borne infections. It is important to use sterile water[22] and to disinfect or sterilize the water bottle on a regular basis.[8] For the same reason, cleaning and disinfection of reusable biopsy instruments, foreign-body retrieval devices, and esophageal balloon dilators is mandatory.

Bacterial translocation and secondary bacteremia following GI endoscopy have been reported in the human literature with rates ranging from 0% to 8% for gastroscopy,[3] 0% to 25% for colonoscopy,[7] and 12% to 45% for esophageal dilation,[23] but the actual risk of dissemination appears to be very low. Antibiotic prophylaxis has been recommended only for patients with mechanical heart valves or a history of endocarditis.[7,23] Bacteremia is also likely to occur in dogs and cats, but has never been documented in these species.

The risk of aspiration pneumonia during upper GI endoscopy[3] can be minimized by endotracheal intubation and close monitoring during the recovery phase of anesthesia. To further reduce this risk, aspiration of esophageal and gastric fluids should always be performed before endoscopic extubation.

Cholangiopancreatography is rarely performed in veterinary medicine, but has not been associated with major or minor clinical complications either in healthy dogs[24] or in dogs with chronic gastrointestinal disease.[25] Transient increases in serum activities of amylase and lipase and serum concentrations of canine trypsin-like immunoreactivity (cTLI) have been reported, but these did not translate into clinical signs.[26] Pancreatitis is the most important complication in human patients undergoing ERCP.[3]

Complications of Therapeutic Endoscopy

Therapeutic endoscopy procedures are more frequently associated with complications[7] and are better documented in small animal medicine than are complications of diagnostic endoscopy.

Perforation is the most serious complication of esophageal foreign body retrieval. It is more likely to occur when the foreign body is lodged in the mucosa.[11] Perforations are usually small, but sometimes very large tears occur with lung lobe visualization and severe pneumothorax (Fig. 27-76). Fatal hemothorax caused by laceration of pulmonary vessels has been described as a delayed complication of foreign-body retrieval in a dog.[15] In a case series of esophageal fishhook foreign bodies,[27] full-thickness lacerations in two of 41 animals was reported, one of which healed without surgical treatment. In one dog, the fishhook was embedded in the esophageal wall near the heart base and retrieval resulted in fatal laceration of a pulmonary vein.[27] The author has experienced an incarceration of a basket foreign body forceps around a foreign body, which was then impossible to retrieve. Surgery was necessary to remove the forceps and the foreign body.

Complications are best documented for dilation of esophageal strictures in dogs and cats. Bleeding is the most frequent complication,[28-30] but rarely requires aggressive treatment.[28-32] Perforation occurred in one of 13 cats in one study[28] and in one of 28 cats in another study.[29] Both cats were euthanized as a result of those perforations.[28,29] In another study, two of 23 animals developed esophageal perforation and secondary pneumothorax, which resolved spontaneously.[30] Adamama-Moraitou and coworkers[33] reported a case series of 13 dogs and seven cats with esophageal strictures. One developed an esophageal perforation and was euthanized. Gualtieri[11] reported perforation in one dog and one cat in a series of 40 cases. One perforation was associated with the application of electrocautery prior to balloon dilation. Other, less-severe complications, such as superficial mucosal tears, diverticulum formation, and aspiration pneumonia have also been reported.[30] In human studies, the rate of perforation associated with esophageal dilation is 0.1% to 0.4%,[31] and complex or malignant strictures are at the highest risk.[31] Most often the perforation is not noted at the end of the procedure,[31]

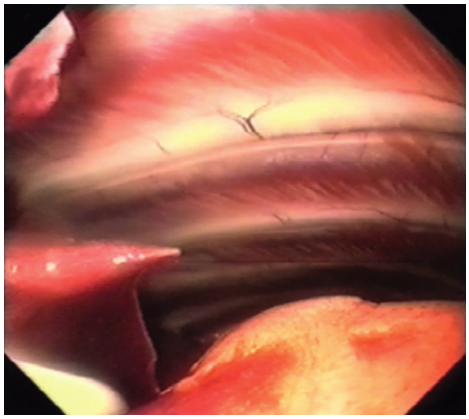


Figure 27-76 Esophageal tear. Endoscopic view of an esophageal tear during esophageal foreign body extraction. Note the fragment of the torn esophagus, the lung lobe margin, ribs, and intercostal muscles.

especially because of extensive hemorrhage, which may obscure the tear.[32] Therefore, the patient should be closely monitored after stricture dilation. If there is any suspicion of a perforation, it is advisable to investigate for a perforation by survey and/or contrast (e.g., using a nonionic, water-based, soluble agent) thoracic radiographs and to closely monitor the patient for respiratory or other clinical signs. Some perforations can heal spontaneously.[30,31] Bacteremia following esophageal stricture dilation is a frequent occurrence in human medicine (12% to 22%), although infectious sequelae appear to be rare.[31] Although bacteremia has not been documented in animals after stricture dilation, it is likely that such bacteremia does take place.

Endoscopically placed gastrostomy feeding tubes are extensively used in dogs and cats. Reports of complications associated with tube placement are more often complications of tube handling rather than tube placement.[34] Complications associated with tube placement include splenic laceration, gastric hemorrhage, peritonitis, and early tube removal,[35] and are the same as have been reported in human medicine.[36] Complications associated with tube placement are usually minor,[37] except for splenic laceration,[38] which can be prevented by careful abdominal palpation before inserting the stylet or needle. Pneumoperitoneum and gastric bleeding[38,39] have been described and gastric bleeding may be associated with secondary melena for a few days after the procedure.[38]

Endoscopic surgery is infrequently reported in veterinary gastroenterology. Transanal endoscopic treatment has been evaluated for benign canine rectal neoplasia in 13 dogs.[40] Reported complications included rectal perforation in two of 13 cases. Both patients had to be euthanized as a consequence. Fatal peritonitis was reported in one of 13 patients, and acute paraplegia and delayed acute rectal bleeding were reported in one of 13 dogs each.[40] Because of these complications, hospitalization for 5 days of monitoring has been recommended following these procedures.[40]

Complications for the Operators

As endoscopy is an invasive procedure, there is the possibility for exposure of the endoscopist and staff to the animal's endogenous bacterial flora, including to some potentially zoonotic agents. A case report of herpes virus transmission from a jet of fluid originating from the biopsy channel[3] underscores the importance of protecting the endoscopy team to avoid such complications.

CARE AND CLEANING OF INSTRUMENTS

Diane Levitan

The importance of proper handling, care, and cleaning of the endoscope and accessories cannot be overstated. The return on investment in endoscopic equipment for veterinary practice is optimized by strict adherence to an established care-and-cleaning procedure, as this will extend the life of the equipment and minimize the need for expensive repairs. Arguably more important, following such guidelines will ensure the greatest level of safety for the patient, staff, endoscope, and accessory equipment. To date, there is little emphasis in the veterinary literature on proper cleaning and disinfection of endoscopes and accessories for gastroenterology; however, there are significant risks imposed on our patients and staff.[1-5] A number of reports document the risk of infection through a contaminated endoscope, specifically with *Salmonella*, *Pseudomonas*, *Mycobacterium*, *Escherichia*, *Serratia*, and *Helicobacter* spp., but also with hepatitis B virus and many more.[1-3] Transmission of infection in humans occurs most commonly because of failure to adhere to proper cleaning and disinfection procedures, contamination of endoscopes in automatic reprocessing machines, and the inability to decontaminate endoscope valves or channels because of endoscopic configuration.[1-3]

Reprocessing refers to the sequence of cleaning, lubricating (if necessary), and high-level disinfecting or sterilizing steps that assure endoscopes and accessories are appropriate for the patient of interest.[6] Every veterinary endoscopy facility should implement strict care-and-reprocessing guidelines for endoscopes and accessories (Boxes 27-1 through 27-4). Detailed training protocols for any personnel involved in the care, use, and reprocessing of endoscopy equipment should be mandatory. Training should include a thorough understanding of the proper use and handling of the equipment, personnel safety measures, knowledge of chemicals used for manual

Box 27-1 Spot Cleaning Protocol

Perform spot cleaning at procedure site immediately after procedure.

- Place all accessories in ultrasonic cleaner with enzyme solution and then clean along with endoscope. Any instruments that break the mucosal barrier should be steam or gas sterilized according to manufacturer's recommendations.
- Wipe the insertion tube with an enzymatic detergent.
- Suction enzymatic detergent through the instrument channel for 30 seconds.
- Suction air through the instrument channel for 10 seconds.
- Attach the air/water channel cleaning adapter; depress to feed water through the air and water channels for 30 seconds.
- Release the air/water channel cleaning adapter to feed air through the air and water channels for 10 seconds.
- Use the special cleaning adapters as recommended in your endoscope's instruction manuals for precleaning.
- Clean all valves with brushes and place valves and removable parts in detergent solution.
- Inspect and attach the water resistant caps.
- Cover the endoscope and transport to the reprocessing area.

Box 27-2 Leakage Testing Protocol

- Connect the leakage tester connector according to manufacturer's guidelines.
- Check that the leakage tester is emitting air and confirm that the connector cap is dry.
- Attach the leakage tester's connector to the water resistant cap and verify that the endoscope is pressurized.
- Immerse the *entire* endoscope in a basin of water and observe for 30 seconds; visually inspect for potential leaks.
- Manipulate the angulation knobs and video switches to check for potential leaks.
- Remove the endoscope from the water and then turn off the air supply.
- Disconnect the leakage tester from the air supply and allow the endoscope to depressurize.
- Disconnect the leakage tester from the water-resistant cap. (Do not remove the water-resistant cap.)

Box 27-3 Manual Cleaning Protocol

- Immerse the entire endoscope in freshly prepared enzymatic detergent solution with angulation in free position.
- Clean the exterior of the endoscope with a soft brush or lint free cloth.
- Brush biopsy/suction channel in the insertion tube with the channel cleaning brush until all debris is removed.
- Brush biopsy/suction channel in the universal cord with channel cleaning brush until all debris is removed.
- Brush suction valve housing and instrument channel port with channel opening brush until all debris is removed.
- Use manufacturer provided cleaning adapters to suction detergent through the suction/biopsy channel for 30 seconds.
- Use manufacturer provided cleaning adapters to inject detergent through the air/water channel.
- Disconnect cleaning adapters when you are certain all channels are filled with detergent.
- Soak the endoscope in the detergent solution for the amount of time recommended according to detergent manufacturer's guidelines.
- Brush and flush the valves and removable parts until all debris is removed.
- Perform the final rinses and air purges using manufacturer's recommended cleaning adapters.
- Thoroughly dry the exterior of the endoscope and all removable parts using a clean lint-free cloth.
- Inspect the endoscope for residual debris and repeat the manual cleaning process if debris remains.
- Prepare compatible valves and removable parts for steam sterilization or high-level disinfection.

Box 27-4 Manual Disinfection Protocol

- Test the high-level disinfection (HLD) potency and record.
- Fully immerse the entire endoscope, valves, and removable parts in a basin of HLD solution.
- Use manufacturer-provided cleaning adapters to suction disinfectant through the suction/biopsy channel slowly until no air bubbles are produced and the channel is completely filled with disinfectant.
- Use manufacturer-provided cleaning adapters to suction disinfectant through the air/water channel slowly until no air bubbles are produced and the channels are completely filled with disinfectant.
- Disconnect all cleaning adapters and let them soak in disinfectant.
- Allow all to soak in HLD solution for the recommended time and temperature.
- Flush air through the endoscope channels using recommended cleaning adapters.
- Use filtered, tap, or sterile water to rinse the endoscope and accessories and flush all channels thoroughly.
- Perform a channel air flush followed by an alcohol purge and an air purge.
- After rinsing, dry or steam sterilize accessories.

and automatic equipment reprocessing (if applicable), and how to meticulously clean endoscopes and accessories. Because specific manufacturer recommendations and guidelines vary, the protocol established in each facility should be specific to equipment in use. Most endoscopy manufacturers can provide excellent resources such as videos, wall charts, and training guides for proper care, use, and cleaning of instruments. All resources are readily available through the manufacturer's Web site or by contacting company representatives. The following recommendations are adopted from standards and guidelines for care and cleaning of these instruments in human medicine[7,8] and should be considered the standard of care for veterinary medicine.

Endoscope Cleaning and Care (Reprocessing)

Intact Endoscope

Endoscopes are complex devices that have many small interconnecting parts, several long narrow channels with bifurcations, and complex connections to external sources. Familiarity with the external and internal anatomy of the endoscope and the ancillary devices is important for proper handling, use, care, and cleaning (see Figs. 27-2 and 27-77). Channels, accessories, small parts, and connections vary by manufacturer, brand, type, and use. Consequently, it is essential to refer to the manufacturer's guidelines for each endoscope. The following general overview applies to most endoscopes used in veterinary medicine.

Equipment and Procedure Checklist

Set up and careful inspection of the endoscope should begin well before the patient is anesthetized. The entire endoscope, forceps, cleaning tools, and accessories should be thoroughly examined and tested for viability. Postprocedure cleaning tools should be set up and readily available to minimize the lag time before cleaning. Suction devices, light source, camera attachments, and air/water supplies must all be clean and in good working order. The surface of the insertion tube should be inspected for dents, bulges, small holes, and other irregularities. The deflection control knobs should be tested for maximal deflection without resistance and that the deflection locks are functioning. If water enters the protected portions of the endoscope, permanent and serious damage will result, therefore leak testing should always be performed prior to the beginning of a diagnostic procedure.

The endoscope should be connected to the light source and camera fittings, and the optical system's focus, field of view, fiber conditions, and video image should be evaluated. A biopsy instrument should be passed through the biopsy channel to ensure smooth passage. All ports should be inspected. The air, water, and suction lines and other connections must be secure and air, water, and suction functions should be tested. The air delivery mechanism should be tested by immersing at least 10 cm of the distal tip of the endoscope in water and covering the air/water valve. A constant stream of air bubbles should emerge from the distal tip. When the valve is uncovered, the flow of air should stop. The lens-cleaning mechanism should also be tested by making sure water comes out of the distal tip when depressing the hole of the air/water valve. Suction should be verified by dipping the distal tip in water and depressing the suction button. Normally, water will move through the suction tube until the button is released, and will stop as the button returns to normal position. If there are additional elements, such as carbon dioxide gas or water feeding channels, similar testing should be performed to ensure their proper function. If the endoscope passes preliminary inspection, the procedure can begin. While the patient is prepared, the endoscope should be kept in a location safe from potential damage, such as in a device specifically made for suspending the endoscope.[4]

During the endoscopic procedure, safe and proper handling of the endoscope is essential. There should be an oral speculum or

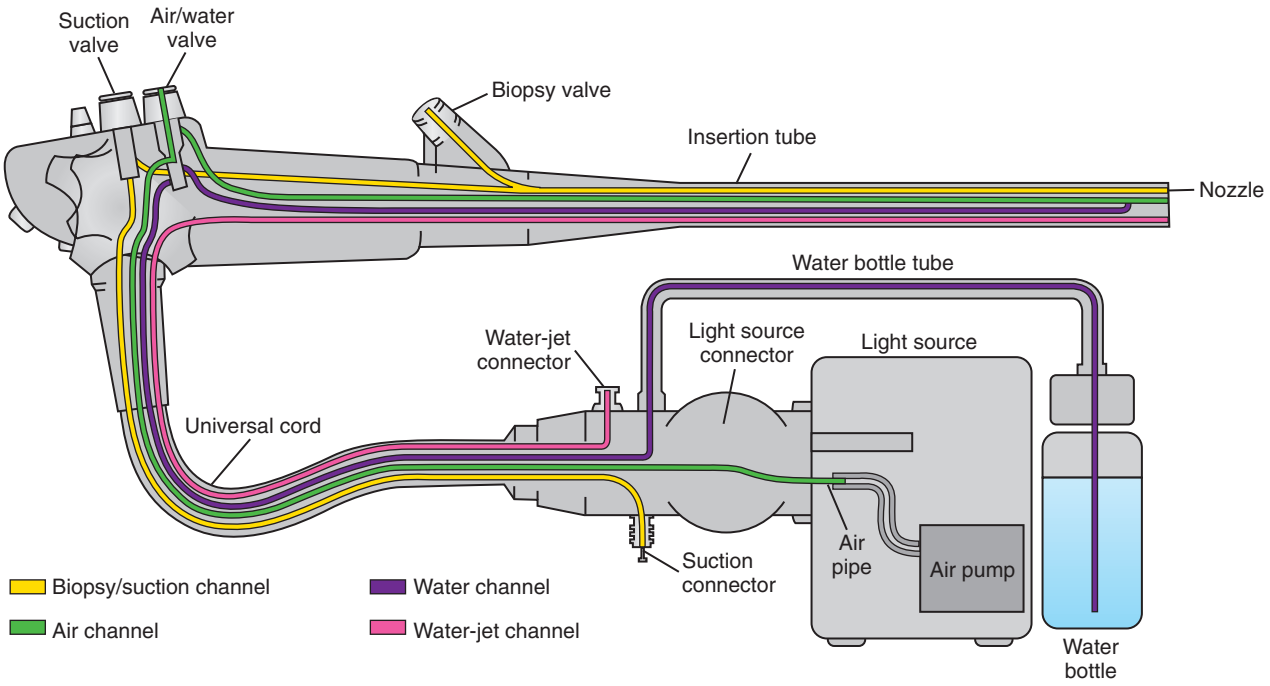


Figure 27-77 Internal anatomy of an Olympus flexible video endoscope. (Reprinted with permission of Olympus America Inc.)

mouth gag in the patient's mouth to prevent severe damage to the endoscope as a result of biting. The insertion tube should never be bent into acute angles during endoscope placement. The endoscopist should be standing in front of the patient at a distance that does not require excessive bending or awkward manipulation of the endoscope. To prevent damage to the shaft and delicate tip, the endoscope must never swing, drag, or slap onto surfaces. Devices used in the instrument channel must be of a diameter and length appropriate for the endoscope characteristics. Forcefully passage of an instrument within the biopsy channel will likely result in severe damage to the channel and the instrument. Resistance during forceps advancement is often the result of attempts to pass the instrument through the distal tip when it is deflected at a sharp angle. In this case, the insertion tube should be straightened inside the patient, the forceps should be advanced until only the tip is visible, and the endoscope should be redirected to the area of interest and the instrument advanced as necessary. Resistance upon advancement of an instrument may also be the result of an excessively firm grip on the biopsy forceps in the closed position. When forceps are gripped tightly in the closed position, the forceps shaft stiffens and will not bend, and the instrument will not move past a bend in the channel. Simply relaxing the grip while maintaining the closed position should allow for normal passage. When attempting to remove sharp foreign objects such as bones, fishhooks, or needles from a patient, the operator should avoid scraping against those sharp surfaces so as to prevent tears or damage to the endoscope liner. Large amounts of debris, such as hair or grass, should not be pulled through the instrument channel. Instead, the entire endoscope should be brought out with the debris in the grasper at the tip of the distal channel. Use of an endoscope in the presence of large amounts of barium, food, or feces will likely result in clogging of distal channels, poor cleaning, resistance to proper disinfection, potential future patient contamination, and potentially costly repairs. The improper use of needles, lasers, diathermy probes, and electrocautery devices can severely damage an endoscope. Therefore, such devices should be used only by individuals trained in proper use and techniques.

To prevent cross-contamination in an endoscopic procedure room, the room should have designated contaminated areas and designated clean areas. Contaminated endoscopes, accessories, and specimens should be handled in areas that are separate from clean counter areas. All contaminated areas should be cleaned and decontaminated between patients. The initial spot cleaning of the endoscope should be done immediately after the procedure and in the same location. The remaining reprocessing steps should take place in a room with conditions conducive to proper cleaning and disinfection of the endoscope and accessories. Federal and state requirements for reprocessing areas in human medicine may not be practical for many veterinary medical suites; however, close compliance is recommended.[9]

The following steps are recommended for reprocessing in a veterinary setting. Most endoscopes in use today are fully immersible in water; however, older endoscopes (manufactured before 1983) may not have this feature. Endoscopes that are not waterproof cannot be adequately cleaned or disinfected and are therefore not recommended for use. Endoscopes that cannot undergo the processes described in these guidelines because of water permeability, age, design, or damage should not be used.[7-9] It is important to note that steps may differ based on the manufacturer's recommendations and that these guidelines may not apply to every endoscope.

All products and methods for cleaning and disinfection/sterilization should be selected based on specific manufacturer recommendations. In preparation for any endoscopic procedure, the following should be prepared and readily available:

- Personal protective gear (gloves, eye protection, nonabsorbent apron or gown, and face shield or surgical mask that will not trap vapors)
- Large container or sink with warm water and freshly prepared low-foaming enzymatic detergent solution at appropriate dilution

- Sponge or soft cleaning cloth (lint-free)
- Specific channel-cleaning brushes
- Specific channel-cleaning and auxiliary adapters
- 30- to 50-mL Luer-lock syringe
- Protective video caps for video endoscope
- Watertight caps
- Leak-testing equipment
- Active disinfectant in covered basin
- Clean, filtered, or sterile water

Initial Spot Cleaning

Spot cleaning should take place immediately following the endoscopic procedure. This step removes gross debris (organic and inorganic) and large numbers of bacteria before they dry on or within the endoscope.

Wearing protective gear (nonabsorbent gown, mask, eye protection, and gloves), the insertion tube is wiped clean with gauze or towel moistened with enzymatic detergent.[2,7,8] Removable waterproof video attachments and accessories should be placed into the enzymatic cleaning solution. To clean the suction/instrument channel, detergent solution should be suctioned for 15 to 30 seconds, which should be followed by suctioning of air for 10 seconds. Suctioning enzymatic cleaner and air through the suction/instrument channel results in agitation of debris and more effective cleaning than suctioning fluid alone.[3] This cleaning step should be repeated using clean water and air. For each endoscope there may be different cleaning attachments and manufacturer's recommendations that should be closely followed. The suction tube, water bottle, video connections, and all valves and removable caps (over instrument channel) should be removed and placed into detergent solution. The endoscope should be disconnected from the light source and a protective video cap attached if using a video endoscope. After this initial cleaning procedure, the scope is ready for reprocessing.[7,8]

Leak Testing

Leak testing detects internal or external damage that may render the scope permeable to fluid and water damage. The manufacturers provide leak testers specific for each endoscope. Before submersion of the endoscope in any solution, the leak tester must be attached and pressurized according to manufacturer instructions. While the device is pressurized, the distal segment of the endoscope is immersed in water, the distal portion of the scope is flexed in all directions, and the immersed tip of the endoscope is closely observed for the presence of a persistent stream of bubbles for at least 30 seconds. A continuous series of bubbles indicate a leak. If no leaks are detected in the distal segment, the entire endoscope is submerged and closely observed for persistence of small bubbles coming from the head of the scope, insertion tube, distal bending section, and the universal cord. Bubbles indicate a leak and the scope must be removed from use and repaired prior to reuse. If the endoscope passes the leak test, it is ready for manual cleaning and further reprocessing.

Manual Cleaning

Manual cleaning of the entire endoscope, including valves, channels, connectors, detachable parts, and accessories is the most important step in reprocessing as it is the final stage for debris removal, sterilization, and infection control. Thorough manual cleaning can remove 99.99% of the bioburden from the endoscope.[2] Because improper cleaning can overwhelm high-level disinfection (HLD) regardless of subsequent steps, meticulous cleaning is essential.[2,10] Failure of adequate manual cleaning is reported to be the most common reason for infection transmission in human endoscopy.[2]

Endoscope cleaning requires the use of a detergent that breaks down organic and inorganic materials, prevents waterborne deposits, and is compatible with the materials being cleaned. The best detergent characteristics are minimal foaming, easy rinsing, and a neutral pH.[7,8] Enzymatic solutions are the most frequently used detergents. Cleaning failure at the enzymatic cleaning stage is commonly a result of improper detergent dilution or inadequate contact time. If the concentration of detergent is too low, adequate cleaning is less likely. When detergent concentration is higher than recommended, the endoscope can be left with residual detergent, which can reduce the efficacy of high-level disinfectants.[7,8,11]

Endoscope Reprocessing

After passing the leak test, the endoscope is carefully coiled and immersed in a basin filled with a freshly made low-foaming enzymatic detergent. While fully submerged, debris is brushed and wiped from the surface of the endoscope. All valves, channel covers, and any other removal parts are detached. A soft brush is used to carefully clean all removed parts and allow them to soak in the detergent. Using recommended cleaning brushes and adapters for each port, all accessible channels in the body, insertion tube, suction port, air/water port, biopsy channel, and any special ports/channels are cleaned. Brushes should be disposable, sterilized, or "high-level" disinfected between cases. Frayed, worn, or bent brushes should not be used as they will have decreased efficacy and may cause damage to the channels. After each passage through a channel, all debris should be removed from the brush before repassing it through the channel. Channels should be brushed until all visible debris is removed. Appropriate cleaning adaptors should come with any endoscope. However, refurbished equipment is often sold without all cleaning adapters and adapters may need to be purchased from the manufacturer of the endoscope. Substitute cleaning equipment is not recommended unless approved by the manufacturer.[7,8]

Cleaning the suction channel requires two steps. To brush from the valve housing to the distal tip, the brush is inserted into the suction valve opening at a 45° angle. To clean from the valve housing to the suction connector, the brush is inserted straight into the center from where is will pass through the universal cord and out at the suction connector. The channel openings are also brushed after passing the brushes through the lumens. Flushing while keeping the scope immersed reduces the possibility of trapping air in the channels. Removal of air is crucial as the detergent cannot contact surfaces where there are pockets of air.

The endoscope is soaked and accessories are cleaned for the period specified by the detergent manufacturer. Enzyme solutions require a specific temperature and contact time to effectively dissolve all organic material. The endoscope should not be left soaking for longer than recommended by the manufacturer.[7-9] After soaking, the equipment is removed from the detergent solution and placed in a clean water bath. The surfaces are wiped with a clean cloth or sponge. Using cleaning adapters, all channels must be flushed with clean water to remove any detergent residues as residual detergent in the endoscope may interfere with the effectiveness of high-level disinfection (HLD) or sterilization.

After rinsing, the endoscope is removed from the water bath and purged by flushing air through all channels. This may require use of the cleaning adapters, syringes of air, or a forced air supply. For forced air supply, the pressure should not exceed 21 psi for most endoscopes; however, some endoscopes may tolerate higher pressures.[7,8] The outside of the endoscope is dried using a soft,

lint-free cloth. Finally, the endoscope and accessories are carefully inspected for any residual debris and if found, the manual cleaning procedure must be repeated. Once clean, the scope should undergo HLD.

High-Level Disinfection

HLD is the accepted standard for reprocessing gastrointestinal endoscopes.[6-9,11,12] HLD specifically refers to the destruction of all microorganisms (i.e., bacteria, viruses, fungi, mycobacteria), with the exception of high numbers of bacterial spores.[12] HLD is required in human medicine because of the contact of the endoscope and accessories with mucous membranes. Sterilization is required only when the endoscope is used for a sterile procedure (e.g., intraoperative procedure, airway, etc.).[11] HLD can be performed manually, or by using an automatic reprocessor. Automatic reprocessors standardize the disinfection procedure and decrease exposure of personnel to high-level disinfectants. However, no automatic reprocessor is currently available that provides adequate cleaning of endoscopes; consequently, all of the steps for manual cleaning of endoscopes must take place prior to using an automatic reprocessor.[7] Because of their expense, size, and limited return on investment, using an automatic reprocessor is impractical in most veterinary settings and thus is not covered further in this text.

Few high-level disinfectants are approved for use by all endoscope manufacturers. Therefore the manufacturer's specifications should be reviewed before choosing a high-level disinfectant. The high-level disinfectant must be prepared for use according to the high-level disinfectant manufacturer's directions. Two disinfectants compatible with most endoscopes are glutaraldehyde and orthophthalaldehyde (OPA). Glutaraldehyde has been used since the 1960s as a sterilant and a high-level disinfectant (commonly known as Cidex, Johnson & Johnson Medical Products; or, Metricide, Metrex Research, Inc.). A 20-minute exposure time is required for HLD when using a 2.4% solution at room temperature. Concentrations range from 2.4% to 3.4% and the maximum use life can vary from 14 to 28 days.[12] Efficacy must be tested before each use with product-specific test strips. Glutaraldehyde is an irritant and users can develop sensitivity, which may manifest as itchy skin, skin redness and swelling, irritation to eyes and mucous membranes, headaches, and/or respiratory symptoms. Glutaraldehyde can be absorbed by inhalation, ingestion, and through the skin. When using glutaraldehyde, a local exhaust system or a ductless fume ventilation system with filters to absorb vapors is required for user safety. Whenever the glutaraldehyde solution is not in use, it should be covered with a tight seal.[12]

OPA 0.55% is a high-level disinfectant introduced in 1999 as Cidex OPA solution (Advanced Sterilization Products). OPA solution achieves HLD in 12 minutes at room temperature, and 5 minutes when used in an automatic endoscope reprocessor at a temperature of 25°C (77°F). OPA is a reusable product and has a maximum shelf life of 14 days.[12] As with glutaraldehyde, the solution must be tested to determine strength prior to each use.

OPA is a clear blue solution with little odor, that is ready to use and requires no mixing. It has a very low vapor pressure and does not require special ventilation or air monitors when handling. It can stain fabric, skin, and many surfaces that it contacts. It is a potential respiratory and skin sensitizer and may result in exacerbation of bronchitis or asthma or dermatitis if there is prolonged, repeated contact. It can also be an irritant to the eyes, skin, nose, and other tissues. OPA solution is contraindicated for cystoscopy procedures on patients with a diagnosis of bladder cancer.[12,13]

HLD is best achieved after the endoscope is thoroughly cleaned, rinsed, and fluid is evacuated from all channels. The disinfectant product must be prepared according to the manufacturer's label instructions. Using a product specific test strip, the minimum effective concentration (MEC) of the biocide must be tested on each day of its use and more frequently if many endoscopes are reprocessed in one day. A log of the results should be kept.[7-9]

The endoscope, all removable parts, and the cleaning adapters are completely immersed in a basin of the HLD. As during manual cleaning, the disinfectant must be injected into all channels of the endoscope until it can be seen exiting the opposite end of each channel and the operator is confident that there are no air bubbles within the channels. All tub contents should be kept completely submerged, including all removed attachments. The soaking basin should be covered with a tight-fitting lid to decrease chemical vapor exposure.[7-9,11,12]

The manufacturer's recommendations should be followed for the time and temperature required to achieve HLD. A timer should be used to ensure proper soaking times. Once soaking times have been met, cleaning accessories are reattached and all channels are completely purged with air before removing the endoscope from the high-level disinfectant.[7-9,11,12]

Residual disinfectant is toxic; therefore, adequate rinsing is essential to protect the next patient (and operator) against injury from exposure to residual chemicals. After the appropriate amount of time, the endoscope and accessories are moved to a clean basin or sink filled with clean water. Sterile water is ideal, but filtered water or tap water are acceptable alternatives.[7-9,11,12] Then all external surfaces and removable parts are wiped and rinsed and all channels are flushed copiously with clean water.

Drying

Bacteria such as *Pseudomonas* or *Mycobacterium* spp. can be found in tap or filtered water and may multiply in moist environments. Therefore it is important to achieve and maintain a dry endoscope.[2] After rinsing, the endoscope and all accessories are moved to a dry surface or bin. The water is purged from the inside of the scope by injecting air into all channels. If forced air is used, endoscope damage can be avoided by maintaining forced air pressures less than 21 psi.[7-9,11,12] Suction is connected and air is aspirated for at least 15 seconds. To assist drying, all channels should be flushed with 70% isopropyl alcohol and then purged again with air. All channel adapters are removed and the exterior of the endoscope and channel adapters are dried with a lint-free soft towel. All removable parts are dried, but are not reattached during storage. Storing the endoscope without the valves and other removal parts aids in drying and decreases the risk of trapping moisture in the channels.[7-9,11,12]

Storage

The endoscope should be suspended vertically with the distal tip hanging freely in a well-ventilated, dust-free area. The endoscope should be stored in a way that protects it from physical damage. Padding on the bottom of the storage area will help prevent damage to the distal tip. Providing good ventilation in the storage area will help keep the endoscope channels dry, thereby reducing the chance of bacterial contamination.[7-9,11,12]

Sterilization

GI endoscopy rarely requires the use of a sterilized endoscope. Should sterilization be required; manufacturer's instructions should be followed for ethylene oxide gas or chemical sterilization.

Endoscopic Accessory Cleaning and Care

Endoscope accessories should undergo the same steps of manual cleaning and disinfection as the endoscope itself and in many instances, sterilization will be required. Careful and thorough manual cleaning with an enzymatic agent is required for all accessories utilized during an endoscopic procedure and should be done as soon as possible after any procedure. All equipment should be disassembled as much as possible and immersed in enzymatic solution following use. Endoscopic accessories that penetrate the mucosal barrier such as biopsy forceps, guidewires, cytology brushes, snares, dilators, cytology brushes, papillotomies, or any cutting instruments should be manually and ultrasonically cleaned and then sterilized using a chemical sterilant, ethylene oxide gas, or autoclave.[7-9,14,15] Ultrasonic cleaning is necessary to effectively remove debris from all spiral coiled, hinged, or complex structured accessories that hand cleaning cannot clean effectively. Any cannula or tubing accessories require thorough flushing with enzymatic detergent. Other accessory items, depending on design, require a combination of flushing and brushing to clean surfaces.[7-9,14,15]

Biopsy forceps have very tight metal coils with a spring-like structure that are surprisingly difficult to clean. One study indicated that manual and ultrasound-only cleaning methods for biopsy forceps were ineffective in removing material from within the biopsy forceps, suggesting that current recommended cleaning methods of reprocessing biopsy forceps are not adequate.[16] Chemical sterilization does not completely penetrate the coils and therefore is ineffective. Steam under pressure (autoclaving) is the only method that will effectively sterilize the coiled instruments, as it can penetrate the metal coils of the spring-like structure and any residual organic material within the coils.[16] When possible, all accessories should undergo heat sterilization via steam under pressure (autoclaving). Whenever an alternative exists, all nonsterilizable, reusable accessories should be phased out.[7,8,14-16] Lubrication of any device should be done after cleaning and before sterilization.[14,16]

For heat-sensitive equipment, the first alternative should be another form of sterilization such as gas plasma sterilization. Chemical disinfection should be the last option to be considered. Single-use biopsy forceps (i.e., forceps that are disposed of after first use) are the safest to use if sterile equipment is required.[14-16] Even though reusable instruments are a more cost-effective, practical solution in veterinary medicine, the user should be aware of the challenges of sterilization. Although commonplace in many practices today, items labeled for single-use should not be reprocessed and/or reused.[7,8,14-16]

Conclusion

In human health care, more health care–associated infections have been associated with contaminated endoscopes than with any other medical device.[3] Comparable data are unavailable for veterinary medicine. Efforts to make endoscopy safer and to eliminate the risk of cross-contamination have resulted in endoscope design changes and a move to create practical disposable or single-use devices. Quality assurance methods to verify adequate cleaning and HLD have also been developed.

The use of nonimmersible endoscopes is no longer acceptable because endoscopes that cannot be completely immersed in liquid cannot be adequately cleaned and undergo HLD.[8] Endoscope design and technology is changing rapidly. For example, autoclavable video bronchoscopes are now available and are designed for effective sterilization.[17] There is industry movement toward the development of flexible gastrointestinal endoscopes that can be easily disassembled for reprocessing. New products such as the Slide-On EndoSheath, a sterile barrier sheath system, slides over the endoscope to eliminate the need for HLD of nasendoscopes.[18] Another example is the Stryker ProtectiScope CS, a colonoscope that has all of the features of leading colonoscopes, but also has a unique disposable sleeve that covers the ProtectiScope CS as it advances into the colon. In addition to the disposable sleeve, all internal and external channels are disposable ensuring that contaminants do not enter the colonoscope.[19]

Policies and procedures for cleaning and reprocessing endoscopes, accessories, and associated equipment are needed in veterinary medicine. These guidelines should be readily available to all users and should be reviewed and revised as necessary to continue to provide the safest procedures for the patients and clinicians. Further advancements in methodology are likely to develop in the next decade. It is important to regularly review, update, and implement cleaning and disinfection protocols. By placing greater importance on disinfection and proper care of the endoscope and its accessories, quality of patient care will undoubtedly improve.

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CHAPTER 28

Laparoscopy

INSTRUMENTATION

Keith Richter

The use of laparoscopy for diagnostic and therapeutic purposes has increased dramatically during the last 20 years. Increased use and acceptance of laparoscopy stems from technical advances in equipment and instrumentation, improved access and training, client expectation, and excellent results with these minimally invasive procedures. Advanced therapeutic procedures will be performed more commonly as veterinarians adopt these techniques. Compared with open abdominal surgery, laparoscopy has several distinct advantages, including less postoperative pain, lower infection rates, improved visualization in many cases, lower cost, and shorter hospitalization times. Laparoscopy also has some advantages over other minimally invasive procedures, such as ultrasound and ultrasound-guided biopsy, including sample quality and direct visualization.

Equipment

Light is transmitted from a remote light source via a fiberoptic light cable to the rigid fiberoptic laparoscope (telescope). Light transmitted through the light cable passes through incoherent bundles (randomly aligned), whereas light passing through the telescope passes through coherent bundles (spatially oriented). This creates a proper image when the lens system focuses the light at the eyepiece. The fibers in the telescope are delicate, and care must be taken to avoid bending or crimping the shaft. Modern telescopes are constructed so they can be sterilized with a conventional steam autoclave. For purposes of illumination, a light source of 150 to 300 watts is required to adequately illuminate the abdomen, particularly in large- and giant-breed dogs.

Size and viewing angles of laparoscopes vary, some of which are depicted in Figure 28-1. Small-diameter scopes (2.7 to 5.0 mm) have a smaller image with a narrower field of view. Light sources with greater intensity and video cameras with greater light sensitivity are needed with smaller scopes. Scopes up to 10-mm diameter can be used, and although these generate a bigger and brighter image than 5-mm–diameter scopes, this advantage applies only to very large dogs. Scopes are also available in various degrees of angulation of view, from 0° (direct forward viewing) to 70° angle viewing. The 0° angle view has the field of view centered on the long axis of the scope, and thus is easier to use and generally preferred for most procedures. A 30° angle scope can be used to view structures to the side of the tip, and through rotation can be used to expand the field of view. Angled scopes are more difficult for inexperienced operators with regard to spatial orientation, and they pose greater difficulty when using instruments through a second or accessory puncture site. The technique of triangulation to find the tip of the instrument is particularly more difficult with an angled field of view. Taking all these factors into account, a forward-viewing (0°), 5-mm outer diameter, 35-cm long scope is preferred for most dogs and cats. As most laparoscopic instruments are 5 mm in diameter, this provides more versatility by allowing the scope and instruments to be interchangeable with the same cannula. The operator must ensure the scope fits properly through the selected cannula, that the light cable has the appropriate connection to the telescope, and that the video camera fits properly onto the eyepiece.

Most scopes have no biopsy channel. Operating scopes have a 5- to 6-mm channel, with an eyepiece extending from the proximal end (see Fig. 28-1C). These scopes allow introduction of instruments through the same puncture site as the scope. This has the advantages of reducing the number of puncture sites and facilitating identification of the instrument tip for inexperienced operators. The major disadvantage of operating scopes is the limited ability to manipulate instruments passing through the channel. An accessory or secondary puncture technique is usually preferred by more experienced laparoscopists (see "Accessory Puncture Sites" section).

Video capabilities can be achieved with a charge-coupled device (CCD) video camera mounted onto the eyepiece of the telescope. These video cameras have a high resolution, an image magnification by 5 to 15×, and a high image quality. Cameras are constructed with a lens, prism assembly, and one or three chips that convert light to an electronic signal. Cameras with three chips (each representing the primary colors of red, green, or blue) generally produce better images than cameras with just one chip. More recently, high-definition (HD) cameras have become available and produce a superior image quality. Video technology is now essential for interventional or operative laparoscopy.

To visualize abdominal structures, a pneumoperitoneum must be created to lift the abdominal wall away from the viscera. This is accomplished by insufflating gas through tubing attached to a Veress needle (Fig. 28-2). The Veress needle has a spring-loaded blunt inner portion and an outer cannula with a sharp point. The sharp point is used to penetrate the abdominal wall. The inner blunt portion is then protruded past the sharp point and is maintained in that position to avoid traumatizing abdominal organs. Gas can be continually insufflated as needed throughout the procedure. Carbon dioxide gas (CO_2) is recommended because it has the advantage of being rapidly absorbed, thereby minimizing the risk of air embolism. Air embolism is a complication that is more likely to take place if using room air. The disadvantage of CO_2 is that it is slightly more irritating to the peritoneal surface and therefore requires a slightly

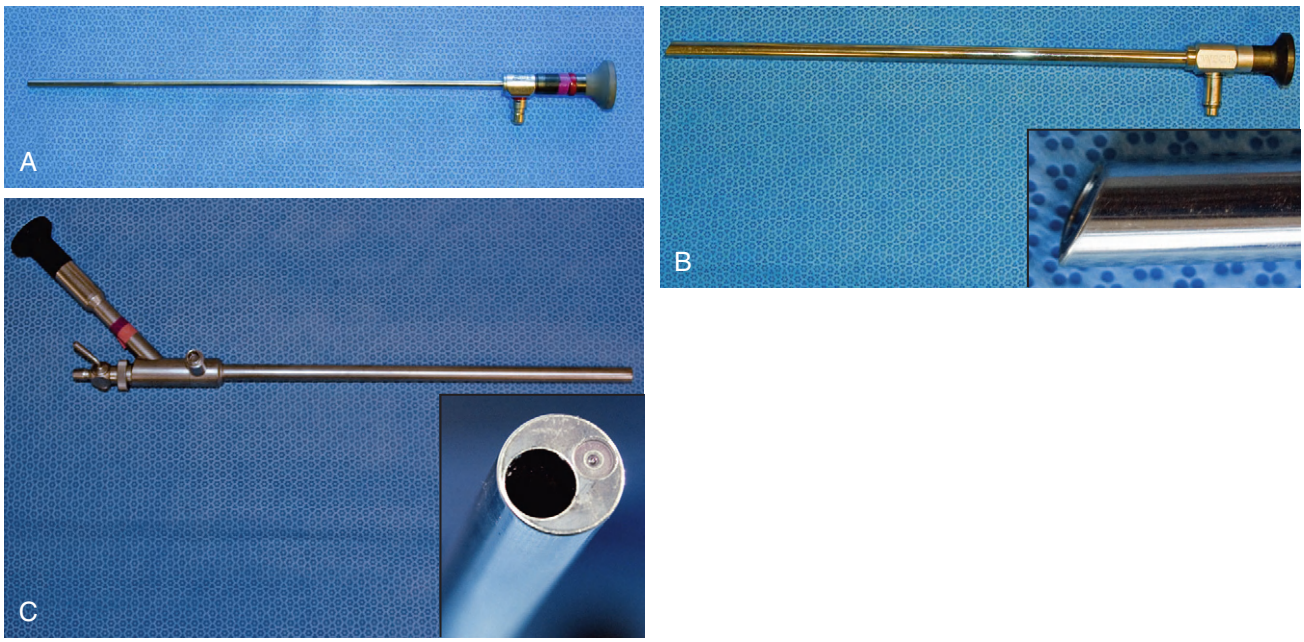

Figure 28-1 Various rigid telescopes. **A**, A 5-mm scope with a 0° angle tip. **B**, A 10-mm scope with a 30° angle tip (insert: close-up of tip). **C**, An 11-mm operating scope (insert: close-up of tip with 5.5-mm channel).

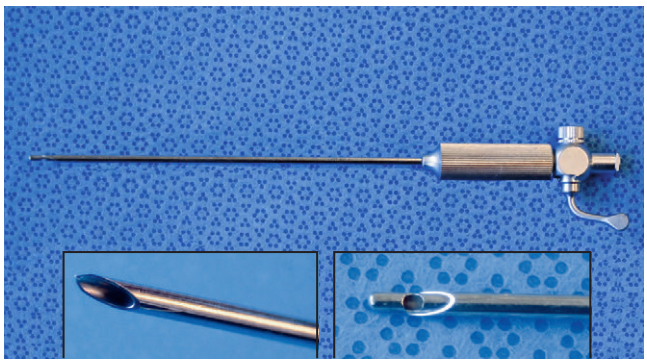

Figure 28-2 **A**, Veress needle. **B**, Close-up of tip with sharp point in position to penetrate the abdominal wall. **C**, Close-up of tip with blunt inner obturator protruded in position to avoid trauma to abdominal organs.

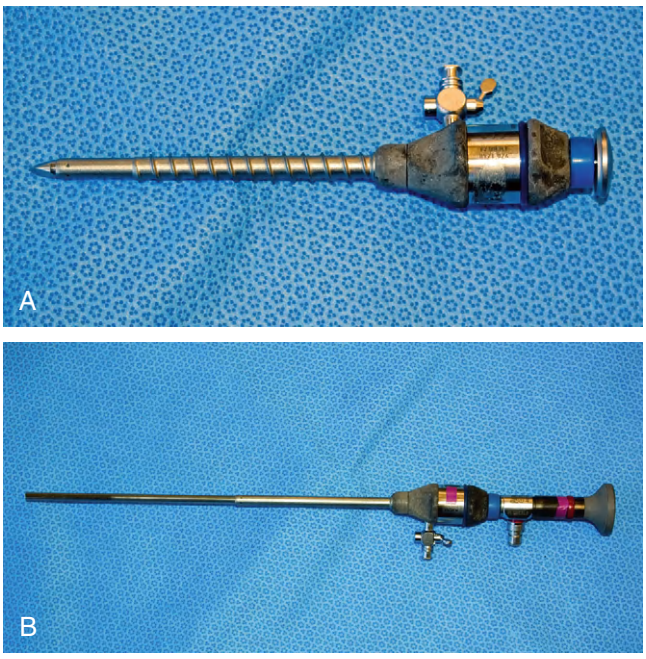

Figure 28-3 **A**, Trocar/cannula assembly with threaded shaft. **B**, Telescope inserted through cannula with smooth shaft.

greater depth of anesthesia. The pneumoperitoneum is maintained throughout the procedure with an automatic insufflator, which continuously administers gas to maintain pressure. Insufflators regulate both flow rate and intraabdominal pressure. Initial gas insufflation should be at a low flow rate (e.g., 1 L/min) to permit accommodation to the increasing intraabdominal pressure. If the pressure suddenly rises during insufflation, it is often a result of omental or mesenteric obstruction, or the incorrect placement of the needle. The position of the needle should be adjusted by gently moving it in and out of the abdomen; occasionally it must be replaced completely. Once optimal insufflation has been achieved, a higher flow rate can be used to maintain desired pressures. Ideally, intraabdominal pressure should not exceed 10 mm Hg (cats and small dogs) to 15 mm Hg (large dogs). Excessive pressure decreases central venous return and reduces diaphragm movement, causing decreased ability to ventilate. These effects are unlikely to occur at recommended abdominal pressures, but should be considered in patients with preexisting cardiopulmonary disease.

After the creation of the pneumoperitoneum, the laparoscope is introduced into the abdomen with the use of a trocar/cannula assembly (Fig. 28-3). The cannula is a metal or hard plastic sleeve with a one-way valve that permits passage of instruments (such as the trocar, laparoscope, and accessory instruments) and prevents the escape of gas. The trocar is a sharp-pointed stylet that is used to penetrate the abdominal wall. Once the trocar/cannula assembly penetrates the body wall, the trocar is then removed, leaving the cannula in place for introduction of the laparoscope.

Trocar/cannula assemblies come in a variety of sizes and styles. Trocars with a pyramidal tip have a cutting edge that penetrates the abdominal wall more readily than trocars with noncutting conical tips, although they are also potentially more traumatic. Some trocars have a retractable blade within the tip. A well-established pneumoperitoneum must be present for this style to be used to avoid the risk of intraabdominal organ trauma. Cannulae are used to allow passage of instruments in and out of the abdominal cavity while maintaining the pneumoperitoneum. They are constructed with a one-way valve to permit introduction of instruments without the escape of abdominal gas. Additionally, there is a rubber seal at the proximal tip to prevent escape of gas when an instrument is in place. Some cannulae have a side port to allow attachment of insufflation lines to introduce gas during the procedure. The shaft of the cannula can be smooth or threaded. A threaded cannula is more stable and unlikely to move within the abdominal wall during the procedure. Sometimes it is desirable for the cannula to move in and out of the abdominal cavity, such as when the cannula is inserted deep into the abdominal cavity for tissue biopsy. In these instances, a smooth nonthreaded shaft is preferred. For imaging purposes, an appropriately sized cannula must be used to ensure adaptation to the telescope and other instrumentation.

Accessory Puncture Sites

Accessory puncture sites are made for introduction of additional trocar/cannula assemblies. Accessory puncture sites permit the introduction of a variety of palpation, biopsy, and surgical instruments. These instruments are elongated, narrower versions of standard surgical instruments. A "basic" laparoscopic accessory pack should consist of a blunt metal probe, "spoon" or "clamshell" style (oval cup) biopsy forceps, grasping forceps, scissors, suction device, cautery instrument, and Babcock forceps (Fig. 28-4). An "advanced" laparoscopic accessory pack should also include retractors, reticulating instruments (which allow the tips to bend or be deflected), clip applicators, suturing devices, advanced hemostasis devices such as the Harmonic scalpel (Ethicon) and the LigaSure device (Covidien), and stapling equipment. The use of stapling equipment permits additional procedures such as vessel ligation and bowel resection.

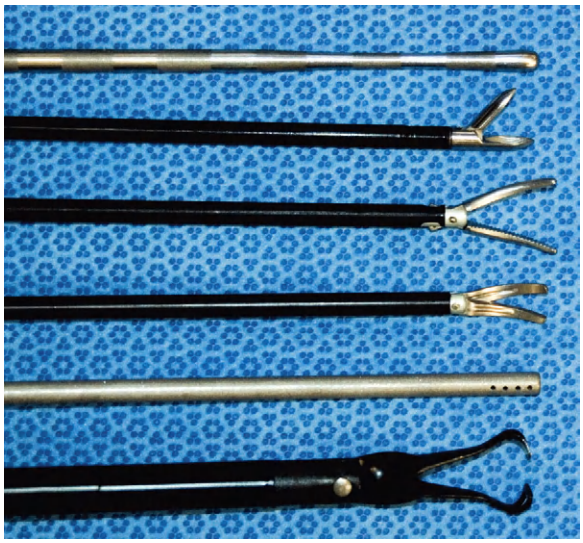

Figure 28-4 Laparoscopic instruments. From *top* to *bottom*: blunt metal probe, "spoon" or "clamshell" style (oval cup) biopsy forceps, grasping forceps, scissors, suction device, cautery instrument, and Babcock forceps.

Indications and Contraindications for Laparoscopy

Common indications for laparoscopy are for the evaluation of hepatobiliary disease. Laparoscopy allows procurement of large specimens (similar in size to surgical biopsies) using a 5-mm "spoon" or "clamshell" forceps (see Fig. 28-4). Samples obtained with these instruments have a superior diagnostic yield compared with needle biopsies, which have a reported 50% concordance with histologic findings from surgical biopsies.[1] Furthermore, the ability to visualize the liver gives the clinician a better feel for the pathologic process present and its distribution. Laparoscopy can also be used to examine and biopsy the right limb of the pancreas, an organ that can be difficult to image with abdominal radiographs and ultrasound. Other organs that can be biopsied via laparoscopy include the kidney, spleen, prostate, intestine, mesentery, omentum, and parietal peritoneum. Laparoscopy can be used to diagnose and stage abdominal tumors through direct visual assessment and biopsy. Laparoscopy can detect lesions less than 1 mm in diameter on the surface of organs. It can guide the aspiration of gallbladder, loculated ascites, and abdominal cysts or abscesses. Laparoscopy can guide transabdominal intrauterine artificial insemination. Laparoscopy can also be used for the evaluation of abdominal trauma. Injuries such as hepatic or splenic laceration, diaphragmatic hernia, bladder rupture, renal rupture, and abdominal hernia can be readily identified. There are also a variety of surgical or interventional procedures that can be accomplished laparoscopically.

Contraindications for laparoscopy include general anesthesia in an unstable patient, coagulopathy, diaphragmatic hernia, abdominal adhesions, and insufficient clinical experience. It must be emphasized that these are all relative contraindications, and the risks of a laparoscopic procedure must be weighed against the benefits of the procedure to the patient.

General Laparoscopic Technique

Several skills are required to perform a successful laparoscopic procedure.[2] The operator must have a good grasp of abdominal anatomy, surgical principles, anesthetic induction and maintenance, and operative use of laparoscopic equipment. Compared with surgery, laparoscopy poses three additional challenges—two-dimensional imaging, lack of tactile sensation, and problems with depth perception—all of which pose significant challenges for the inexperienced laparoscopist. The operator must be familiar with the general feel of the instruments, and how slight movements of the camera head can result in wide excursions of the image. Tactile sensation can be developed with practice through the use of a blunt probe. Fluctuant structures can usually be distinguished from solid structures using the blunt probe. There is also a fulcrum sensation that occurs with instrument movement. Because the instruments and scope are entering the abdominal cavity through a cannula, movement of the tip is in a direction opposite to that of the handle. Thus, when the hand and handle are moved upward, the tip of the instrument moves downward. When the hand and handle are moved to the left, the tip of the instrument moves to the right. Another necessary skill necessary is triangulation, because the angle of the scope and the angle of the instrument form a triangle. Triangulation permits the operator to find an instrument placed through a secondary or accessory cannula in the field of the scope. The angle of entry of each component of the triangle must be recognized to

avoid frustration when attempting to find the instrument tip. One technique that is helpful is to move the scope further away from the anticipated point of the instrument tip. This will increase the field of view. Once the tip of the instrument is located, the scope can be moved closer to the instrument to improve visualization. At this point the instrument and scope are moved in parallel so that the instrument tip never leaves the field of view. This technique will reduce unnecessary anesthesia time. The skill of triangulation becomes more challenging when using an angled scope (such as a 30° telescope). If the viewing angle is directed upward and an instrument is inserted from the side, it appears to come from below and to the side of the field of view.

Laparoscopy is best performed under general anesthesia. The position of the dog or cat and the location of the various puncture sites depend on the procedure, patient's size, and organ of interest. Because the port placement is so critical to a successful procedure, placement of the ports must be carefully planned and the site marked on the patient ahead of time to ensure a sterile field. In general, ports should not be placed too close together to avoid crowding of instruments with each other or with the scope. Furthermore, triangulation to locate instruments and subsequent manipulation of instruments is more difficult when they are placed too close to the scope. If it is determined that port placement is not acceptable, it is often better to place an additional port to allow completion of the procedure than to struggle through the procedure with suboptimal port location. Prior to starting the procedure, the urinary bladder should be emptied.

A right lateral or right lateral oblique approach is generally preferred for the liver, gallbladder, biliary tract, pancreas, right kidney, and right adrenal gland. The main advantage of this approach is that it avoids the falciform ligament, which is commonly encountered with a midline approach. The main disadvantage of a right-sided approach is the inability to see most left-sided abdominal structures. A midline approach is occasionally used for more complete evaluation of the liver (more of the liver can be seen by this approach than by a right-sided approach) and many interventional surgical procedures. Although the falciform ligament may impede the procedure, it can be avoided by placing the central port just lateral to midline and caudal to the umbilicus. In a lateral approach, the scope is placed several centimeters lateral to midline, depending on the size of the patient. A left-sided approach is seldom used, but is necessary to visualize the left kidney and left adrenal gland.

Complications of Laparoscopy

Potential complications of laparoscopy include those related to general anesthesia, inadvertent organ damage during instrument introduction, excessive bleeding during biopsy or other intervention, other surgical complications, overdistention of the abdomen, air embolism, subcutaneous instillation of gas, tension pneumothorax if the diaphragm is inadvertently punctured, and postoperative infection. Operator experience, good patient planning, and meticulous attention to procedural detail minimizes the probability of these complications. Postoperative pain should be anticipated and should be addressed with appropriate analgesics.

Laparoscopic Surgery

Many laparoscopic surgical procedures are currently being performed on dogs and cats. These include ovariectomy and hysterectomy, adrenalectomy, bile duct exploration, gastropexy, cystotomy with calculus removal, cryptorchid testicle removal, jejunostomy tube placement, splenoportography, cholecystectomy, and others. Limitations of laparoscopic surgery include the two-dimensional image, restricted freedom of movement of the instruments, restricted sense of touch, limited opportunity to move the position of instruments once cannulae have been placed, the need for extensive training, and limitations on instrumentation available for laparoscopy. As clinicians and equipment manufacturers address technical limitations, many surgical procedures should become more amenable to laparoscopic surgery.

Newer Laparoscopic Techniques

One recently developed innovative laparoscopic technique described in human beings is natural orifice transluminal endoscopic surgery (NOTES). This technique involves insertion of an endoscope into a natural orifice (such as the stomach, vagina, or colon), access to which is then used to perforate the wall to gain entrance to the peritoneal cavity. Many interventional procedures can be performed using this technique. The approach is thought to limit postoperative pain, decrease wound problems, and offer improved cosmesis. Transvaginal cholecystectomy is the main procedure being performed to develop the NOTES technique, although other surgical procedures can also be performed with this approach. There are many challenges to overcome to accomplish these procedures successfully. Luminal access can be achieved with new steerable trocar/cannulae. Flexible scopes have been developed with multiple steerable channels to allow introduction and manipulation of a variety of instruments to be used for the surgical procedure. Tissue or organ retraction is also very challenging. This has been overcome by use of special intraluminal retraction devices (Endograb, Ethicon), articulated graspers, and deployable devices (T-tag suture devices). Closure devices also have been developed, including endoscopically deployed clips. These include the Resolution Clip (Boston Scientific) and the QuickClip2 (Olympus).

Another method of overcoming these technical challenges is to combine a single puncture transabdominal laparoscopic port with transluminal access (called hybrid NOTES). This improves retraction and allows more versatile instrumentation.

The single-incision laparoscopic surgery (SILS) is another newly introduced technique. This technique permits the introduction of multiple instruments through one large port into the abdominal cavity. Several manufacturers have developed these devices. Furthermore, gently curved rigid instruments have been developed for this technique. The gentle curve permits better triangulation of instruments despite their insertion into a common port. In addition, reticulated instruments with steerable tips make this technique more versatile.

Intraoperative ultrasound (IOUS) during laparoscopic cholecystectomy is becoming increasingly commonplace in human laparoscopic surgery. High-resolution ultrasound probes are integrated into the tip of laparoscopically deployed instruments. The use of IOUS can help define biliary anatomy, including the entire common bile duct. Abnormalities, such as common bile duct calculi, sludge, or aberrant biliary anatomy, can be identified. The procedure only adds 5 to 7 minutes to a cholecystectomy, and can potentially change the management of the patient.

Only time will tell whether NOTES, SILS, or IOUS will be routinely applied in dogs and cats. Controlled clinical trials will be necessary to define the role of all laparoscopic procedures in veterinary medicine.

LIVER AND BILIARY TRACT

Eric Monnet and David C. Twedt

Laparoscopy is a simple procedure associated with few complications. Despite the advent of newer laboratory tests, imaging techniques, and ultrasound-directed fine-needle biopsy, laparoscopy remains a valuable tool when appropriately applied in the diagnostic plan in patients with suspected hepatobiliary disease. Laparoscopy can be used to safely evaluate the liver and the biliary system. Laparoscopy can replace laparotomy for the visual inspection of the liver and biliary system, and to obtain biopsies. Laparoscopy may reveal small (0.5 cm or less) metastatic lesions, peritoneal metastases, or other organ involvement that is not easily identified by other imaging techniques.

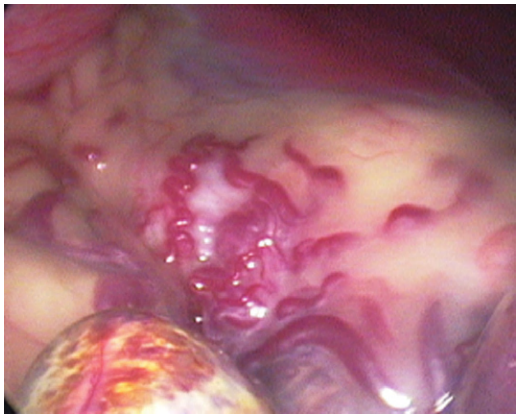

Figure 28-5 Acquired portosystemic shunts in a dog with end-stage liver disease.

Preparation, Restraint, and Surgical Considerations

With few exceptions, laparoscopy is performed under general anesthesia. However, because liver biopsy is a procedure of relatively short duration, it can be accomplished in some patients under light sedation and local anesthesia at the cannulation sites. If the pneumoperitoneum with CO_2 insufflation interferes too much with the excursion of the diaphragm and ventilation of the patient, general anesthesia with intubation and positive ventilation will be required.

The right lateral approach is recommended for diagnostic evaluation of the liver and extrahepatic biliary system. With this approach the right limb of the pancreas can also be identified, evaluated, and biopsied. During the right lateral approach, the patient is in left lateral recumbency and the portals are placed in the caudal part of the abdominal cavity from the right side. Two portals are sufficient to perform a liver biopsy. A ventral approach can also be used to visualize the liver, gallbladder, and biliary tract. In the ventral approach, the primary portal is placed on the midline caudal to the umbilicus. The secondary portal is introduced in either the right or left side of the abdominal cavity. With the ventral approach the left lobes of the liver can be more readily visualized although the falciform ligament may hinder visualization of the anterior abdomen, especially in obese animals during a ventral approach.

Ascites, prolonged bleeding time, and poor patient condition are the only relative contraindications to laparoscopy. If ascitic fluid accumulation is mild, it can be removed prior to or during the laparoscopic procedure. Closed suction drainage can be placed in the abdominal cavity at the end of the procedure to prevent continued leakage through the portal sites. Coagulation parameters (prothrombin time, partial thromboplastin time, buccal mucosal bleeding time) should be evaluated prior to laparoscopy and liver biopsy. Although coagulopathy is a relative contraindication to liver biopsy, coagulation status does not necessarily predict whether the patient will bleed from laparoscopy or liver biopsy. Laparoscopy does permit the operator to visually select biopsy areas that are less vascular and to monitor the extent of bleeding following a biopsy.[1]

Evaluation of the Liver and Liver Biopsy

Eighty-five percent of the liver surface can be visualized during routine laparoscopy As with exploratory laparotomy, the liver is evaluated for size, color, shape, and sharpness of edges. For the diaphragmatic surface of the liver, an angle endoscope can be used to image the more cranial aspects of the liver. A palpation probe is used to manipulate the different lobes and to visualize the visceral surface of the liver and extrahepatic bile ducts. Grasping forceps should not be used to manipulate liver lobes because the liver parenchyma is often too friable and at risk for traumatic injury and bleeding. With the right lateral approach, the portal vein can be evaluated for size and turbulent flow. Acquired shunts can be observed across the omentum and around the left kidney if portal hypertension is present (Fig. 28-5).

Portal pressure can be measured directly after exteriorization of a loop of jejunum and catheterization of a jejunal vein. Manometry is used to measure portal pressure, and a portovenogram can be performed to further evaluate the portal vasculature. After completion of the portovenogram and measurement of portal pressures, the catheter is removed and the loop of bowel is returned into the abdominal cavity.

Laparoscopic liver biopsy is considered by many to be the preferred method of obtaining liver tissue for routine histopathology.[1] A 5-mm cup biopsy forceps provides sufficient liver tissue for routine analysis and is superior in quality to 18-gauge (G) needle biopsy.[2] During laparoscopy, the biopsy forceps can be directed toward lesions of interest and to monitor for excessive bleeding. The liver biopsy can also be obtained with an ultrasonically activated scalpel.[3] Ultrasound scalpels provide good tissue sampling for histologic analysis with minimal bleeding from the biopsy site. The amount of collateral tissue damage induced with an ultrasonically activated scalpel is similar to the damage induced by the cup biopsy forceps. The cup biopsy forceps causes crush injury to collateral tissue, whereas the ultrasound-activated scalpel causes thermal injury at collateral sites. The authors recommend the use of a 5-mm oval cup biopsy forceps for most liver biopsies, and the ultrasonically activated scalpel for biopsy of vascular masses involving the liver.

Postbiopsy, the biopsy site must be closely monitored for excessive bleeding. The amount of bleeding associated with routine liver biopsy is usually minimal. If bleeding is considered to be excessive, several steps should be taken. First, the palpation probe can be placed into the biopsy site and pressure applied over the area with the tip of the probe. Alternatively, a small piece of saline soaked Gelfoam can be placed into the biopsy site using laparoscopic grasping or biopsy forceps. These options are sufficient to control excessive bleeding in most instances.

In general, the liver should be biopsied on the surface and at an edge (Fig. 28-6), although some have suggested that edge biopsies may not reflect pathology of deeper samples because the subcapsular tissues are more reactive and fibrotic. It is always important to biopsy

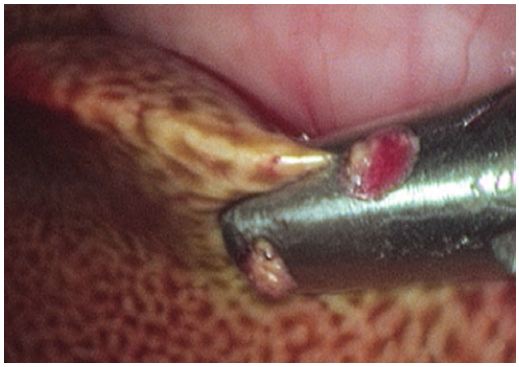

Figure 28-6 Biopsy of the liver with a 5-mm cup biopsy forceps.

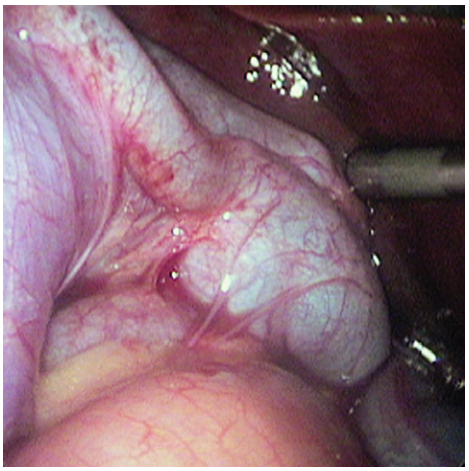

Figure 28-7 Severe dilation of the common bile duct in a patient with bile duct obstruction.

three to four areas of the liver, including areas that appear grossly normal as well as abnormal. The biopsy forceps cups should be tightly closed over the tissue biopsy for approximately 15 to 30 seconds before pulling the sample away from the liver.

Evaluation of the Biliary Tract

The extrahepatic biliary tract can be examined during laparoscopy when the quadrate liver lobe is retracted toward the diaphragm. The hepatic, cystic, and common bile ducts can be evaluated for their size, color, shape, and patency. Dilation of the bile ducts is readily appreciated at the time of laparoscopy (Fig. 28-7).

The size and health of the gallbladder can also be evaluated at the time of laparoscopy. A palpation probe is used to palpate the gallbladder to assess its stiffness or flaccidity. An 18-G spinal needle can be advanced percutaneously into the gallbladder to sample bile for culture and cytology, and to decompress the gallbladder and biliary system (Fig. 28-8). The needle has to be introduced in a location caudal to the insertion of the diaphragm. The line of insertion of the diaphragm on the last rib is outlined by a line of fat, which can be used as a reference point. If the needle is introduced through the diaphragm, there is a significant risk of inducing a pneumothorax with diffusion of CO_2 under pressure from the abdomen. The gallbladder should be emptied as much as possible to prevent leakage of bile from the puncture site into the abdominal cavity.

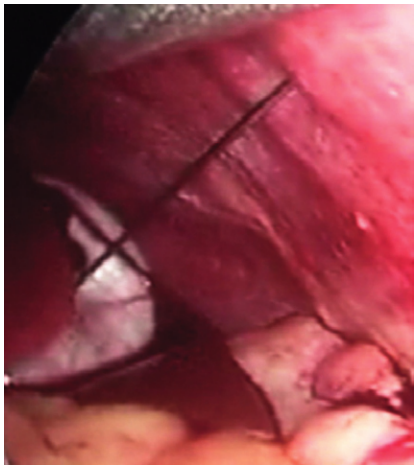

Figure 28-8 Aspiration of the gallbladder with an 18-gauge spinal needle.

At the conclusion of the procedure, the instruments and telescope are removed and the pneumoperitoneum is vented. The cannulas are then removed and the puncture sites are sutured in a routine manner to conclude the laparoscopic procedure. For postoperative pain management, the authors recommend bupivacaine locally at the trocar cannula sites and also systemic analgesia (see Chapter 38).

PANCREAS

Thomas Spillmann

The era of laparoscopy in human and veterinary medicine began in 1901 when Georg Kelling of Dresden, Germany, performed the first celioscopy in a dog.[1,2] There were many anatomic descriptions reported thereafter, but it was not until 1957 that the use of laparoscopy in the diagnosis of intraabdominal disease was first reported. In that year, Hans Eikmeier of Giessen, Germany, published his habilitation thesis on the laparoscopic diagnosis of canine liver disease.[3] The laparoscopic diagnosis of canine pancreatic diseases was first reported in the early 1970s, and the authors concluded that the technique might include the possibility of tissue sampling for histologic examination.[4-6] With the advent of noninvasive abdominal ultrasonography, laparoscopy was nearly forgotten as a diagnostic tool. With renewed emphasis on minimally invasive procedures in both human and veterinary medicine, laparoscopy has experienced a resurgence of interest and application.[7-10]

The advantages of diagnostic laparoscopy in comparison to other advanced imaging techniques, such as contrast-enhanced computed tomography or endoscopic ultrasonography, are less-expensive equipment, technical ease of the procedure, and feasibility of direct sampling of biopsies from regions of interest.[11-16]

Indications

Laparoscopic examination of the pancreas is indicated when the clinical signs, laboratory test results, and other imaging findings provide evidence for the existence of a pancreatic disorder that demands further macroscopic and histologic examination without an obvious need for diagnostic or therapeutic laparotomy.[10,16-18]

Tissue sampling at the time of laparoscopy enables the further differentiation of the many primary diseases of the pancreas and liver. In dogs, laparoscopy is used mainly to diagnose chronic pancreatic disease, such as chronic pancreatitis and subclinical pancreatic acinaratrophy.[10,16-18] In cats, the addition of liver biopsy and laparoscopy-assisted small intestinal full-thickness biopsy to the procedure enables diagnosis of concurrent cholangiohepatitis, pancreatitis, and inflammatory bowel disease (termed "triaditis" by some authors).[16,19,20]

Contraindications and Limitations

As with other laparoscopic procedures, the general contraindications for laparoscopic examination of the pancreas include poor patient condition with increased anesthetic risks, hemorrhagic diathesis, diaphragmatic hernia, abdominal effusion (especially septic peritonitis), abdominal adhesions, and renal, cardiac, or pulmonary insufficiency.[10,16-18]

The specific contraindications for laparoscopic examination of the pancreas include mass-forming pancreatic diseases (with or without extrahepatic biliary tract obstruction) such as pancreatic necrosis, pseudocyst, abscessation, and neoplasia. Mass-forming disease processes of the pancreas are better differentiated via laparotomy, which offers the possibility of immediate surgical intervention, such as debridement, omentalization, and resection of necrotic areas.[21] Surgery also permits the restoration of patency to an obstructed common bile duct through surgical placement of temporary or permanent stenting.[22]

For pancreatic pseudocysts, surgical intervention is indicated when pseudocysts are symptomatic, in a phase of growth, complicated (infected, hemorrhagic, or associated with biliary or bowel obstruction), concurrent with chronic pancreatitis, and when malignancy cannot be excluded. Depending on the mode of presentation, cystic morphology, and available technical expertise, the recommended treatment options include percutaneous catheter drainage, duodenoscopy, or surgery.[23,24] In dogs and cats, ultrasound-guided cystic puncture with cystic fluid evacuation has shown distinct clinical usefulness.[25,26] Among surgical treatment options, cystoduodenostomy, cystic omentalization, and biliary diversion have a more favorable outcome than cystogastrostomy.[27-29] The reader is referred to Chapter 60 for further information and detail.

Multiple abdominal adhesions represent a general contraindication for many laparoscopic procedures.[10,18] Unfortunately, there are no routine imaging techniques for the identification of pancreatic or peri-pancreatic adhesions prior to laparoscopy. If adhesions are encountered at the time of laparoscopy, a decision should be made to advance to laparotomy if the goals of laparoscopy cannot be achieved.

Technical Requirements

Standard laparoscopic equipment is needed, including light source, automatic CO_2-insufflation unit, endoscopy camera, monitor, and computer or video recorder for procedural documentation. Sterilized instrumentation needs to include a Veress insufflation needle and obturator, one optical trocar, one or two working trocars, a rigid laparoscope (0° or 30° viewing angle), and grasping and biopsy forceps.[10,17,30,31]

Use of a 10-mm–diameter optic containing an integrated working channel (Fig. 28-9) is well worth the investment. This particular instrumentation permits the pancreas to be maintained in place with a grasping forceps while taking a pancreatic biopsy through the working channel. If a more conventional optic is available, two working trocars will be needed to simultaneously negotiate the grasping (duodenal) and biopsy (pancreatic) forceps in the sampling of pancreatic tissue. Laparoscopy scissors are useful if small, nonvascular adhesions must be broken down.

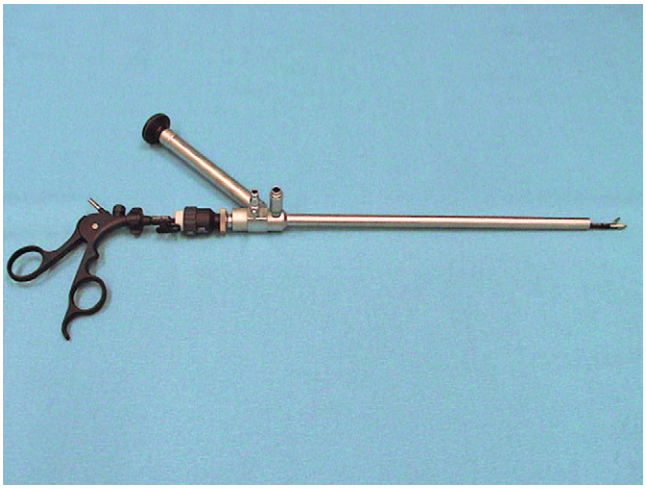

Figure 28-9 Hopkins straight-forward telescope with angled eyepiece and integrated instrument channel with inserted click line dissecting and biopsy forceps. (Courtesy of Karl Storz, Tuttlingen, Germany.)

Patient Preparation

As with other laparoscopic procedures, patient screening should include complete blood count, serum chemistry, and coagulation times (prothrombin, partial thromboplastin, buccal mucosal bleeding) to assess for the risk of anesthesia and abnormal bleeding tendencies.[10,17,30,31] Animals should be starved for a period of 12 to 18 hours prior to laparoscopy to ensure an evacuated upper gastrointestinal tract. Gaseous gastric distention can be managed with orogastric intubation in the anesthetized patient. To the extent possible, the distal colon/rectum and urinary bladder should be evacuated of feces and urine, respectively, before trocarization. Insufflation of CO_2 into the abdominal cavity increases intraabdominal pressure (IAP), which may lead to spontaneous emptying of the urinary bladder when the patient is anesthetized. Therefore, it is recommended that a urinary catheter and collection system be placed in dogs prior to the procedure. This decreases the risk of accidental urine contamination of the operation field. Prior to laparoscopy, the operation field is prepared as for an aseptic laparotomy to allow immediate surgical intervention in case of pathologic findings or complications that demand a surgical approach.[10,17,30,31]

Anesthesia

General anesthesia is necessary to perform laparoscopy. Canine patients can be premedicated with butorphanol and medetomidine, followed by anesthetic induction with propofol. Other induction protocols for dogs include a diazepam and L-methadone combination, or premedication with atropine, acepromazine, and morphine. Anesthesia is maintained with inhaled isoflurane (1% to 2%) in oxygen.[17,32] In cats, induction can be performed with ketamine and xylocaine before intubation for isoflurane inhalant anesthesia.

A study on the hemodynamic and respiratory effects of increased IAP and positive end-expiratory pressure in 10 healthy anesthetized

dogs undergoing laparoscopic pelvic lymphadenectomy revealed that an increase of IAP up to 15 mm Hg had no negative effect on the cardiovascular system. However, when increased IAP was combined with increased positive end-expiratory pressure (8 cm H_2O), arterial CO_2 and fractional end-tidal CO_2 measurements revealed significant CO_2 retention. Study results led to the recommendation for expanded cardiopulmonary monitoring during general anesthesia in high-risk patients.[33] Another study assessed the cardiopulmonary effects of laparoscopic surgery in five dogs anesthetized with thiopental and maintained with halothane at 1.5 times minimal alveolar concentration in oxygen. Abdominal insufflation of CO_2 to a pressure of 15 mm Hg for 180 minutes resulted in significant increases in heart rate, minute ventilation, and saphenous venous pressure, and decreases in pH and partial pressure of oxygen in arterial blood (PaO_2). However, the observed changes were well within physiologically acceptable limits.[34] Studies by the author in 23 dogs undergoing laparoscopy with an intraabdominal CO_2 pressure of 11 mm Hg revealed no side effects of an anesthetic regimen using diazepam and L-methadone for induction and spontaneous, partly assisted isoflurane inhalation for maintenance of anesthesia. The same IAP can be used in cats. When possible, anesthetic monitoring should include clinical examination of reflexes, spontaneous breathing, and pulse, as well as pulse oximetry, capnography, and blood pressure measurement.[17]

Patient Positioning and Procedure

For placement of the optic trocar, the dog or cat is placed in dorsal recumbency. When an optic trocar for a 10-mm optic is placed, a 1-cm–long incision is made into the skin over the linea alba with a scalpel about 1 cm caudal to the umbilicus. For smaller-diameter optics, the length of the skin incision is adjusted accordingly. In the center of the surgical wound, a Veress needle is pushed through the abdominal wall into the abdominal cavity to create a capnoperitoneum with an end IAP of 11 mm Hg. The Veress needle is removed and the optic trocar is put in place. After connecting the trocar with the automatic CO_2 insufflator, the optic is introduced for the first general examination of the abdominal cavity. Using an endoscopic camera and monitor allows for a more convenient laparoscopic examination and better documentation of the findings than direct viewing through the optic.

After the initial examination, a working trocar (5- or 10-mm diameter, depending upon patient size) is placed into the right cranial quadrant of the abdominal wall, several centimeters caudal to the last rib. The patient is then moved into slight left lateral recumbency (30° to 45°). In this position, the optic can still be moved easily but the small intestine can glide to the left side, giving view to the cranial duodenum and the pancreas on the right side. In some cases, it will be necessary to push the intestine to the left by introducing a grasping forceps through the working trocar or the working channel of the optic.

When the pancreas is visible, a grasping forceps is introduced through the working trocar to grab the cranial duodenum close to the pylorus. Lifting the cranial duodenum toward the abdominal wall allows visualization of nearly the entire ventral part of the pancreas, except the distal tip of the left pancreatic lobe, which can be covered by the stomach and intestine, especially in large-breed dogs. Using the grasping forceps, the duodenum can be moved caudally to examine the dorsal part of the pancreas. Instrument-induced trauma to the pancreas can be minimized by grasping the intestine only.

Pancreatic Biopsies

A pancreatic biopsy is not as dangerous as once thought, although biopsy of the pancreas should always have ample justification. Studies in healthy dogs and in dogs with pancreatic diseases, such as subclinical pancreatic acinar atrophy and chronic pancreatitis, show that multiple pancreatic biopsies taken via laparoscopy or laparotomy cause no serious complications. The danger of inducing acute pancreatitis is almost negligible.[10,17,32,35-39] However, careful selection of the biopsy site is strongly recommended. Biopsies can be taken without apparent intra- or postoperative complications by using an endoscopic cup forceps,[17] endoscopic Metzenbaum scissors distal to a tissue Endoclip, and sampling with a harmonic scalpel.[32]

Pancreatic biopsies should be taken from the margins of the organ or from macroscopically changed areas, avoiding deep tissue biopsies that might injure major vessels or pancreatic ducts (Fig. 28-10).[10,17] Multiple biopsies should be taken even from macroscopically inconspicuous areas, as pancreatic inflammation tends to occur in discrete areas within the pancreas rather than diffusely throughout the entire organ. Single biopsies are seen as insufficient to exclude pancreatitis.[40]

Histologic assessment can be carried out according to a recently suggested grading system for nonneoplastic lesions of the exocrine pancreas. The histologic grading scheme includes scoring the biopsy for neutrophilic inflammation, lymphocytic inflammation, pancreatic necrosis, peripancreatic fat necrosis, edema, fibrosis, atrophy, and hyperplastic nodules.[41]

Laparoscopic Findings

The normal pancreas has a pale cream color and is coarsely lobulated (Fig. 28-11). In some cases the pancreas can appear diffusely granulated, with no histologic evidence of an abnormality. Because a morphologically normal appearance does not exclude histologic abnormalities, multiple biopsies should be taken to confirm normality.

Pancreatic pathology can vary in appearance. Loss of tissue can be a sign of pancreatic acinar atrophy of varying degree (Figs. 28-12 and 28-13). Histology helps to differentiate the finding from that of advanced chronic pancreatitis (Fig. 28-14). Swelling of the organ

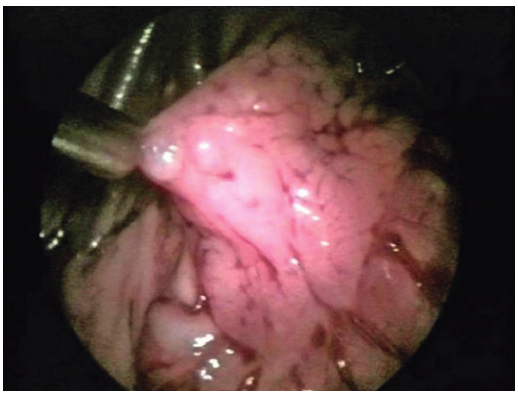

Figure 28-10 Laparoscopic biopsy with an endoscopic cup forceps from a localized nodule of the pancreas of a Maine Coon cat histologically confirmed as focal chronic-purulent inflammation with fibrosis. (Used with permission from Rust S, Litzlbauer H-D, Burkhardt E, Moritz A, Spillmann T. Chronic pancreatitis, IBD and cholangitis in a Maine Coon cat. *Kleintierpraxis* 50: 171–182, 2005.)

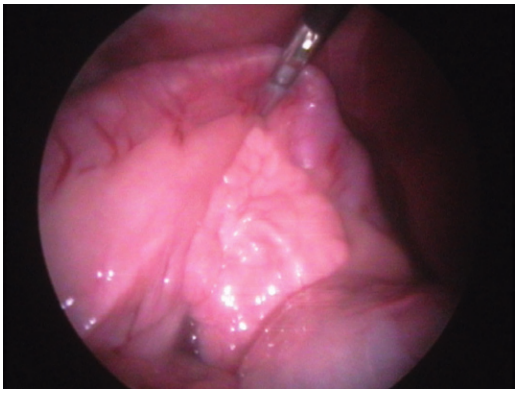

Figure 28-11 Laparoscopic picture from a Parson Russel Terrier with histologically confirmed normal pancreas.

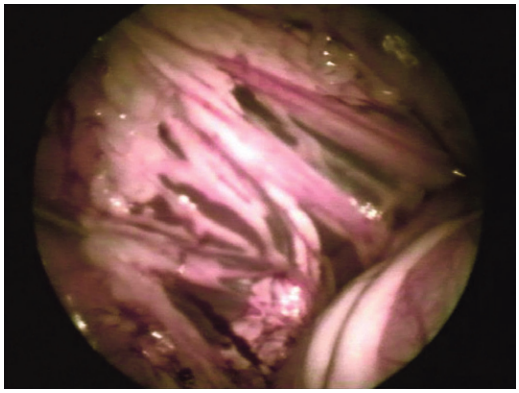

Figure 28-12 Laparoscopic image from a German Shepherd dog with histologically confirmed partial pancreatic acinar atrophy. The exocrine pancreatic tissue is markedly reduced. (Used with permission from Spillmann T. Introduction and validation of modern laboratory and imaging techniques for the diagnosis of acute and chronic exocrine pancreatic diseases in dogs. Habilitation thesis [German], Büchse der Pandora Verlag, Wetzlar, p. 138, 2002.)

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Figure 28-13 Laparoscopic image from a Hovawart dog with end-stage pancreatic acinar atrophy. The exocrine pancreas has completely disappeared. (Used with permission from Spillmann T, Moritz A, Burkhardt E. Diagnostic value of laparoscopy for pancreatic diseases in dogs. *Tierarztl Prax* 28[K]: 349–55, 2000.)

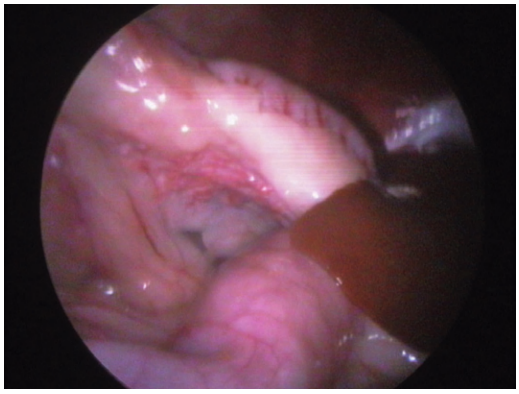

Figure 28-14 Laparoscopic image from a Cavalier King Charles Spaniel with severe loss of pancreatic tissue. The remaining pancreas is reddened and atrophied. Histology revealed chronic pancreatitis with marked interstitial fibrosis and severe atrophy.

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Figure 28-15 Laparoscopic picture of a mixed breed dog with histologically confirmed chronic pancreatitis. The image shows an adhesion of the right pancreatic (duodenal) lobe to the gastric wall. (Used with permission from Spillmann T, Moritz A, Burkhardt E. Diagnostic value of laparoscopy for pancreatic diseases in dogs. Tierärztl Prax 28[K]: 349–55, 2000.)

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Figure 28-16 Laparoscopy of a Cocker Spaniel one year after surviving severe necrotizing pancreatitis. The image shows marked adhesions of the pancreas to liver, duodenum, and omentum that hinder visualization of the pancreas. (Used with permission from Spillmann T, Moritz A, Burkhardt E. Diagnostic value of laparoscopy for pancreatic diseases in dogs. *Tierarztl Prax* 28[K]: 349–55, 2000.)

can be a sign of acute or chronic pancreatitis. Adhesions with the surrounding organs or the abdominal wall have been reported in cats and dogs with chronic pancreatitis or as part of the healing process following acute necrotizing pancreatitis (Figs. 28-15 and 28-16).

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CHAPTER 29

Histopathology

STOMACH

Brian Wilcock

Like other portions of the gastrointestinal (GI) tract with which it shares embryologic origin, the stomach consists of a tunica muscularis, submucosa, muscularis mucosa, and an innermost mucosa. Almost all of the histologic lesions of clinical significance arise within the mucosa, so endoscopic biopsies are preferred to full thickness biopsies for investigation of almost all gastric diseases. The only exceptions are those that seem restricted to the submucosa or tunica muscularis based on ultrasonographic evaluation (i.e., suspected smooth muscle tumors, pythiosis, and pyloric muscular hypertrophy). The advantages of endoscopic biopsies over full thickness samples have been described elsewhere, but from the perspective of the pathologist the advantages are the greater number of samples that can be taken and the ability to specifically sample abnormal mucosa. The small size and limited depth of the samples are not usually problematic.

Gastric mucosa is similar to that of other portions of the GI tract in that it has a luminal surface of columnar epithelium rich in goblet cells, branched or coiled glands embedded in a fibrovascular lamina propria, and a population of resident leukocytes within the lamina propria. Because the stomach is adapted primarily for secretion rather than absorption, and because its acid environment does not permit much of a resident bacterial population, the leukocyte population is less than is found in the more distal portions of the GI tract. That should make detection of changes in leukocyte numbers easier than elsewhere in the GI tract. That same inhospitable environment also means that there are few infectious causes of gastritis compared with the numerous viral, bacterial, and protozoal diseases of the small and large intestine.

The stomach is divided into several anatomic regions that differ in histologic character and function. Most proximal is the cardia, which surrounds the entry of the esophagus into the stomach, and most distal is the pyloric antrum leading to the sphincter that separates the stomach from the duodenum. In between, and occupying about two-thirds of the stomach, is the gastric body. The gastric fundus is an outpouching of the gastric body at its proximal end where it joins the cardia. This nomenclature is not absolutely standardized, and many authors refer to the combined fundus and body as the "fundic region" and habitually refer to biopsies from this region as being from "fundic mucosa."[1,2] Each of these regions has distinctive histologic appearance, but the transition from one portion to the other is not abrupt and in some biopsies the mucosa has an appearance intermediate between one region and the other.

Almost all gastric biopsies, whether endoscopic or full thickness, are taken from the fundic mucosa and from the pyloric antrum. In all regions, the mucosa is divided into three horizontal zones. In the fundic/body region, the deepest 60% to 80% of the mucosa is occupied by densely packed branched glands consisting of mucus-producing cells and a variety of secretory cells. The glands are connected to the luminal surface by a narrow neck known as the foveola. In contrast to the more distal portions of intestine, the germinal population for all of the gastric epithelium lies at the junction between the glands and the foveolae, a region known as the isthmus, rather than at the base of the glands (Fig. 29-1). These germinal cells migrate upward to replenish the mucus neck cells and surface epithelium, and downward to repopulate the glands as part of normal mucosal turnover and in the event of unexpected epithelial loss. The overall mucosal turnover time is 4 to 5 days—a time that dictates the speed of wound healing, and the rate at which shallow ulcers disappear. The risk of a false-negative biopsy result when investigating episodic gastric disease has not been sufficiently emphasized.

The glands are populated by a mixture of pyramidal, brightly eosinophilic cells that produce hydrochloric acid and cuboidal chief cells with a more basophilic, foamy cytoplasm containing secretory granules of various types including precursors of pepsin and zymogen. Chief cells predominate in the deeper two-thirds of the fundic glands. Mucus-filled columnar cells similar to mucus neck cells persist throughout the full length of the glands. The fourth and final cellular constituent of the epithelium consists of neuroendocrine cells that are inconspicuous in routine histologic preparations.

The glands are separated from the underlying muscularis mucosa by a layer of dense fibrous tissue that varies substantially in thickness. They are separated from one another by a very small amount of fibrovascular lamina propria containing a mixture of lymphocytes, plasma cells, mast cells, and eosinophils. In the normal fundic stomach, the fibrous tissue and the leukocytes are most visible in the superficial 20% of the mucosa. The deeper glands are packed against each other with essentially no intervening lamina propria (Fig. 29-2). Defining the normal reference range for the fibrous tissue and for each cell population is essential to the proper identification and classification of gastric inflammatory disease—a goal that remains elusive.

Within the pyloric antrum, the glandular volume is substantially less, occupying less than 50% of the mucosal thickness. The glands are less branched than those of the fundic mucosa and are populated primarily by mucus-producing cells. They are separated from one another by more fibrous lamina propria than in the fundic mucosa, and leukocytes are about twice as numerous as in fundic stomach. Failure to recognize the differences in normal histologic structure

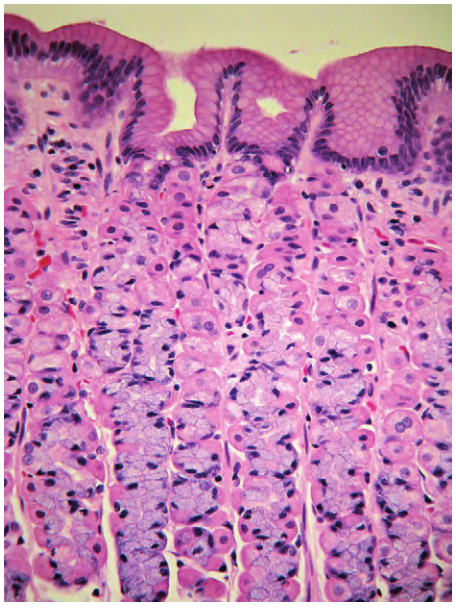

Figure 29-1 Normal canine fundic mucosa. The glands occupy 80% of the mucosal thickness and are densely packed with almost no intervening connective tissue and very few leukocytes. The inconspicuous germinal population lies at the junction between the glands and the foveolae, a region known as the isthmus.

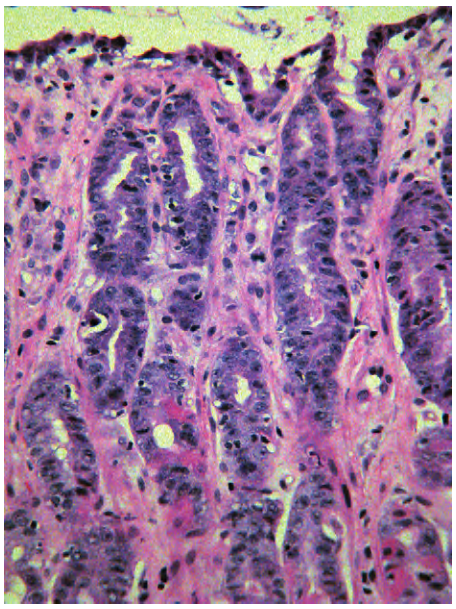

Figure 29-2 Persistent shallow gastric ulceration, with flattening and basophilia of the surface epithelium combined with loss of the foveolar mucus neck cells in favor of an expanding population of hyperchromatic germinal cells. As is typical for chemical or mechanical gastric ulceration, there is very little recruitment of leukocytes.

between fundic and pyloric mucosa can result in incorrect diagnoses of inflammation, fibrosis, and/or glandular atrophy in samples of pyloric stomach.

Histologic Classification of Gastric Disease

The most useful classification of gastric disease is based on histologic character, as there is rarely sufficient insight into etiology or pathogenesis to propose any other basis. Gastric lesions are classified as:

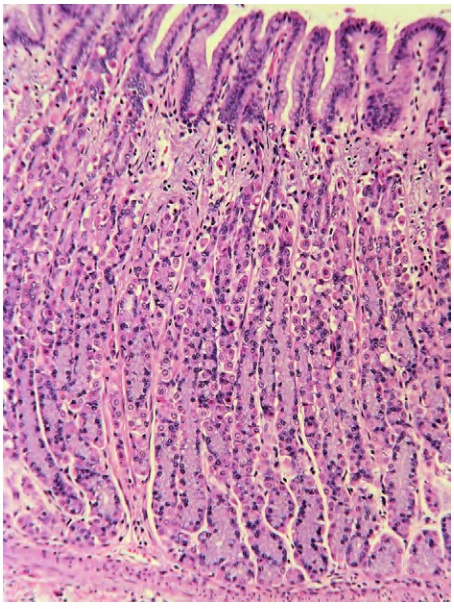

Figure 29-3 Uremic gastropathy, dog. Note the typical horizontal band of acute epithelial necrosis affecting mostly the parietal cells in the middle third of the mucosa. In severe cases there is mineralization of degenerate smooth muscle in the muscularis mucosa and submucosal blood vessels.

- Gastric ulceration
- Mucosal atrophy and fibrosis
- Mucosal inflammation and its consequences
- Proliferative disease including neoplasia

These lesions are not mutually exclusive, but most examples of gastric ulceration have surprisingly little inflammation, and most examples of gastritis do not have ulceration. It is worth emphasizing that gastric lesions are common in dogs and cats even when there are no clinical signs. This is particularly true of mucosal fibrosis and atrophy.

Gastric Ulceration

The stomach is surprisingly susceptible to transient shallow ulceration caused by ingested materials ranging from abrasive foods to household chemicals, numerous common garden and woodland plants, an endless variety of clothing items or household decorations, and hairballs. Although one would assume that the abundant mucus lining the stomach would protect it from abrasion, such is not the case. The mucus is probably more important for protection against endogenous acid.

Ulceration caused by mechanical abrasion is usually shallow and transient. Like other portions of the alimentary system, shallow ulcers heal within hours by flattening and sliding of adjacent epithelium followed by replacement of mucus cells generated by a transient increase in mitotic activity within the isthmus zone at the base of the foveolae. The regenerating epithelium is flatter and more basophilic, with little mucus and slight irregularity in orientation of the nucleus (Fig. 29-3). Shallow ulcers heal completely within just a few hours. The adjacent superficial lamina propria will usually have at least some edema and perhaps even hemorrhage, but the leukocytic reaction is usually minimal. A few neutrophils may be found in the very superficial lamina propria or intermingled with some fibrin and mucus filling in the ulcer. The paucity of leukocytes is in part because the injured tissue is sloughed into the intestinal lumen so that there is little chemical stimulus for leukocyte

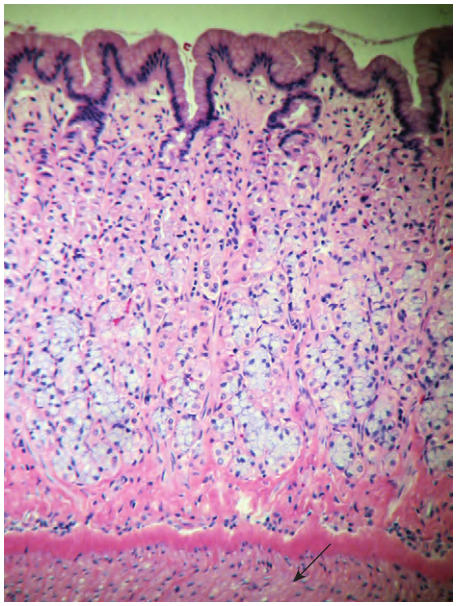

Figure 29-4 Normal feline stomach with a substantial amount of fibrous tissue between the base of the glands and the muscularis mucosa, including the very distinctive lamina densa (*arrow*).

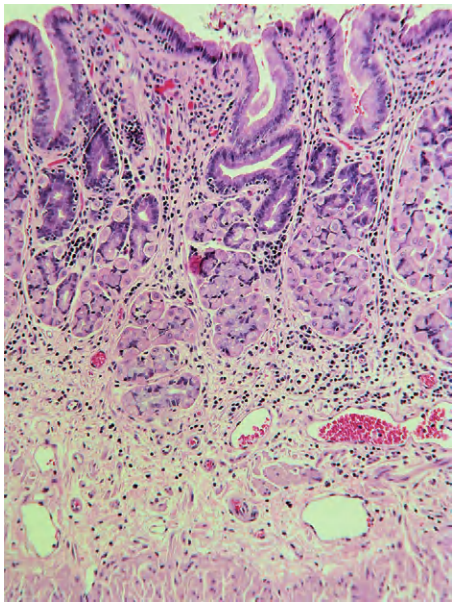

Figure 29-5 Canine fundic stomach with glandular atrophy, glandular nesting, and lamina propria in the absence of any significant infiltration of leukocytes. This is a common lesion, but with no proof that it is medically significant.

recruitment, and partly because the stomach has almost no resident bacteria to contaminate the wounds. With deeper or more persistent ulceration, there will be more obvious hyperplasia and basophilia within the isthmus region reflecting a greater need for mitotic replacement of injured epithelium. Deeper ulcers that have destroyed the isthmus and portions of the lamina propria will take longer to heal and will require stromal proliferation to build a scaffold for effective epithelial healing, but remodeling is extremely effective and it is rare to see any permanent residual scarring. Regardless of the severity of the original lesion, the usual outcome is histologic normalization (Fig. 29-4).

Causes of ulceration other than mechanical abrasion are numerous and include histamine-induced ulceration in dogs with mast cell tumor,[3,4] accidental chemical ingestion, ulcers caused by steroidal and nonsteroidal antiinflammatory (and occasionally other) drugs,[5-7] and exercise-induced ulcers that are best documented in racing sled dogs.[8] In general, the histologic character of the ulceration provides no clue as to the pathogenesis. Careful estimation of the age of the lesions (distance of epithelial sliding, restoration of the normal columnar epithelial shape and normal cytoplasmic eosinophilia, and the maturity of subepithelial fibrosis) will often allow the clinician to identify the causative drug or event. Progression to perforation is rare and usually requires continued application of the injurious stimulus (e.g., continued administration of ulcerogenic drugs or persistent histamine production by a mast cell tumor).

Gastric Necrosis Other Than Ulceration

Epithelial necrosis not typically associated with superficial ulceration is seen with uremia and sometimes with mucosal ischemia secondary to thromboembolic disease, submucosal vasculitis, or gastric dilation/volvulus.

Uremic gastropathy occurs almost exclusively in dogs and its exact pathogenesis remains unknown. The distinctive lesions include mineralization and necrosis of the parietal cells occupying the middle third of the gastric mucosa, mineralization of basement membranes of the glands and of the submucosal blood vessels, and mineralization of degenerate smooth muscle within the muscularis mucosa or even tunica muscularis (Fig. 29-5). Mineralization of submucosal blood vessels may become extensive, involving the full thickness of the vessel wall and accompanied by medial necrosis and endothelial destruction.[9]

With ischemic injury related to vasculitis or vascular occlusion, the character of the lesion depends on the duration and completeness of obstruction. In gastric volvulus, venous obstruction is complete and the intensely congested gastric wall dies following infarction. The mucosa dies first, undergoing coagulation necrosis that quickly becomes lost amid diffuse hemorrhage. In cats with vasculitis caused by feline infectious peritonitis (FIP) or in dogs with disseminated intravascular coagulation (DIC), the necrosis is often patchy.

Gastric Mucosal Fibrosis and Atrophy

Varying degrees of mucosal fibrosis and glandular atrophy are common in biopsy samples of the gastric mucosa. Such lesions have received almost no attention in the veterinary literature, but are common sources of confusion for pathologists attempting to interpret endoscopic biopsies. Some have referred to this as "atrophic gastritis," with no proof that the pathogenesis of the fibrosis is linked to previous inflammatory disease. In the only study to specifically address this question, noninflammatory atrophy and/or fibrosis was seen in 128 of 482 vomiting dogs. Similar lesions were also seen in five of 19 clinically healthy dogs.[10] It is not clear whether the fibrous tissue represents a true increase in the volume of collagen or simply a condensation of resident collagen subsequent to glandular atrophy. The two lesions (mucosal fibrosis and glandular atrophy) are almost always concurrent.

There remain numerous questions related to gastric atrophy and fibrosis, including these:

1. What is the normal amount of fibrous tissue within the lamina propria in different portions of the stomach?
2. Does it increase with age?

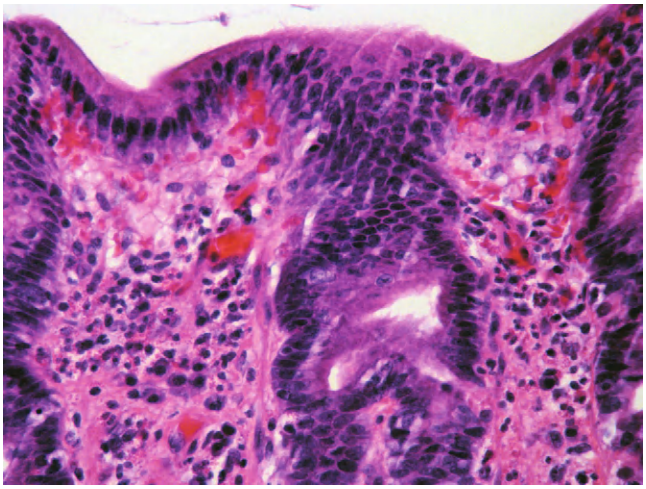

Figure 29-6 Superficial mucosal eosinophilic gastritis, dog. This microscopic field corresponds to Southorn's "mucosal unit." In this instance, it has approximately twice the allowable number of leukocytes, and five times the normal number of eosinophils. Despite the severity of the infiltration, note that the overlying epithelium (as usual) remains virtually normal.

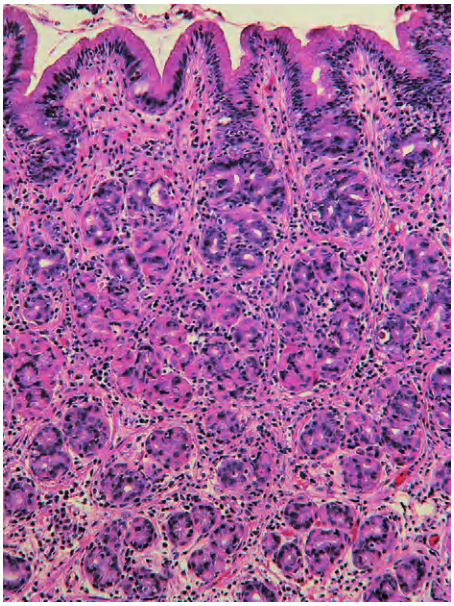

Figure 29-7 Transmucosal gastritis, dog. There is a threefold increase in mononuclear leukocytes throughout the lamina propria, with some mild glandular nesting accentuated by the inflammatory edema and fibrosis. The lack of architectural effacement distinguishes this, even at low magnification, from lymphoma.

3. How commonly is such fibrosis a marker of previous inflammatory disease?
4. Is it permanent?
5. Is it functionally significant, significant only as a diagnostic marker, or not significant at all?

Normally, the glands within the fundic mucosa lie against each other with almost no intervening fibrous tissue. There is a small amount of loose connective tissue among the foveolae, and there can be substantial fibrous tissue separating the base of the glands from the muscularis mucosa. The amount of fibrous tissue in this deep location is greater in cats than in dogs. In cats there is also a distinct, very dense band of hyalinized fibrous tissue just superficial to the muscularis mucosa, known as the *lamina densa* (Fig. 29-6). Within the pyloric antrum there is substantially more fibrous tissue throughout the lamina propria, so any diagnosis of mucosal fibrosis in the pyloric stomach should be viewed with skepticism.

Dogs and cats with chronic gastritis often have persistent mucosal edema that matures into fibrosis. Concurrent inflammatory injury to the gastric glands is followed by regeneration that creates "nests" of hyperplastic glands embedded within the fibrous tissue (see "Atrophic Gastritis" section). It is also common to see the combination of fibrosis and glandular nesting with no evidence of active inflammation and no clinical history of gastric disease (Fig. 29-7). The glands within these nests usually have at least some degree of atrophy of the parietal cell mass with a relative increase in the prominence of the columnar mucus-producing epithelial cells. The combination of glandular atrophy, dysplastic repair, and mucus (intestinal) metaplasia represents a strong risk factor for progression to gastric carcinoma in people,[11] an association that has not been proven in dogs.

Gastritis

The gold standard for the histologic diagnosis of gastritis is an increase in mucosal leukocytes accompanied by other evidence of inflammation such as hyperemia, edema, and bystander injury to the adjacent structural components of the mucosa (e.g., epithelial injury or reparative fibrosis). That gold standard is met in a proportion of the cases, but not in all. The lack of uniformity in the criteria used to diagnose gastritis impacts on the credibility of virtually all of the published literature on the prevalence, classification, etiology, and treatment of gastric inflammatory disease. To many, gastritis is defined simply as an increase in the number of leukocytes within the lamina propria beyond the normal range. The most obvious problem with this definition is that we do not know the normal range. Less obvious but even more fundamental is the question of whether an increase in leukocytes within a tissue designed to respond to antigenic challenge by increasing the number and activity of resident leukocytes should be interpreted as "inflammation." An increase in lymphocytes or plasma cells in a lymph node is usually assumed to reflect an appropriate and purposeful response to antigenic stimulation. In the intestinal lamina propria, the largest lymphoid organ in the body, a similar increase in lymphocytes and plasma cells is generally viewed as pathologic and therefore deserving of therapeutic intervention. The distinction between adaptive and pathologic lymphoid proliferation lies not just in the number of leukocytes, but also in the phenotype and cytokine production profile of the cells. These complexities are beyond routine histopathology and immunohistochemistry, but should not be ignored.

Normal Gastric Mucosal Cellularity

Only three studies address the critical question of the reference range for leukocyte types in the normal canine gastric mucosa. The first reports findings from examination of endoscopic biopsies from 20 clinically normal young adult dogs (Table 29-1).[12] These dogs had no history of vomiting or diarrhea for at least 2 months prior to entering the study, and were all fed a standardized diet and had the same husbandry conditions. Leukocytes were identified with light microscopy and immunohistochemistry, and were counted separately in both superficial and deep lamina propria in "mucosal units" of 250 μm^2 (corresponding to approximately one-half of a ×40 microscopic field). Within the superficial lamina propria of the fundic mucosa, this corresponds to a rectangle of tissue

Table 29-1 Leukocyte Numbers in the Superficial Gastric Mucosa of Healthy Dogs

Cell Type	Superficial Fundic*	Superficial Pyloric†
Lymphocytes (CD3 and CD79)	8.4 (1.5-27.0)‡	22.9 (11.5-32.0)§
Plasma cells	1.6 (0-5.8)‡	6.8 (0.5-15.5)§
Eosinophils	0.5 (0-2.0)‡	2.7 (0-6.0)§
Total leukocytes**	10.4 (3.6-26.2)‡	32.6 (20.0-46.5)§

*Number of cells within a rectangle of lamina propria encompassed horizontally by three foveolae, and vertically to the level of the first parietal cell.
†Number of cells in a square of lamina propria encompassed by two adjacent foveolae with the deep border at the foveolar–glandular junction.
‡Mean (range) of three cell counts in each of 20 dogs.
§Mean (range) of two cell counts in each of 8 dogs.
**Sum of $CD3^+$ and $CD79^+$ lymphocytes, plasma cells, and eosinophils, but excluding mast cells and unidentified cells.
Source: Adapted with permission from Southorn EP. An improved approach to the histologic assessment of canine chronic gastritis. DVSc Thesis, University of Guelph, Ontario, Canada, 2004.

incorporating three adjacent foveolae and the associated lamina propria, and extending vertically to the level of the first parietal cell. Within the pyloric antrum, the "mucosal unit" corresponds to an area of lamina propria bordered by two adjacent foveolae, with its deep border capturing the most superficial portion of the gastric glands.

The other two studies were not specifically designed to provide data about normal gastric mucosal cellularity or other features relevant to the diagnosis of gastritis. Nonetheless, both provide a series of pictorial templates of normal and diseased stomachs in an attempt to reduce interobserver variation in interpretation of gastric histopathology. Neither study provided any information about how the photographic templates identified as "normal" were selected.

The first of these studies was based on 18 client-owned dogs with GI disease and eight dogs euthanized for nonenteric disease. None of the dogs had been treated with antibiotics, corticosteroids, or antacids in the months prior to sampling. Lesions within the fundic mucosa alone were graded by two pathologists using pictorial templates adapted from the human Sydney system that depicts various severities of atrophy, fibrosis, and cellular infiltration. The results from the eight "normal" dogs were not separately identified when tabulating the results (presented as the mean grading results from all 26 dogs).[13]

The second and much larger study provided not only a series of pictorial templates, but also a brief text to guide the grading of GI biopsies, including those from stomach. It included pictorial templates for leukocyte accumulations, fibrosis, ulceration, and other parameters within the fundic and antral mucosa.[14]

In both of these latter studies in which the pictorial templates were specifically designed to reduce interobserver variation, the results showed poor correlation among grading scores assigned by different pathologists. Painful though it is, we must collectively confront the reality that it is essentially impossible to compare results from different studies claiming to evaluate causation or therapy of "gastritis." In most published studies of gastritis in either dogs or cats, the descriptions of leukocyte numbers or the published photographs of lesions claimed to represent mild and even moderate gastritis would be considered "normal" using criteria in the three studies listed previously. This is particularly true of the many studies attempting to establish the pathogenicity of *Helicobacter* spp. for dogs and cats in which any histologic changes were described as mild increases in superficial mucosal cellularity.[15-23]

Histologic Classification of Gastritis

The previously mentioned problems notwithstanding, there is no doubt that genuine gastritis does exist and is quite common. Most cases are part of more generalized GI inflammatory disease,[24] but some are purely or predominantly gastric. There is no evidence that histologic classification based on the distribution or type of leukocytes has relevance to pathogenesis, treatment, or prognosis, nor is there evidence to the contrary. Thus it is appropriate to use (at least for the moment) a classification system that reflects histologic changes, with the expectation that at least some of these differences will eventually prove to have etiologic, therapeutic, or prognostic significance.

Superficial Mucosal Gastritis

Most examples of gastritis in dogs and cats involve leukocyte infiltration of the superficial 20% of the mucosa. In almost all cases, the surface epithelium remains normal. In most cases, lymphocytes and plasma cells predominate, but there are almost always at least some eosinophils. Neutrophils are rarely present, but their presence almost always means nearby or recent ulceration. There may be a concurrent increase in intraepithelial lymphocytes, and in cats there can be an increase in intraepithelial large granular lymphocytes (formally known as globular leukocytes) that are of unknown significance. Edema accompanies the leukocytes and there is often activation of resident fibroblasts and blood vessels (Figs. 29-8 and 29-9).

It has been traditional to describe the predominant cell type (lymphocytic, plasmacytic, eosinophilic) as part of the classification system, but there is no evidence that this is useful.[7,14,24] First, there is no uniformity between laboratories in how well eosinophils, mast cells, or even plasma cells are stained. Second, pathologists differ in defining what proportion of cells is required before that cell type is considered "predominant." Some will diagnose a lesion as "eosinophilic" if they believe that the eosinophils are the most numerous cells entering the tissue on an hourly basis, even if they are outnumbered by lymphocytes or plasma cells that have accumulated over weeks and months. Others use a more traditional approach and name the lesion based on the cell type that is most numerous within the tissue at the time of assessment. That means that almost any chronic gastritis will be classified as "lymphoplasmacytic." Until everyone uses the same convention for naming such lesions, subclassification based on the predominant cell type will remain unreliable. It makes more sense to simply list each identifiable cell type as a percentage of the total infiltrate, so that such information can later be analyzed to see if it influences therapeutic response or other clinical parameters.

Transmucosal Gastritis

Approximately 30% of samples identified as having gastritis by conservative histologic criteria have an increase in leukocytes with variable degrees of edema and/or fibrosis throughout the full thickness of the lamina propria, causing separation of the gastric glands from each other and from the underlying muscularis mucosa (Figs. 29-10 and 29-11). There usually is no obvious necrosis within the glands or along the surface. Lymphocytes and plasma cells predominate, but eosinophils are often conspicuous and sometimes even predominant.

Even though it is unusual to see actual necrosis, there often is some glandular atrophy so that the glands appear in isolated nests

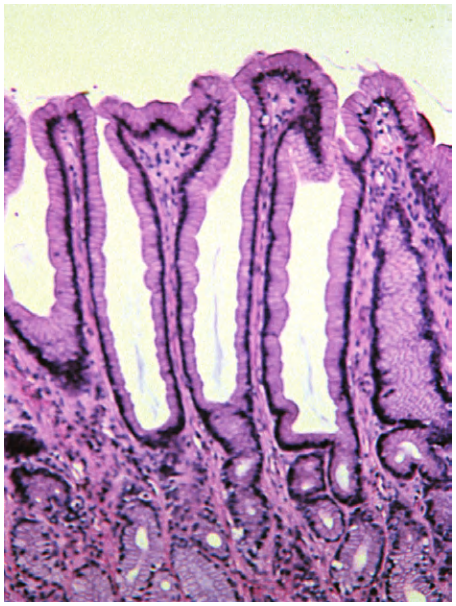

Figure 29-8 Focal gastric pyloric mucosal hypertrophy, dog. The hypertrophy is limited to the foveolae and surface epithelium. The elongation of the foveolae may be so marked that a routine endoscopic biopsy will capture only the surface and foveolar epithelium and none of the underlying pyloric glands. This justifies a presumptive diagnosis of mucosal hypertrophy in an endoscopic biopsy.

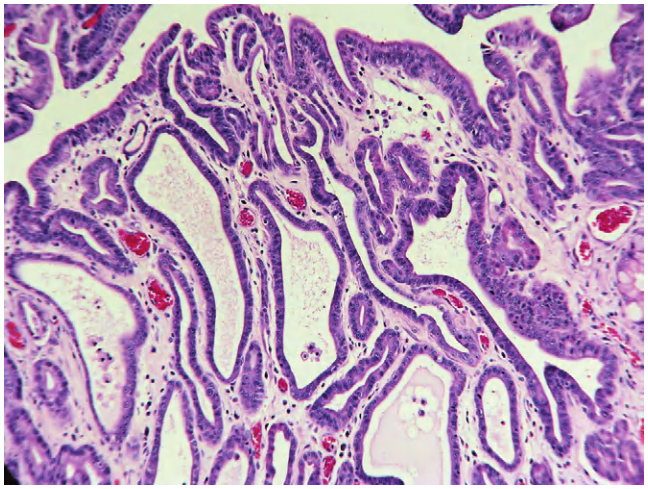

Figure 29-9 Gastric polyp within the fundic mucosa, cat. In contrast to pyloric mucosal hypertrophy, the proliferation here is by hyperchromatic germinal epithelium with a little mucus production and parietal cell differentiation. Cystic glandular dilation is common. The lack of invasion into the lamina propria distinguishes this from papillary gastric carcinoma (which would be exceedingly rare in a cat).

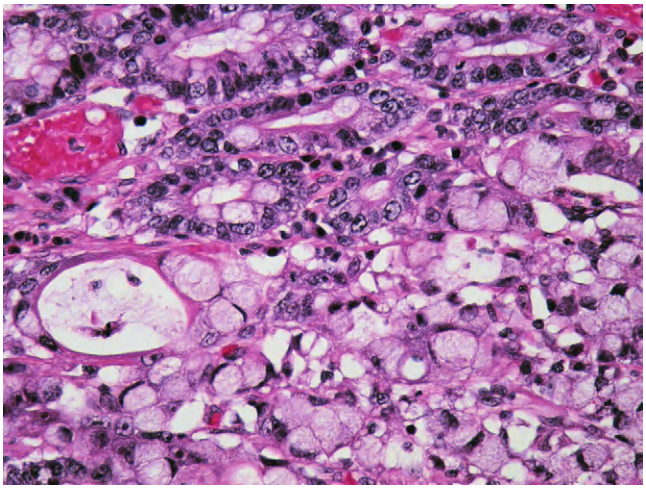

Figure 29-10 Early gastric carcinoma in the fundic mucosa, dog. In early cases, the diagnosis can be difficult and is based on detecting invasion and replacement of lamina propria by monotypic mucus-producing epithelial cells. Formation of tubules is not common within the intramucosal portion of such tumors.

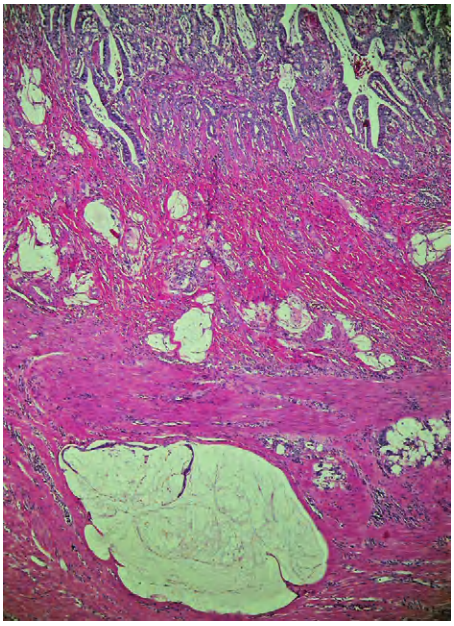

Figure 29-11 Gastric carcinoma, dog. There is abundant reactive fibrosis induced by transmural invasion of a mucus-producing tubular carcinoma. The large lakes of mucin within the tunica muscularis are often more obvious than the tumor cells themselves.

separated by a mixture of leukocytes, edema, and fibrosis. This is probably the precursor for the lesion usually referred to as atrophic gastritis, an extremely frequent but controversial microscopic entity that usually has no clinical counterpart.

Atrophic Gastritis

Atrophic gastritis is a purely descriptive name for chronic gastritis that combines the elements of chronic inflammation, glandular atrophy, regenerative glandular nesting, and mucosal fibrosis. Lymphofollicular hyperplasia may accompany these changes. There is reduction in overall mucosal thickness and in most cases an obvious reduction in the number of parietal cells with a corresponding absolute or relative increase in the proportion of mucus-producing epithelial cells within the glands. If there are functional consequences to the reduction in glandular mass, they are rarely recognized clinically. Pathologists are not uniform in the criteria used to make this diagnosis, so it is difficult to assess the scattered literature related to pathogenesis and clinical significance. Atrophic gastritis may be just the residual lesion of transmucosal gastritis described previously. Atrophic gastritis has also been used as the

name for the parietal cell atrophy and neuroendocrine cell hyperplasia that precedes the development of anaplastic and neuroendocrine gastric carcinomas in Norwegian Lundehund dogs with a distinctive, familial protein-losing enteropathy.[25]

Etiologic Classification of Gastritis

The majority of cases classified as gastritis by histologic criteria have no identified cause. The list of potential causes includes infectious agents, chemical irritants, toxic plants, and immune-mediated diseases.[7] Most of the chemical and plant irritants cause transient gastric ulceration rather than true gastritis, and the inclusion of various allergic or other immune-mediated pathogeneses is based on assumptions rather than proof. Because the stomach is not a site of any significant protein absorption, assumptions of immune-mediated disease may be more appropriate for small intestine than stomach.

Instances of gastritis with a known cause are almost always related to specific infections. These represent a very small proportion of all examples of gastritis, and for most of these agents infection is not usually linked to clinical signs of gastritis or to significant histologic lesions. Parasitic agents include the nematodes *Physaloptera*, *Gnathostoma*, and *Cylicospirura* in dogs and cats, and *Ollulanus* in cats alone. Infrequent but devastating examples of infection with the fungus *Pythium insidiosum* cause mucosal and submucosal suppurating granulomas in the stomach and elsewhere in the GI tract of dogs. The stomach is an occasional victim in the course of systemic fungal diseases (e.g., blastomycosis, cryptococcosis). Finally, the crusade to establish *Helicobacter* as a cause for clinically significant gastritis or gastric ulceration in dogs or cats has triggered more descriptions of alleged gastric lesions than has any other proposed agent of gastric disease.

Parasitic Gastritis

Among the nematode parasites that may infect the stomach and cause histologic lesions, the only ones usually considered of potential significance are *Physaloptera* and *Ollulanus*. *Gnathostoma* and *Cylicospirura* may cause small submucosal suppurating granulomas, but they do not cause clinical signs. Infection with *Physaloptera* has been reported to cause persistent vomiting in dogs, and elimination of the worms following treatment resulted in reversal of clinical signs.[26] Descriptions of histologic lesions are few and vague.

Ollulanus is sometimes listed as a cause of vomiting in cats. It has been described as a cause for fibrosis, lymphofollicular hyperplasia, and increased intraepithelial large granular lymphocytes in cats, but in the original report there was no clinical disease associated with the infection.[27] In some cats the worms can be seen embedded within the foveolae, with no histologic changes. The association between *Ollulanus* infection and apparent increases in intraepithelial large granular lymphocytes remains unproven. The latter is a frequent observation in the stomach and small intestine of cats with GI disease and is of unknown significance.

Cryptosporidiosis has been reported in the stomach of cats and dogs, but with no proof of pathogenicity.[28]

Pythiosis

P. insidiosum is an aquatic oomycete fungus found primarily in tropical and warm temperate climates. Most reported cases in dogs have been from the southeast United States, but the disease is seen worldwide. Lesions in the stomach have the same histologic character as those seen elsewhere: destructive coalescing necrotizing granulomas found randomly within submucosa, tunica muscularis, or within the serosa.[29,30] The diagnosis depends on identifying characteristic fungal hyphae. These are often difficult to see without special stains (e.g., periodic acid-Schiff [PAS] or silver stain), but the necrotizing lesions throughout the stomach wall are not easily mistaken for anything else.

Helicobacteriosis

Helicobacter spp. are normal inhabitants of the surface and foveolae of dogs and cats. In dogs, most infections are with *Helicobacter bizzozeronii* or *Helicobacter heilmannii*, while in cats *H. heilmannii* and *Helicobacter felis* predominate. These large spiral bacteria are easily seen in routine endoscopic biopsies, and their detection is enhanced by the use of silver stains. More elaborate and sensitive detection methods (e.g., polymerase chain reaction [PCR] or tissue urease activity) are research tools rarely if ever used in a diagnostic setting. In the past 15 years, there have been at least nine studies specifically examining the relationship between *Helicobacter* infection, development of histologic lesions, and clinical disease. None of these studies has proven any causal relationship between infection and disease.[13,15-20] All but one, however, have claimed that infection is associated with an increase in gastric mucosal leukocytes, fibrosis, and lymphoid follicles. The problem is that the increased leukocytes claimed to represent "gastritis" invariably fall within the normal range for gastric mucosal cellularity as established by Southorn and as subsequently adopted by the World Small Animal Veterinary Association (WSAVA) Gastrointestinal Standardization Group.[12,14] Most of those studies had no uninfected control against which to measure the claims for increased cellularity. Even if one were to accept the hypothesis that colonization by *Helicobacter* causes a small increase in mucosal leukocytes (including lymphofollicular hyperplasia), the most plausible explanation is that the *Helicobacter* simply represent an increased antigenic challenge to the resident mucosal leukocytes that respond in an entirely appropriate fashion, analogous to what occurs when gnotobiotic animals are first introduced to a "normal" bacterial flora.[31]

Gastric Proliferative Disease

Proliferative changes within the stomach include focal adenomatous hyperplasia in the form of gastric polyps, more diffuse but rare canine hypertrophic gastropathy, and genuine neoplasms.

Focal Adenomatous Hyperplasia

Focal adenomatous hyperplasia occurs in two forms. The more prevalent is focal pyloric mucosal hypertrophy in which the foveolae of the pyloric antrum become greatly exaggerated and form villus-like protrusions covered by mature and otherwise normal epithelium.[32] The lamina propria sometimes contains an increase in eosinophils, but it is unknown whether those examples with eosinophils have a different pathogenesis than those without. It is unknown whether the eosinophils are involved in the development of the lesion, are the result of the lesion, or are unrelated.

The prevalence of these lesions is directly related to the frequency of endoscopy and many are clinically silent. They become significant only if they grow large enough and if they are located where they may cause pyloric obstruction. The diagnosis is difficult to confirm in endoscopic samples. If orientation and depth are both perfect, then the diagnosis is based on seeing the biopsy filled with superficial and foveolar epithelium with no glands because the increased thickness of the foveolar region occupies the entire capacity of the biopsy forceps (Fig. 29-12).

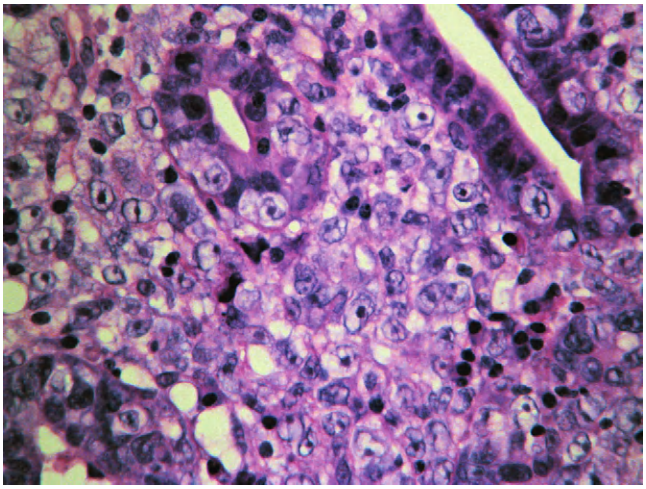

Figure 29-12 Large cell "lymphoblastic" lymphoma, cat. Typically, these form a solitary discrete mass originating within the lamina propria. This is traditional lymphoma with architectural obliteration by a diffuse sheet of large monotypic lymphocytes (in a cat, virtually always B cells), here leaving only a few lingering remnants of preexistent glands.

Less prevalent than pyloric mucosal hypertrophy is focal adenomatous hyperplasia creating polyps in the gastric body or fundus. These are about three times more prevalent in cats than in dogs. In contrast to the proliferation of mucus-laden superficial epithelium typical of pyloric mucosal hypertrophy, these gastric polyps are formed primarily by papillary proliferation of hyperchromatic glandular epithelium forming branching and sometimes cystic tubules. Most of the epithelium is hyperchromatic and primitive columnar epithelium with no mucus production, but with occasional maturation into parietal and chief cells. They differ from papillary adenocarcinomas by not showing any invasion across the basement membrane and into the lamina propria or submucosa. The lack of invasion is the only reliable criterion distinguishing gastric polyp from a well differentiated papillary adenocarcinoma. There is no proof that these lesions progress to neoplasia.

Gastric Neoplasia

Although a wide variety of neoplasms are reported within the stomach,[35,36] the majority fall into one of three groups: gastric carcinoma, lymphoma, and smooth muscle tumors.

Gastric Carcinoma

Mucus-producing, scirrhous tubular adenocarcinoma is the most common tumor of the canine stomach, but gastric carcinomas are almost nonexistent in cats. In dogs, they usually occur as a regional plaque-like thickening with ulceration in the distal body or within the pyloric antrum. Ulcerated tumors may be confused both macroscopically and microscopically with chronic ulcers that have stimulated abundant reactive fibrosis and dysplastic epithelial repair.

The earliest recognizable histologic lesion is focal obliteration of mucosal glandular architecture by proliferating polygonal epithelial cells that violate the basement membrane of the glands/crypts to proliferate as individualized cells within the lamina propria. These cells, which may not be easily recognized as epithelial cells, may be found only deep within the lamina propria. They may be difficult to capture in endoscopic biopsies especially if the tumor is arising in pyloric mucosa (the thickness of the pyloric mucosa makes it difficult to capture the deep third of the mucosa). There will be times in which full-thickness samples are required to confirm the diagnosis, but that is the exception rather than the rule. The tumor cells invade the submucosa and then the tunica muscularis. In most cases, the initial invasion is in the form of slender cords or tubules of mucin-producing epithelium within or surrounding lymphatics. They penetrate the serosa and exfoliate into the peritoneal cavity to seed the omentum and mesentery. In most cases the tumor cells are well differentiated and form easily recognizable tubules, but some examples comprise only lakes of mucin within the tunica muscularis, or nodules of reactive fibrous tissue on the mesentery or omentum. In such cases, the use of a PAS stain will accentuate the mucus within the cytoplasm of the anaplastic epithelial cells that will be around the mucus or buried within the fibrous tissue.

It is traditional to subclassify gastric carcinomas based on histologic pattern (e.g. papillary, tubular, scirrhous),[35] but most examples exhibit substantial regional variation that includes more than one subtype. In addition, there is no proven prognostic or therapeutic significance to these patterns so it is difficult to justify subclassification.

Lymphoma

The identification, classification, and treatment of alimentary lymphoma in dogs and cats is a "work in progress," with dramatic changes in our understanding arising from more widespread use of immunohistochemistry and clonality testing. Most of what was written prior to 2005 is more or less irrelevant and even misleading, especially with respect to cats. Alimentary lymphoma in cats is very different from that in dogs, although the differences are perhaps less obvious in gastric lymphoma than in examples affecting small intestine.

Feline Gastric Lymphoma. Lymphoma in the stomach of cats occurs in two different forms. The first and more prevalent is solitary large B-cell lymphoma that occurs as a space-occupying mass. The second is diffuse infiltrative small T-cell lymphoma that occurs in the stomach only as part of more generalized alimentary lymphoma that affects primarily the small intestine. There are a few cases that conform to neither of those descriptions, including a few large granular cell lymphomas and "mixed" or "histiocytic" lymphomas with intermingled eosinophils, T cells, and B cells.

Small cell lymphocytic (usually T-cell) lymphoma in the stomach is initially detected as an excessive accumulation of monotypic, hyperchromatic small lymphocytes within the superficial lamina propria and the epithelium. The accumulation is usually diffuse and may result in obliteration of the distinction between the lamina propria and the epithelium. As the disease progresses, tumor cells invade deeply into the lamina propria, obliterating glandular architecture, and spread throughout submucosa and tunica muscularis to completely replace the gastric wall. At that stage, the diagnosis is simple, but it is more challenging when dealing with early disease in endoscopic biopsies. The question is always the same: is this severe lymphocytic gastritis or early lymphoma? With inflammatory bowel disease, the increased cells are usually a mixture of lymphocytes and plasma cells, and there is no obliteration of the distinction between epithelium and lamina propria.

Large-cell (lymphoblastic) lymphoma is a more traditional lymphoma in the sense that it creates an unmistakable "mass" with early obliteration of mucosal architecture and invasion across the gastric wall. Perhaps because this disease is typically focal and limited to

the stomach rather than being part of a more diffuse GI disease, the lesion is usually advanced at the time of initial diagnosis; consequently, histologic confirmation via endoscopic or ultrasound-guided core biopsies is not usually problematic. Most examples seem to arise from the diffuse lymphoid population in the superficial third of the gastric mucosa. The tumor spreads rapidly to destroy mucosal, submucosal, and muscular architecture, creating a diffuse sheet of monotypic large lymphocytes with nuclei at least twice the diameter of a red blood cell. Epitheliotropic behavior is rarely observed. In a series of 26 sequential examples studied in preparation for this chapter, all were confirmed as B-cell lymphomas. In a recent published study, nine lymphomas limited to the stomach were all immunoblastic B-cell lymphomas.[37]

Large granular lymphoma is a rapidly progressive transmural lymphoma with a unique histologic and cytologic appearance. The cells are pleomorphic large lymphocytes with distinctive large red cytoplasmic granules. The nuclei are often cleaved or even convoluted. The malignant cells are often accompanied by other cell types, including small benign lymphocytes, eosinophils, and fibroblasts. Most published examples have arisen in distal small intestine, but there are a few that arise in the stomach. At least in the small intestine, almost all are $CD3^+CD8^+$ T-cell tumors that probably arise from intraepithelial lymphocytes. Historically, these tumors were mistaken for mixed transmural granulomatous inflammation or mast cell tumors.

Canine Gastric Lymphoma. Approximately 5% of all canine lymphomas arise within the alimentary tract, and only a small percentage of those arise within the stomach. Gastric lymphoma is substantially less prevalent than gastric carcinoma. It is perhaps for this reason that these tumors have received less attention than feline GI lymphomas. There have been no studies specifically of canine gastric lymphomas, and it is necessary to extrapolate from information derived from GI lymphomas in general. In four different published studies, 54 of 65 canine intestinal lymphomas subjected to immunohistochemical characterization were of the T-cell phenotype and the majority of the others were not classifiable.[38-41] There are case reports of epitheliotropic lymphomas and of eosinophil-rich T-cell tumors, but it is not clear whether these are anything other than just variants of "ordinary" T-cell lymphomas.

Leiomyoma and Leiomyosarcoma

Any published estimates of the prevalence of smooth muscle tumors must be viewed with skepticism. In part this is because smooth muscle tumors are usually small and affect tunica muscularis only, so the majority do not cause clinical signs and cannot be detected endoscopically. Estimates of prevalence therefore differ in studies based on clinical signs as contrasted with postmortem studies.[42,43] Further confusion arises from the fact that many of those tumors initially classified as leiomyosarcomas based on traditional histopathology have been reclassified as gastrointestinal stromal tumors (GISTs) on the basis of immunohistochemistry (positive for CD117, negative for smooth muscle actin).[44,45] Those papers addressed small intestinal, cecal, and colonic tumors rather than specifically looking at those in stomach, and in addition specifically addressed smooth muscle tumors initially diagnosed as poorly differentiated leiomyosarcomas rather than more common, mature leiomyomas. It is therefore a mistake to assume that all tumors previously diagnosed as well-differentiated smooth muscle tumors are at risk of having that diagnosis "overturned" by immunohistochemistry.

Smooth muscle tumors usually occur as focal, solitary, discrete masses arising within the tunica muscularis. They represent a continuum from benign to malignant, with no precise histologic division between leiomyoma and leiomyosarcoma. Those with discrete, purely expansile growth and formed of histologically and cytologically mature smooth muscle cells are called leiomyomas. At the other end of the spectrum are primitive stromal tumors with invasive growth, increased mitosis, and only vague resemblance to smooth muscle cells that have traditionally been classified as leiomyosarcomas. Many examples lie in the middle of that continuum, and pathologists are not uniform in how they classify these. Leiomyomas are formed by cells virtually indistinguishable from normal smooth muscle, except that they grow in interlacing bundles to create a disorganized nodule clearly different from the surrounding, laminar arrangement of the tunica muscularis. These tumors may protrude outward through the serosa or inwardly to cause bulging of the mucosa with subsequent ulceration.

The poorly differentiated tumors are comprised of pleomorphic spindle cells with the usual criteria of malignancy, including regional invasion. Any decision to refer to these as smooth muscle tumors rather than GISTs is subjective and should be confirmed with immunohistochemistry.

There is poor correlation between histologic appearance and biologic behavior. As a group, the smooth muscle tumors have a relatively good postoperative prognosis with prolonged postoperative tumor-free intervals and survival times regardless of histologic appearance.[45] For those tumors that behave aggressively, the initial histologic appearance (i.e., leiomyoma vs. leiomyosarcoma) is not predictive.

INTESTINE

Michael Day

Small Intestinal Biopsies

Assessment of tissue pathology has now become a routine component of the clinical evaluation of small intestinal disease. The traditional means of sampling the small intestine is by laparotomy and the collection of full-thickness surgical biopsies of the duodenum, jejunum, and ileum. This method of sample collection provides a greater chance of meaningful diagnostic outcome and it has been suggested that assessment of full-thickness biopsies increases the likelihood of successful diagnosis of alimentary lymphoma.[13,35] Most clinicians are familiar with the benefits of fixing such samples while the tissue is stretched over a cardboard base to avoid artifactual "curling" of the specimen during fixation. The histology laboratory should then be able to prepare a longitudinal section of tissue with well-orientated mucosa through to serosa (Fig. 29-13). Laparoscopy may also permit collection of intestinal biopsies, but the diagnostic value of such samples has not been formally evaluated.

Increasingly, however, both first opinion and referral practitioners have access to flexible endoscopy and this technique has become the preferred means of acquiring small intestinal mucosal biopsies. Although many clinicians will only sample the duodenal mucosa, wherever possible the ileum should also be sampled as there is evidence that many small intestinal diseases may have focal anatomical distribution. The challenges of successful endoscopic biopsy are numerous and are dealt with elsewhere in this text. From the pathologist's perspective, the number, size, and handling of such samples is directly related to outcome (i.e., a meaningful histopathology report). A minimum of six to eight biopsies of duodenal and ileal mucosa should be collected, and these should be sufficiently

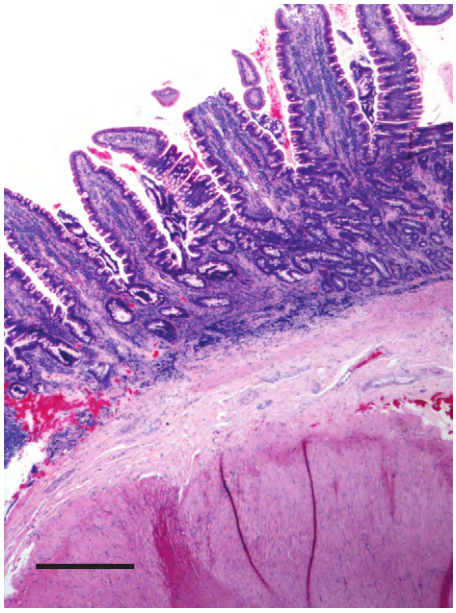

Figure 29-13 A full-thickness biopsy of the canine jejunum. The sample is well-orientated and includes mucosa, submucosa and muscularis. This biopsy has normal histologic microarchitecture. Hematoxylin and eosin stain; bar = 1 mm.

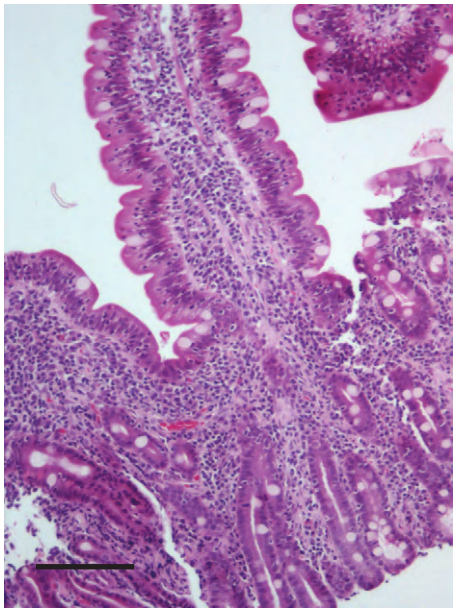

Figure 29-14 An adequate endoscopic biopsy of the feline duodenum. The sample is well-orientated and includes both villus and cryptal mucosa to the level of the muscularis mucosa. This biopsy displays changes consistent with mild lymphoplasmacytic enteritis. Hematoxylin and eosin stain; bar = 500 μm.

deep to include the entire mucosa to the level of muscularis mucosa (Fig. 29-14). The diagnostic value of biopsies that comprise only individual villi that are "scythed" from the surface is severely limited (Fig. 29-15).

Consideration should also be given to the handling of such samples postcollection.[72] For transport, it is often optimal to place these delicate tissues between prewetted purpose-designed plastic "sponges" that can be sandwiched directly into a histologic cassette.

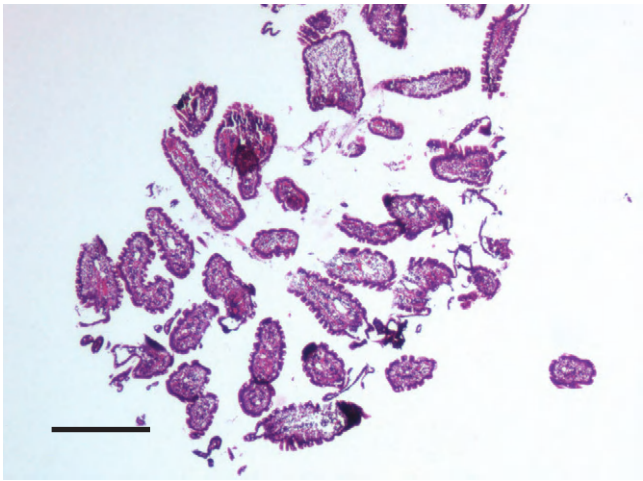

Figure 29-15 An inadequate endoscopic biopsy of the small intestine. The sample comprises individual villi cut in either cross- or longitudinal-section. The villi are fragmented and no cryptal tissue is present for evaluation. Hematoxylin and eosin; bar = 1 mm.

This prevents disruption of the tissue following any vigorous agitation that might occur while the samples are in transit. Most histology laboratories are willing to supply these sponges and cassettes. Although it may appear a basic comment, where samples are submitted from different levels of the small intestine they should be sent in separate, clearly labeled, sample pots containing an adequate volume of formalin for rapid fixation. Samples should be submitted as soon as possible after collection as for some specialized (e.g., immunohistochemical) procedures it is optimal to process tissues into paraffin wax within 24 hours of collection.

The skill of the histology technician should not be underestimated in this regard. The process of embedding these minute tissue samples in molten paraffin wax while maintaining correct orientation and alignment within the block is highly demanding, and better results are obtained if the laboratory is well-practiced in these methods.

The clinician should pay particular attention to the history submitted with the samples. The more information that the pathologist has concerning the clinical presentation and suspected differentials, the more likely an informative and helpful report will ensue. A final consideration is that the microscopic interpretation of intestinal biopsies (particularly endoscopic samples) is not a simple procedure. There is considerable interobserver variation in assessment of intestinal biopsies between different pathologists.[71] The WSAVA Gastrointestinal Standardization Group has proposed that intestinal biopsies should be evaluated in a systematic way using a "tick-box" list that encourages the pathologist to examine and record all of the salient aspects of the samples.[11] In this way, the clinician can be ensured that all relevant components of the tissue were examined, even if they were histologically normal. Most initial microscopic evaluation will be done with sections stained by hematoxylin and eosin (H&E), but the pathologist should be able to follow this up where required with other histochemical stains (e.g., for identification of some infectious agents, for delineation of collagen in fibrosis).[10] It is also now generally possible for the pathologist to request immunohistochemical labeling, particularly in the case of phenotypic identification of round cell or stromal tumors. Clinicians should always develop a close working relationship with their

pathology laboratory, and feel comfortable about contacting the pathologist to discuss further any particular case.

This section provides an overview of the major histopathologic diagnoses made from small intestinal biopsies collected from dogs and cats. As such, the information is not an exhaustive list of minor disorders, but focuses on those of greatest clinical relevance.

Small Intestinal Histology

The basic tissue microarchitecture of the canine and feline small intestine is similar. The orderly arrangement of villus-crypt units (Fig. 29-16) is broken only by the intermittent presence of organized secondary lymphoid aggregates (Peyer's patches or individual lymphoid follicles) with characteristic modified overlying dome-shaped mucosa (Fig. 29-17). Morphometric measurements of canine villus length and crypt depth are reported for different ages of dog,[47] but such investigations do not appear to have been carried out with feline small intestine. Similarly, parameters such as the mean number of goblet cells per unit of a defined number of enterocytes and the mean lamina propria total cellularity per unit area have been reported for the dog.[21]

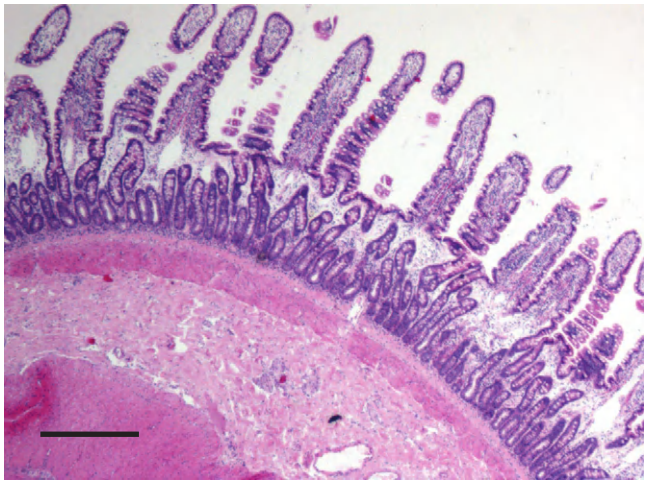

Figure 29-16 Small intestinal histology. Full-thickness biopsy of canine jejunum showing regular villus and cryptal microarchitecture. There is mild edema of the superficial cryptal lamina and one or two lacteals are mildly dilated. Hematoxylin and eosin stain; bar = 1 mm.

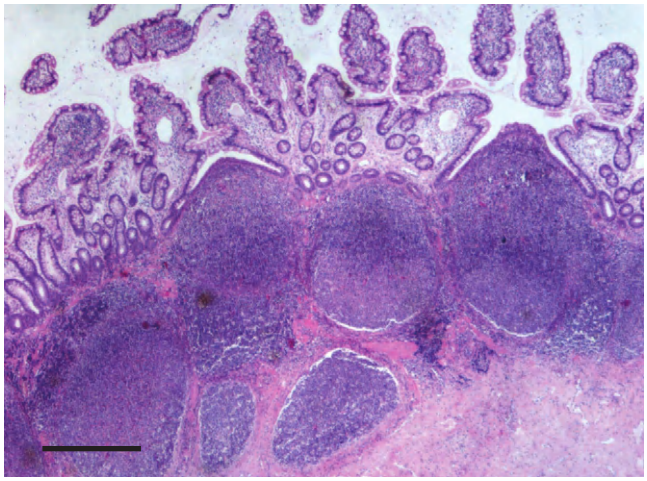

Figure 29-17 Small intestinal histology. Full-thickness biopsy of canine ileum showing a Peyer's patch lying within the mucosal–submucosal tissue. Note the modified "dome" shape of the villi overlying the lymphoid tissue and the extension of the perifollicular lymphoid population to the base of the enterocyte layer. Hematoxylin and eosin stain; bar = 1 mm.

The mean numbers of major leukocyte subpopulations within the canine duodenum, jejunum, ileum, and Peyer's patches have been defined by immunohistochemistry or flow cytometric assessment of disaggregated mucosal tissue.[21,24,27,57] The most interesting of these data report a trend toward an increasing number of lamina propria eosinophils and a decrease in immunoglobulin (Ig) A plasma cells from duodenum to ileum. Data are also available for vertical assessment of the villus and cryptal lamina propria. Plasma cells (of the IgG, IgM, and IgA classes) are enriched toward the base of the villus and cryptal regions, whereas the majority of T lymphocytes are located within the villus tips.

Similar data are reported for the feline small intestine[66] but these highlight some interesting differences between the two species. While cats also have more T cells in the villus (compared with cryptal) lamina propria, there is only enrichment of IgM and IgA plasma cells within cryptal lamina propria—with equal numbers of IgG plasma cells in villus and cryptal lamina. Also in contrast to the dog, cats have increasing numbers of T cells from duodenum to ileum, and an increase (as opposed to a decrease) in IgA plasma cells from anterior to distal small intestine. The two most striking differences between these species lies with epithelial expression of class II molecules of the major histocompatibility complex (MHC) and with the numbers of intraepithelial lymphocytes (IELs) (Fig. 29-18). Whereas dogs display constitutive epithelial expression of MHC class II, the normal feline enterocyte layer is devoid of this molecule.[20,66] Additionally, cats have significantly more IELs than dogs, with an increasing number of these cells from duodenum to ileum (there is no anatomical difference in the dog). The majority of feline IELs are $CD8^+$ (with an $\alpha\alpha$ homodimer)[52] and express the αE integrin that likely mediates their interaction with the epithelium.[73] It has been suggested that some of these changes may reflect the relatively greater number of microbial flora that are proposed to lie within the small intestinal lumen of the cat.[32,45]

Inflammatory Disease of the Small Intestine

Noninfectious Inflammatory Disease

Chapter 4 discusses inflammatory disease of the small intestine of the dog and cat. The three major noninfectious inflammatory diseases of the canine small intestine are idiopathic inflammatory bowel disease (IBD), food responsive diarrhea (FRD; also referred to as dietary hypersensitivity or food allergy), and antibiotic-responsive diarrhea (ARD; small intestinal bacterial overgrowth [SIBO]). The first two of these are also well-recognized in the cat. These disorders likely share elements of pathogenesis relating to the interaction between the intestinal immune system and bacterial or food antigens, and there is probably a pathologic continuum with overlap between the three entities.[23] A range of canine breed–associated enteropathies (e.g., those affecting Irish Setters,[50] soft-coated Wheaten Terriers,[61] Norwegian Lundehunds,[14] and Basenjis[4]) also likely fits within this pathologic spectrum. The clinical and pathologic definition of these specific diseases remains problematic, but all may involve a small intestinal mucosal inflammatory response, generally characterized by lymphoplasmacytic and/or eosinophilic infiltration.[29,30,32,67,74] Alternatively, examples of all three disorders are commonly found where there is no clear evidence for intestinal inflammation.

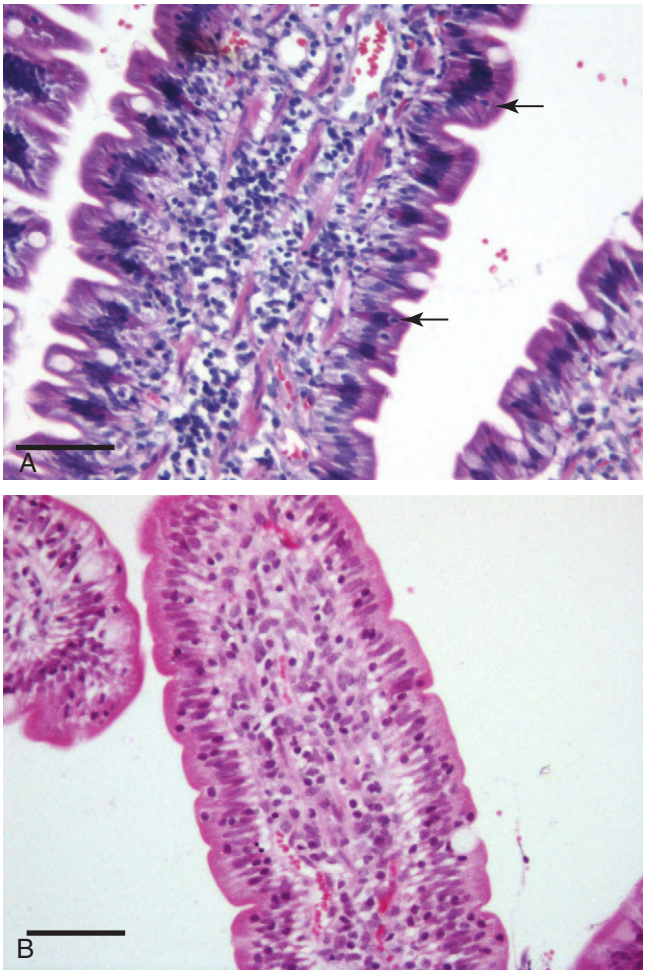

Figure 29-18 Intraepithelial lymphocytes. Villus epithelium from dog (**A**) and cat (**B**) showing the greater number of intraepithelial lymphocytes present in the cat. Hematoxylin and eosin stain; bar = 100 μm.

Given these difficulties, the WSAVA Gastrointestinal Standardization Group produced a monograph on the characterization of the small intestinal (specifically duodenal) inflammatory response per se, without relating these changes to any specific disease entity.[11] The monograph describes the major morphologic and leukocyte infiltrative changes that might occur in the small intestinal inflammatory response, and proposes descriptions of mild, moderate, and severe inflammatory change. The morphologic criteria that define small intestinal inflammation include villus stunting and fusion (Fig. 29-19), epithelial injury, crypt dilation, distention or abscessation (Fig. 29-20), lacteal dilation, and fibrosis. The types of inflammatory infiltrate that may occur are lymphoplasmacytic, eosinophilic, or neutrophilic (Fig. 29-21). Mixtures of these three types of response may also occur. Additionally, assessment of the IEL count is an important component of such evaluation, as elevation of IELs may occur in these inflammatory disorders.

The utility of examination of intestinal biopsies for the diagnosis and monitoring of these inflammatory enteropathies is widely debated. In some canine studies, histopathologic score correlates with the clinical score[31,41] (the "canine IBD activity index" [CIBDAI]) although this has not been replicated elsewhere.[1] Even where histopathologic grade may correlate with clinical severity, repeat biopsy following successful therapy may not necessarily reveal a reduction in the intensity of histopathologic change.[19]

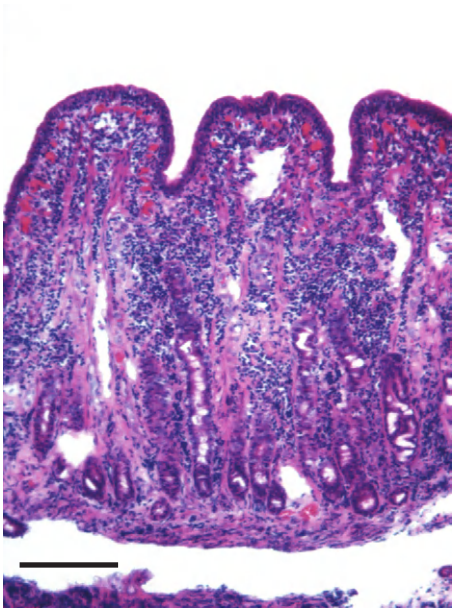

Figure 29-19 Villus stunting. Endoscopic biopsy from a dog with lymphoplasmacytic enteritis. In this well-orientated biopsy, the marked reduction in height of the villi may be clearly appreciated. Hematoxylin and eosin stain; bar = 500 μm.

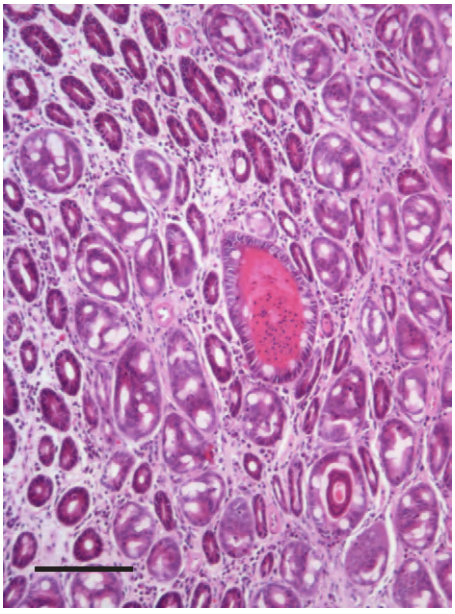

Figure 29-20 Crypt abscess. This biopsy of small intestinal mucosa has been cross-sectioned through the level of the crypts. Although not the optimum orientation for assessment, the central crypt is clearly dilated and filled by an accumulation of bright eosinophilic secretion and degenerate granulocyte nuclei. Individual "crypt abscesses" are considered an incidental feature within otherwise normal mucosa. Hematoxylin and eosin stain; bar = 500 μm.

Histopathology forms one part of a similar proposed composite feline IBD clinical severity scoring system.

Lymphangiectasia

The WSAVA criteria include villus lacteal dilation, which may arise secondary to a mucosal inflammatory response in which there is occlusion of lymphatic outflow. Extensive lacteal dilation is also a

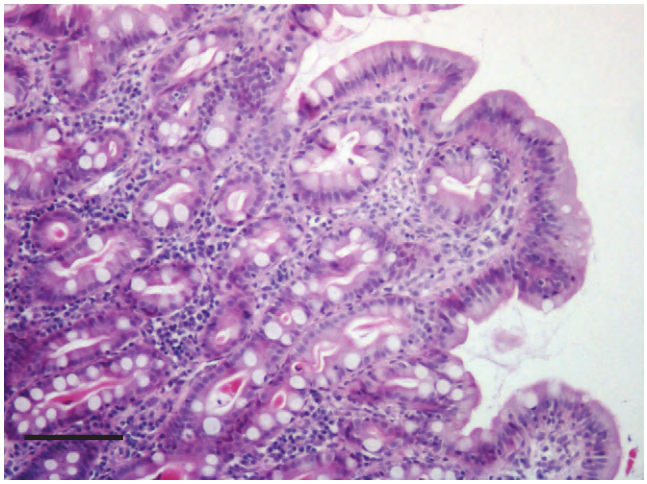

Figure 29-21 Lymphoplasmacytic enteritis. Small intestinal biopsy from a cat with lymphoplasmacytic enteritis. There is marked villus stunting and an infiltrate of predominantly lymphocytes and plasma cells into the lamina propria. Crypts have minimal change in this sample. Hematoxylin and eosin stain; bar = 500 μm.

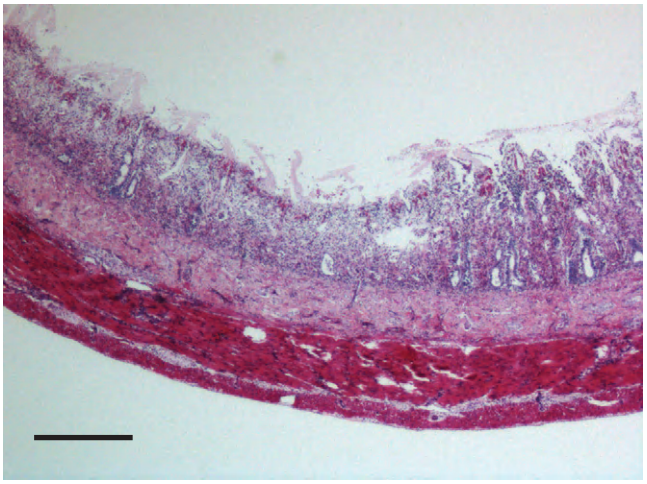

Figure 29-23 Parvovirus infection. Intestine taken at necropsy examination from a pup with polymerase chain reaction (PCR)-confirmed canine parvovirus infection. There is loss of villus structure and almost complete cryptal destruction. Hematoxylin and eosin stain; bar = 1 mm.

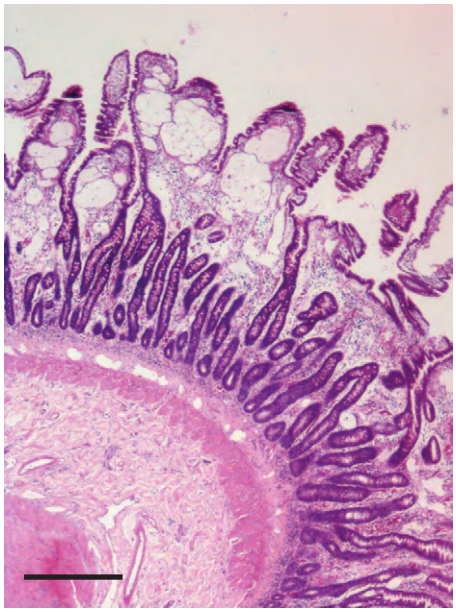

Figure 29-22 Lymphangiectasia. In this full-thickness biopsy there is marked ballooning dilation of the villus lacteals with reduction in the height of the affected villi. There is also lymphatic dilation within the pericryptal mucosa and the submucosa. Hematoxylin and eosin stain; bar = 1 mm.

hallmark of the entity termed *lymphangiectasia*, in which there is "ballooning" dilation of the lacteals accompanied by lamina propria edema and loss of lymphatic fluid (and associated cells and protein) into the intestinal lumen (protein-losing enteropathy) (Fig. 29-22). Affected villi are generally blunt. Lymphatic vessels in the submucosa, muscularis, serosa, and mesentery may also be dilated. Lymphangiectasia is recognized in the dog and may be a congenital developmental disorder or be acquired secondary to occlusion of lymphatic outflow by inflammatory or neoplastic processes.[37,58] Increased lamina propria cellularity is described in some cases, and specific elevation in the numbers of IgG plasma cells has been described. Lymphangiectasia may be accompanied by the formation of discrete microgranulomata (lipogranulomas) within the submucosa or deeper regions that generally center upon lymphatic vessels.[63] These inflammatory foci contain numerous highly vacuolated macrophages (lipophages) that take up the lipid-rich chyle that leaks from affected vessels. It is more likely that these lesions are a sequel to, rather than an initiating cause of, occluded lymphatic outflow. These key lesions may only be visualized on full-thickness (as opposed to perendoscopic) biopsy. As a distinct histopathologic syndrome, some dogs with protein-losing enteropathy have prominent crypt dilation/abscessation with mild lymphatic dilation, but an absence of villus pathology or mucosal inflammatory infiltration.[70]

Infectious Disease

Inflammatory change within the small intestine may also arise secondary to numerous defined causes, including parasitic, protozoal, bacterial, fungal, or viral infection. One example of such change is that which accompanies parvovirus infection of the cryptal epithelia. The hallmark features of parvoviral enteritis in dogs and cats are extreme villus atrophy, crypt dilation, and distention, with characteristic epithelial necrosis and bizarre squamoid morphology of surviving cells, and minimal lamina propria inflammation (Fig. 29-23).[5,64] Later in the course of disease there may be crypt hypertrophy as a consequence of compensatory crypt epithelial hyperplasia/regeneration. Feline leukemia virus has been proposed as a cause of cryptal necrosis similar to that caused by parvovirus. By contrast, feline (and canine) coronavirus enteritis causes loss of enterocytes from the tips of villi rather than affecting the crypts. Antigen from all three feline viruses may be identified within intestinal tissue by immunohistochemistry.[34] Crypt epithelial proliferation and mucosal erosion may occur in young pups with *Campylobacter* enteropathy and these bacteria may be identified within the crypt epithelial cell cytoplasm.[12] By contrast, in canine peracute hemorrhagic gastroenteritis (most often affecting young animals of toy and miniature breeds and suggested to have clostridial etiology; *Clostridium perfringens* type A) there is hemorrhagic necrosis of the mucosa with sparing of the crypts. In both dogs and cats, clinical disease and intestinal pathology associated with "attaching and effacing"

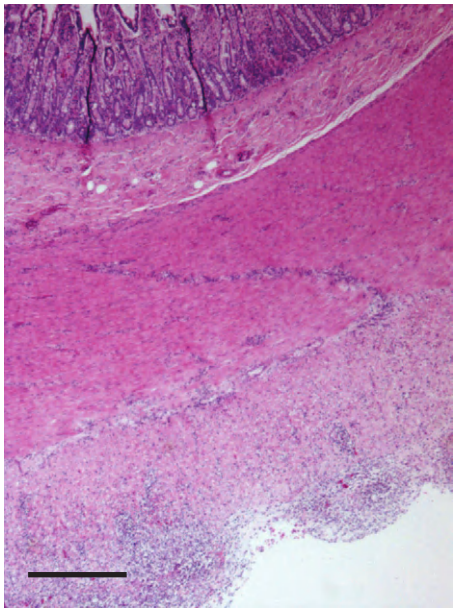

Figure 29-24 Feline infectious peritonitis. Intestine taken at necropsy examination from a cat with feline infectious peritonitis virus infection. There are discrete pyogranulomatous foci over the serosal surface extending into the muscularis. The mucosal and submucosal structure is unaffected. Hematoxylin and eosin stain; bar = 1 mm.

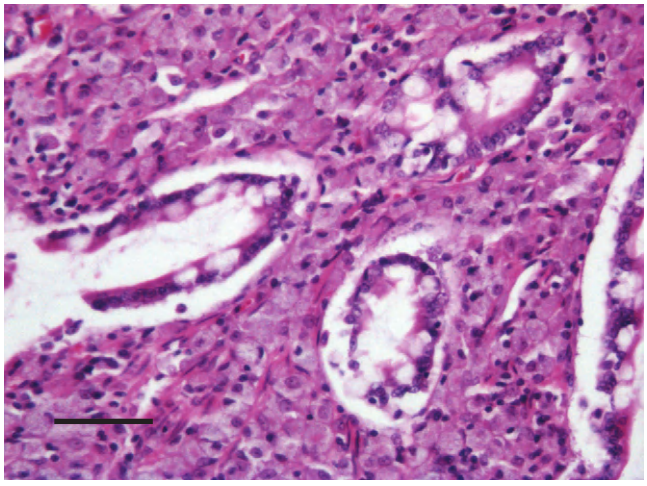

Figure 29-25 Intestinal mycobacteriosis. Section of intestine from a dog showing diffuse infiltration and aggregation of macrophages with expansive pale cytoplasm. Ziehl Neelsen staining of a serial section revealed that these cells contained large numbers of acid-fast organisms. In this dog, the primary lesion was intestinal (with secondary systemic dissemination) and thought to have occurred secondary to ingestion of an infected wild rodent. Hematoxylin and eosin stain; bar = 100 μm.

Escherichia coli (AEEC) is recognized but in many cases other concurrent intestinal pathogens are identified.[65]

A further specific example of a relatively common small intestinal inflammatory lesion is that which accompanies FIP virus infection. In this instance, the pathology is generally serosal (rather than mucosal) and characterized by the presence of vasculocentric pyogranulomatous reactions thought to be initiated by the deposition of antigen–antibody immune complexes (Fig. 29-24). Granulomatous enteritis secondary to mycobacterial infection may also occur in cats and dogs following ingestion of unpasteurized bovine milk or infected small rodent prey (Fig. 29-25). In certain geographical areas

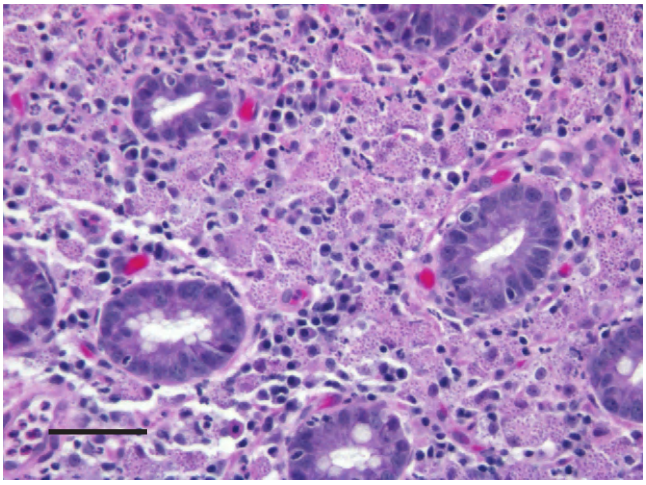

Figure 29-26 Histoplasmosis. Section of colon from a dog showing diffuse infiltration and aggregation of macrophages containing numerous cytoplasmic organisms with morphology consistent with *Histoplasma*. Although primarily a large intestinal disease, this infection may also involve the ileum. Hematoxylin and eosin stain; bar = 100 μm.

(e.g., the southern United States), granulomatous enteritis caused by the fungus *Histoplasma capsulatum* is prevalent in dogs.[7] Canine histoplasmosis most commonly affects the ileum and colon and organisms are prominent within the cytoplasm of infiltrating macrophages (Fig. 29-26). Hemorrhagic granulomatous enteritis may also occur in canine "salmon poisoning" in which dogs ingest salmon infected by the fluke *Nanophyetus salminicola*, which transmits the causative rickettsial organism *Neorickettsia helminthoeca*. Granulomas with prominent eosinophil infiltration may surround fragments of migrating *Toxocara canis* in the intestine of young dogs with poor husbandry. This change is generally considered an incidental finding, but has been termed *canine multifocal eosinophilic gastroenteritis*. The attachment of hookworms to the small intestinal mucosa may also induce local tissue damage related to the ingestion of blood by the parasite. Tapeworms also attach to the intestinal mucosa, but they generally have minimal clinical significance for the host. Although primarily a colonic infection, *Tritrichomonas foetus* may also infect and induce inflammation in the ileum of cats. Small intestinal giardiasis is not uncommon in young dogs and cats, but the *Giardia* organisms produce little intestinal pathology other than damage to the enterocyte microvillus border.

Neoplastic Disease of the Small Intestine

Alimentary Lymphoma

Neoplastic disease of the small intestine remains the major differential for inflammatory disease of this organ and is not an uncommon diagnosis in dogs and cats. These tumors may be of epithelial, mesenchymal, or hemopoietic origin. A frequent small intestinal neoplasm is alimentary lymphoma, which may concurrently involve other regions of the GI tract or mesenteric lymph nodes. Alimentary lymphoma is the most common tumor of the small intestine in cats. With the advent of successful vaccination and testing programs for feline leukemia virus (FeLV) infection there has been a change in the epidemiology of feline lymphoma. This disease now occurs principally in an older cohort of cats, is more likely to be unassociated with FeLV infection, and most frequently has alimentary

distribution.[62] In one study from Australia (where FeLV infection is uncommon), 15 of 118 cats with lymphoma had only intestinal involvement, a further 20 cats had alimentary lymphoma with involvement of other abdominal viscera, and another 25 cats had alimentary lymphoma with concurrent involvement of nonabdominal viscera.[18] In a retrospective study from California, 186 of 257 cases of feline lymphoma were recorded as having primary intestinal disease. Moreover, the incidence of intestinal lymphoma had increased in the latter 10 years of this 1983 to 2003 survey.[38] Feline alimentary lymphoma may give rise to a discrete nodular mass(es) within the intestine and/or may involve diffuse infiltration of the intestinal wall without producing mass lesions. The tumor may arise at any level of the gastrointestinal tract.

Feline alimentary lymphoma is generally considered to arise within the mucosa and to infiltrate into submucosa and muscularis (Fig. 29-27). Three distinct morphologic/phenotypic variants are described: small-cell lymphocytic villus lymphoma, large-cell or lymphoblastic lymphoma, and large granular lymphoma. Small-cell lymphocytic villus lymphoma affects older cats and begins as an accumulation of small T lymphocytes at the base of the villus. These cells gradually extend throughout the lamina propria and into the epithelium, and eventually the infiltrate becomes transmural.[6] Large-cell (lymphoblastic) lymphoma affects cats of any age and is a more aggressive, rapidly progressing, transmural tumor that forms nodular masses and metastasizes to mesenteric lymph nodes. At least a proportion of these tumors are of the B-cell phenotype. Large granular lymphoma is an aggressive metastatic form of disease involving large epitheliotropic lymphocytes with distinctive eosinophilic cytoplasmic granules that contain the molecule perforin immunohistochemically.[9,33] This finding suggested that these cells may be either cytotoxic T lymphocytes or natural killer (NK) cells, but further phenotypic investigation revealed that they are $CD3^+$ and also express a CD8αα homodimer, and are therefore likely to be intraepithelial T lymphocytes.[51] These large granular lymphocytes are also considered to be the same population as "feline globular leukocytes." Recent immunophenotypic studies have characterized the majority of feline alimentary lymphomas as being T-cell in phenotype (some of which may be epitheliotropic), but B-cell lymphoma or mixed phenotype tumors also occur.[40,68] By contrast, other studies report a dominance of B-cell lymphoma affecting the feline alimentary tract.[17] There is no clear evidence that immunophenotype is associated with survival time for feline alimentary lymphoma.[46]

The greatest challenge in the diagnosis of feline alimentary lymphoma is distinguishing early incipient neoplasia from chronic lymphoplasmacytic inflammatory disease. It is well-recognized that lymphoplasmacytic enteritis may progress to alimentary lymphoma in the cat, as is also documented for human patients with celiac disease.[2,38,40] The microscopical distinction between lymphoid inflammation and neoplasia is very difficult, but adjunct tests such as immunohistochemistry or molecular "clonality testing" increasingly have been shown to have a role in determining whether an infiltrating population of lymphocytes is clonal (and therefore neoplastic).[40,69]

Although canine alimentary lymphoma shares gross and microscopic features with the feline disease, there is no evidence for a specific etiologic agent. Canine alimentary lymphoma most commonly arises within the small intestine. The lesions may be diffuse or nodular and involve a number of segments of the gut. There are fewer data on the immunophenotype or molecular rearrangements of canine alimentary lymphomas (epitheliotropic T-cell lymphomas are more common than B-cell, mixed, or null cell tumors), and although a transition from lymphoplasmacytic enteritis to lymphoma is suggested to occur in the dog, this has not been well characterized.[15] In one retrospective study of 44 cases of GI lymphoma (of which 29 involved the small intestine) there were more $CD3^+$ T-cell tumors (n = 33) than either $CD20^+$ B-cell tumors (n = 3) or tumors expressing neither marker (n = 8). The T-cell tumors were invariably epitheliotropic.[8] Canine alimentary T-cell lymphoma may be accompanied by a significant infiltration of eosinophils, a state that must be distinguished from intestinal mast cell tumor.[42]

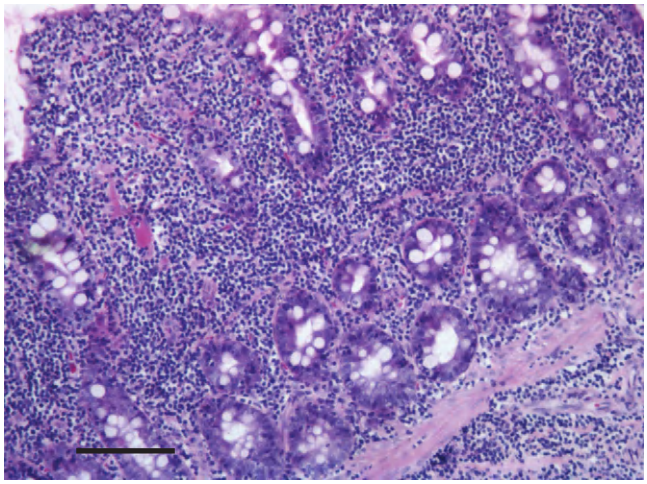

Figure 29-27 Alimentary lymphoma. Full-thickness biopsy from the ileum of a cat with alimentary lymphoma. In this section there is marked villus stunting with widespread infiltration of the lamina propria by a monomorphic population of small lymphocytes. These cells display epitheliotropism and also extend into the submucosa. The appearance is consistent with small-cell lymphocytic lymphoma and these are likely of the T-cell immunophenotype. Hematoxylin and eosin stain; bar = 500 μm.

Other Round-Cell Tumors

Solitary extramedullary plasmacytomas of the small intestine are rarely identified in dogs and cats and are considered to be low-grade malignancies. The malignant plasma cells are pleomorphic and arranged in packets. Immunoglobulin light chain amyloid (AL) may be associated with the tumors. The diagnosis may be confirmed by immunohistochemical evaluation of expression of immunoglobulin heavy and light chains.[49] These tumors are not associated with multiple myeloma of bone and affected animals are rarely paraproteinemic.

Uncommon examples of other intestinal round-cell tumors are recorded. Intestinal mast cell tumor is more common in cats than dogs and most frequently arises in the ileum and jejunum, respectively. These tumors may be difficult to identify when there is a prominent accompanying eosinophil infiltration or lack of metachromatic staining of mast cell cytoplasmic granules. Intestinal mast cell tumor carries a poor prognosis, with frequent metastasis and evidence of gastrointestinal ulceration.[59] The rare hypereosinophilic syndrome may involve the alimentary tract and is more commonly reported in cats[28] than in dogs.[48]

Intestinal Adenocarcinoma

A second important small intestinal neoplasm is adenocarcinoma which may also arise at other levels of the gastrointestinal tract. Most alimentary adenocarcinomas are of gastric origin in dogs,

whereas the majority appear to be intestinal in cats.[36,44] Within the small intestine, these tumors generally appear as solitary annular and stenosing masses and may be extensively infiltrative and metastatic to the serosa, mesentery, and via lymphatics to mesenteric lymph nodes. Transcoelomic or hematogenous metastasis is rare. Microscopically, there is often a marked scirrhous reaction with small nests of pleomorphic tumor cells embedded within this matrix (Fig. 29-28). The cells may form acinar structures or small aggregates, or be individual in distribution. The classic appearance of a "signet ring cell" is consistent with the secretory nature of the neoplastic epithelia. Some adenocarcinomas display "lakes" of pale mucinous material that may be identified by the Alcian blue/PAS reaction. Occasional carcinomas have a more solid lobular appearance and lack acinar differentiation or evidence of mucin production. Some tumors have evidence of metaplastic formation of bone or cartilage. Tumor cells of adenocarcinomas would be expected to express cytokeratin but not vimentin on immunohistochemical evaluation. Benign epithelial polyps or adenomas are rare in the canine and feline small intestine.[39]

Carcinoid

An intestinal carcinoid is a tumor of neuroendocrine cells of the mucosa that is rarely documented in dogs (mostly colonic) and cats (mostly ileal). These lesions are an important differential for carcinoma and distinguishing between these tumors may require immunohistochemical or electron microscopic evaluation. Grossly, carcinoids may be annular stenosing or nodular in appearance. They display similar infiltrative and metastatic behavior to adenocarcinomas. The histologic pattern is of nests or cords of cells packeted by fine bands of connective tissue stroma. The neoplastic cells have a granular, eosinophilic cytoplasm and label positively for synaptophysin and chromogranin by immunohistochemistry.[54]

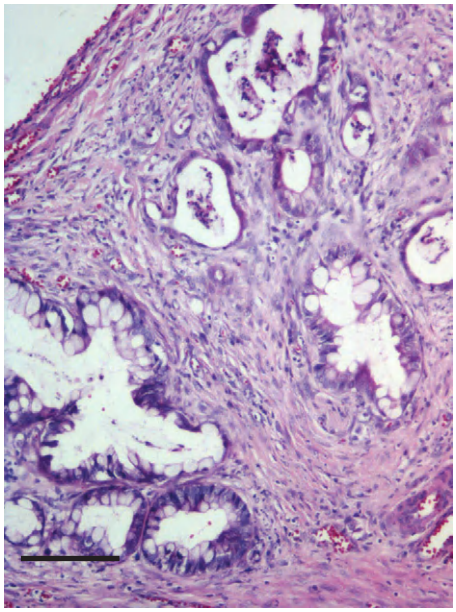

Figure 29-28 Adenocarcinoma. This section of canine colonic adenocarcinoma shows obliteration of normal microarchitecture by irregular infiltrative acinar elements within a scirrhous matrix. These tumors may arise at any level of the gastrointestinal tract. Hematoxylin and eosin stain; bar = 500 μm.

Intestinal Mesenchymal Tumors

Stromal neoplasms also arise in the small intestine, in particular the leiomyoma or leiomyosarcoma of smooth muscle origin. These are generally solitary nodular masses that most often arise in the muscularis of the small intestine of dogs and are considered uncommon in cats. The tumors are comprised of interlacing bundles of strap-like spindle cells with abundant eosinophilic cytoplasm compatible with the tissue of origin. Leiomyosarcomas generally have greater cellular pleomorphism and mitotic activity than leiomyoma. Leiomyosarcomas may be infiltrative but late-stage metastasis to mesenteric lymph nodes and/or liver is uncommon. Other intestinal stroma may rarely give rise to neoplastic lesions such as fibrosarcoma, myxosarcoma, or hemangiosarcoma.[55] Hemangiosarcoma may also metastasize to the small intestine from other primary sites. Nerve sheath tumors or tumors of ganglionated plexuses (ganglioneuroma) are also rare within the small intestine. The histogenesis of stroma cell neoplasms may be confirmed by immunohistochemical evaluation. Leiomyosarcomas will express vimentin, desmin, and muscle-specific actin (these molecules are also found in skeletal muscle) and the specific smooth muscle molecule α-smooth muscle actin. Expression of factor VIII–related antigen characterizes hemangiosarcoma.

Occasional tumors with morphology consistent with leiomyosarcoma fail to label with smooth muscle markers immunohistochemically and are classified as GISTs.[3,16] These tumors are thought to arise from the interstitial cells of Cajal or from a precursor cell that gives rise to these cells in addition to smooth muscle cells. GISTs may express immunohistochemically vimentin, S-100, neuron-specific enolase and c-kit. It would appear that many of the tumors previously diagnosed as intestinal leiomyosarcoma in fact may have been GISTs as defined by retrospective immunohistochemical evaluation.[53]

Miscellaneous Disorders of the Small Intestine

A variety of other disorders, many of which are relatively uncommon, may give rise to pathology within the small intestine of dogs and cats. Small intestinal inflammation might arise secondary to traumatic events or the presence of a penetrating or blocking foreign body. Intussusception of lengths of small intestine may occur and if sufficiently chronic lead to the development of adhesions and severe inflammatory responses. The cause of intussusception is often not identified, but in dogs this lesion may be secondary to inflammatory disease, parasitic infection, linear foreign bodies (e.g., string) or prior handling of the intestine during surgery. Ischemia may arise following mesenteric torsion or volvulus of lengths of the small intestine. Loops of intestine may be involved in external herniation from the abdominal cavity (e.g., diaphragmatic, umbilical, ventral, inguinal, or perineal hernia).

Proximal duodenal ulceration (peptic ulcer) is recognized most commonly in the dog and has complex pathogenesis that may result in concurrent ulceration of the pyloric antrum. There is a progression from mucosal erosion to deep ulceration with vascular thrombosis, and in some cases to perforation through the intestinal wall. Perforation may result in "silent healing" by omental adhesion and serosal granulation or may lead to hemorrhage and loss of luminal content into the peritoneum. Causative factors may include mast cell tumor leading to histamine-induced hypersecretion of gastric acid, pancreatic islet cell tumors or gastrinomas secreting excess gastrin (Zollinger-Ellison syndrome), administration of glucocorticoid or nonsteroidal antiinflammatory drugs, trauma, or major surgical intervention.

Rare examples of degeneration and inflammation of the muscularis (visceral myopathy) are reported, but the pathogenesis of this disorder is poorly understood.[26] Dysautonomia is recognized in both the cat (Key-Gaskell syndrome) and dog.[25,56] The etiology of this condition is uncharacterized but the clinical presentation may include constipation and ileal impaction. Characteristic lesions are present within the neurons of autonomic ganglia, including those of the myenteric plexus. These cells may be hypereosinophilic and shrunken with nuclear pyknosis or karyorrhexis. Cytoplasmic vacuolation and lack of Nissl granules is reported, and the surrounding stroma may contain mononuclear inflammatory cells. Finally, amyloid deposition may occur within the intestine of older dogs but is considered to be an incidental finding.[60]

COLON

Brian Wilcock

If one were to look at the records from any surgical pathology diagnostic laboratory, the picture that emerges with respect to the pathology of the canine and feline colon is very different from the impression one might get by reading standard clinical textbooks. Except for cases in which neoplasia is suspected, 90% of colonic histopathologic assessments are done on endoscopic biopsies. Among those cases in which histologic lesions are identified, at least 95% are interpreted as either lymphoplasmacytic or eosinophilic colitis, without offering any insight into the exact etiology or pathogenesis. Colitis may occur alone or as part of generalized GI inflammatory disease, usually interpreted by default as IBD. Because it is easier and more reliable to assess changes in mucosal morphology and leukocyte numbers in colonic biopsies than in those from the small intestine, assessment of the colonic mucosa is often helpful, even in those cases in which clinical signs suggest primarily small intestinal disease. Indeed, there is not a strong correlation between the assumed site of disease based on clinical signs and where the histologic lesions are most obvious.

Although the literature describes a plethora of bacterial, fungal, and parasitic agents capable of inducing colitis in dogs and cats, proving a causal link between such infections and clinical disease remains elusive. Most of the agents described can be isolated from clinically healthy dogs and cats, and many are part of the normal flora. For most, fulfilling Koch's postulates has proven impossible, especially when it comes to the experimental reproduction of disease.[1,2] Even for those in which a causal role has been proven, the diagnosis is rarely based on histologic assessment of colonic biopsies.

Our dismal record in correlating histologic lesions with a specific infectious agent or immune phenomenon may just be temporary as new molecular techniques to better identify potentially pathogenic colonic bacteria on the basis of genotype, identify and measure toxins, and identify potential agents of disease within the actual tissue biopsies move from the research laboratory into more general diagnostic use. While we all eagerly await this diagnostic revolution, this section reflects the current reality that specific infectious diseases are rarely identified as a cause of colonic lesions in dogs and cats.

Normal Colonic Mucosa

Interpretation of suspected colonic ulcerative or inflammatory disease requires a firm grasp of the normal range of colonic histology, mucosal kinetics, and principles of GI wound healing (Box 29-1).

Box 29-1 The Fundamental Rules of Colonic Biopsy Interpretation

- Colonic inflammatory disease is virtually always diffuse and uniform, so numerous biopsies are unnecessary.
- Because even very small decreases in absorptive efficiency can result in profound diarrhea, even very subtle colonic lesions can be clinically significant.
- Because colonic ulceration heals very rapidly and usually without any residual changes, biopsies must be taken during active clinical disease so as to avoid the risk of a misleading false-negative result.
- Leukocytes should not exceed four cell layers between adjacent crypts, and eosinophils should not appear in the superficial half of the mucosa.
- Credible etiologic candidates are rarely seen.

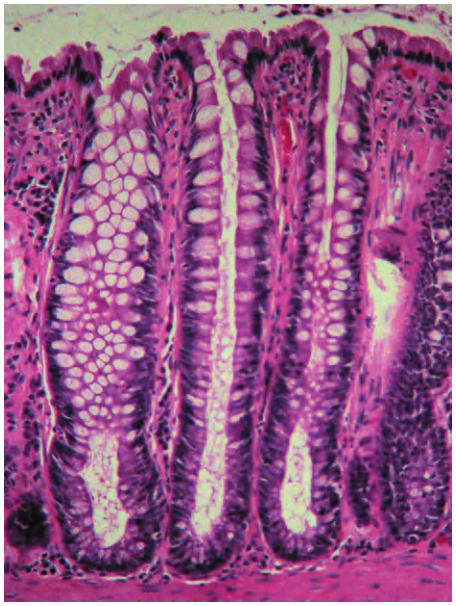

Figure 29-29 Normal canine colonic mucosa, with numerous goblet cells and a sparse population of leukocytes within the lamina propria separating adjacent crypts. Hematoxylin and eosin stain.

The normal canine colonic mucosa is made up primarily of straight cylindrical crypts oriented perpendicular to the underlying muscularis mucosa. The crypts lie against each other, surrounded by a cell-poor lamina propria populated by stromal cells, vessels, and a sparse population of lymphocytes, plasma cells, eosinophils, and mast cells. The base of each crypt is separated from the muscularis mucosa by no more than four cellular layers, in which eosinophils are often prominent. In dogs, crypt length varies from 400 to 600 μm, and in two-dimensional histologic sections consists of two parallel columns each with about 100 simple columnar epithelial cells. The lining of the superficial three quarters of the crypts appears dominated by goblet cells, but in fact the crypts are populated by a mixture of goblet cells, neuroendocrine cells, columnar absorption of epithelium, and germinal basal cells. Goblet cells are claimed to account for only approximately 10% of the total, but the distended mucus goblets often seem to crowd out the other cells and in routine histologic sections create the visual impression of an almost pure goblet cell population (Fig. 29-29). The number of recognizable

goblet cells in endoscopic biopsy specimens is only half that in specimens obtained at necropsy examination,[3] probably because mild irritation from enemas and instruments used in preparation for colonic biopsies results in disgorgement of some of the goblet cells.

Mitoses are found only in the basal third of the crypts and are generally inconspicuous in routine sections. The mean mitotic index throughout the colon is 1.13 mitoses per 100 cryptal epithelial cells, or about two mitoses per crypt.[3] Cells migrate from the base of the crypt to exfoliate from the luminal surface over an interval of about 4 days, representing the overall mucosal turnover time.

The crypts are separated from one another and from the muscularis mucosa by a small amount of cell-poor fibrovascular lamina propria containing no more than four layers of cells.[4] Eosinophils are often particularly conspicuous between the base of the crypts and the muscularis mucosa, and staining with toluidine blue will identify moderate numbers of mast cells that are essentially unrecognizable in ordinary H&E stains. Lymphocytes and plasma cells predominate throughout the more superficial lamina propria, although they may be accompanied by substantial numbers of eosinophils within the deep half of that mucosa. Eosinophils are not found in the superficial half of the lamina propria (Fig. 29-30). Intraepithelial lymphocytes are present throughout, but are much less obvious than in small intestine (with a mean of 1.5 intraepithelial lymphocytes per 100 enterocytes).[3]

Lymphoid aggregates are uniformly distributed within the deep lamina propria and superficial submucosa. Crypts may occasionally penetrate through the muscularis mucosa and into one of these submucosal lymphoid follicles, creating what are sometimes referred to as "submucosal glands." The follicles are particularly large in dogs and cats younger than about 2 years of age, and they can be seen from the external surface when examining the colon during exploratory surgery. They are commonly mistaken for significant lesions (like ulcers, tumor nodules, or parasitic cysts). The key to the distinction is that these lymphoid follicles are all the same size and shape, and never coalesce.

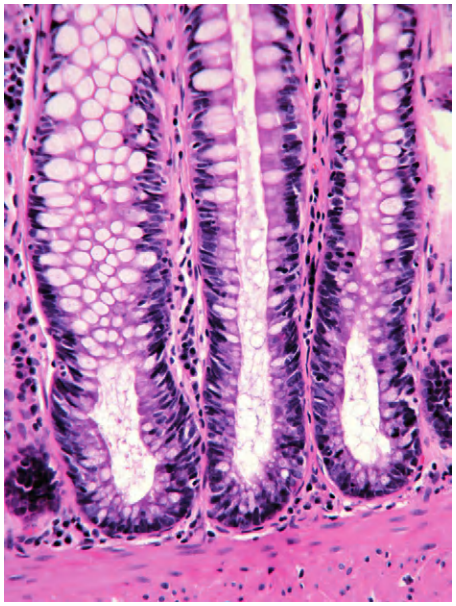

Figure 29-30 Normal canine colonic mucosa. No more than four layers of leukocytes (lymphocytes, plasma cells, eosinophils) separate adjacent crypts from one another and from the underlying muscularis mucosa. Hematoxylin and eosin stain.

General Pathology of the Colon

The reactions of the colon to injury are the same as in the rest of the GI tract. The common lesions include ulceration, depletion of recognizable goblet cells, shortening or elongation of crypts, and changes within the lamina propria that include edema, fibrosis, and increased leukocytes. Hypertrophy of the muscularis mucosa is a fairly common lesion of unproven significance. Changes within the submucosa are much less prevalent and ordinarily are seen only as part of invasive transmural disease occurring as a sequel to primary mucosal disease (the most notable exception being submucosal vasculitis in colonic FIP infection in which the mucosa often remains normal).

Ulceration

Surface ulceration triggers a rapid (minutes-to-hours) flattening and sliding of adjacent epithelium to quickly seal the defect. Any significant surface ulceration also stimulates increased mitotic activity in the basal half of the crypts with migration of flattened, hyperchromatic, immature epithelial cells upwardly to replenish those lost (Fig. 29-31). Temporary increases or decreases in cryptal length reflect the transient imbalance between epithelial loss and cryptal mitotic replacement.

Goblet Cell Atrophy

Even the mildest surface irritation results in almost instantaneous evacuation of goblet cells, particularly from the basal half of the crypts, resulting in cryptal distention with mucus and a disappearance of visible goblet cells. In truth, the cells are still present and it is only the goblets of stored mucin that have disappeared. The goblet cells continue to rapidly produce and export mucin, but the storage goblets will only reappear once the surface irritation has resolved and mucin production once again exceeds demand. The combination of reparative epithelial flattening and mucus accumulation may cause these crypts to appear cystic (Fig. 29-32).

Propria Edema and Fibrosis

Acute edema within the lamina propria is a common lesion that is probably just an endoscopic biopsy artifact because in most cases it is not accompanied by any other evidence of colonic disease.

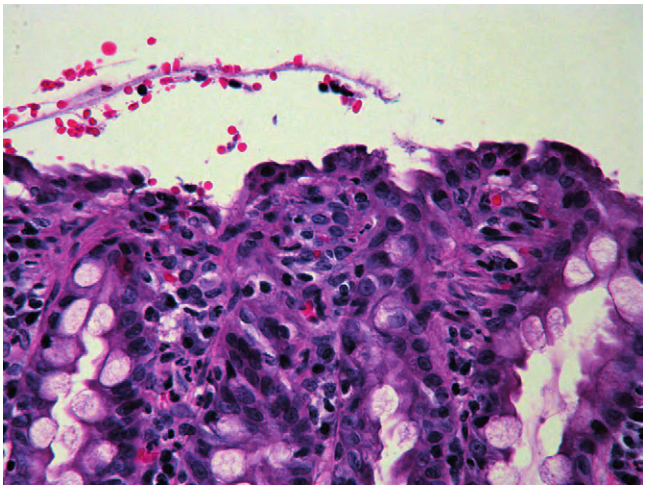

Figure 29-31 Canine colonic mucosa with recent superficial ulceration healing by epithelial sliding. Following a single injury, such healing occurs within hours and leaves no residual footprints. Hematoxylin and eosin stain.

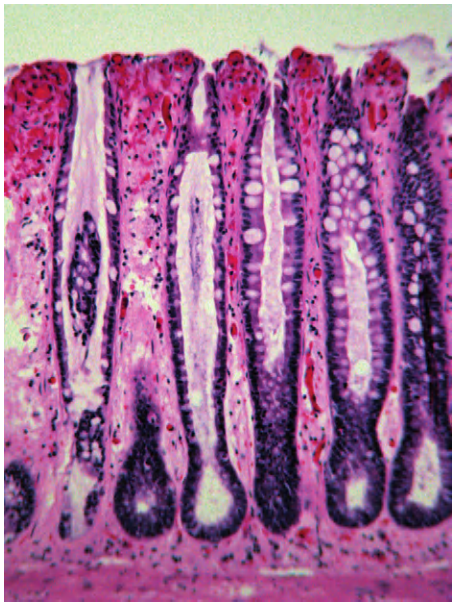

Figure 29-32 Even mild surface injury results in evacuation of goblet cells and cryptal epithelial flattening as a prelude to regeneration. The combination creates the impression of "dilated" crypts filled with mucus. Hematoxylin and eosin stain.

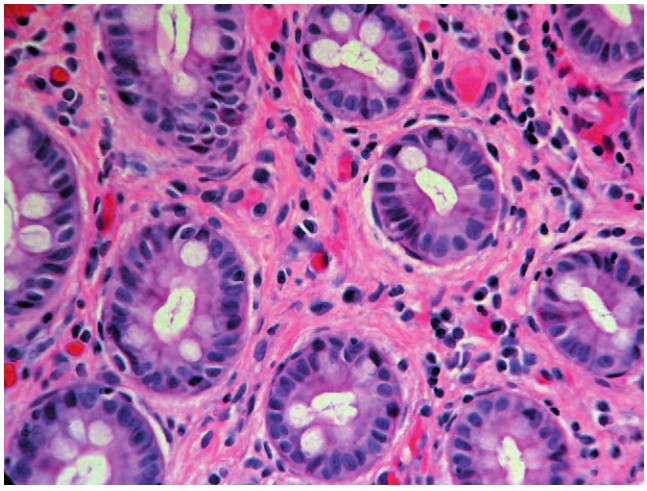

Figure 29-33 Diffuse fibrosis within the colonic lamina propria, a common lesion assumed to be a footprint of previous mucosal inflammation. It has no proven functional significance. Hematoxylin and eosin stain.

Significant edema, of course, can occur as an early manifestation of inflammatory disease or, rarely, as a manifestation of impaired venous or lymphatic drainage.

Propria fibrosis causing abnormal separation of the crypts or separation of the crypts from the muscularis mucosa is probably the most common lesion seen in colonic biopsies (Fig. 29-33). It is reasonable to assume that it is a footprint of previous inflammatory disease, but that is just an assumption. We do not know if it has any functional significance.

Increased Propria Leukocytes

As in other portions of the GI tract, perceived increases in leukocytes within the lamina propria is the traditional basis for the diagnosis of colitis. It is worthwhile noting that colonic ulceration may occur without any significant increase in leukocytes, and there are

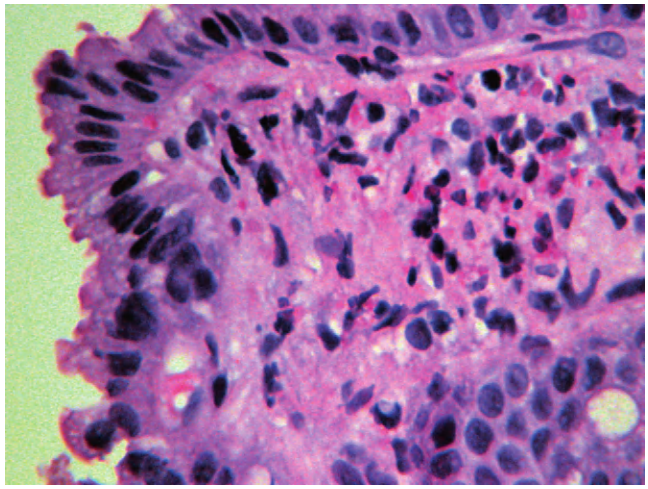

Figure 29-34 Canine eosinophilic colitis. Although eosinophils are normal in the deep half of the mucosa, they are normally absent from the superficial mucosa. The proportion of eosinophils required to classify colitis as "eosinophilic" has not been defined. Hematoxylin and eosin stain.

many examples of increased leukocytes in which there is no evidence of epithelial injury (Fig. 29-34). Developing valid and uniform criteria for assessing the mucosal cellularity and for promoting acceptable interobserver agreement among pathologists remains problematic within the colon as in other parts of the GI tract. Part of the problem lies with incredible variation in histologic staining from laboratory to laboratory, so that recognizing eosinophils, mast cells or sometimes even plasma cells is problematic.[5] Additionally, the range in leukocyte numbers among clinically healthy dogs is quite wide (although much less so than in small intestine). In the only study of its type, normal dogs had up to four layers of lymphocytes, plasma cells, and eosinophils separating adjacent crypts from one another.[4] There is no published range for eosinophil numbers, but eosinophils should be virtually absent from the superficial half of the mucosa.[3]

Additional information about normal colonic mucosal cellularity comes from two studies directed specifically at lymphocyte subpopulations. In healthy dogs, the mean number of immunoglobulin-containing cells and $CD3^+$ T cells per linear millimeter in routine histologic sections is approximately 300. Slightly less than half are T cells.[6,7] In 11 dogs with clinically diagnosed IBD, the mean increased to 438. The proportional increase among IgG^+, IgA^+, and $CD3^+$ cells was similar. In this study, only the IgM^+ cells failed to increase significantly.[6] There remains the fundamental question about whether an increase in leukocytes within any portion of the intestinal lamina propria should be considered "pathologic," or simply an appropriate physiologic response to antigenic challenge.

Because economic realities preclude immunohistochemical staining and arduous cell counting for the vast majority of diagnostic samples, the identification and characterization of colitis in dogs and cats is based upon simple rules of thumb (like a maximum of four cell layers separating the crypts from one another or the muscularis mucosa)[4] or on clear photographic templates illustrating acceptable and excessive cellular ranges.[8]

There are certainly some biopsies in which leukocytes exceed the limit of four layers separating adjacent crypts, and in which the increase in leukocytes is accompanied by other evidence of mucosal damage like edema, cryptal or surface epithelial injury, or distorted cryptal repair. The appearance of neutrophils anywhere within the

lamina propria is abnormal and usually indicates current or recent ulceration. Only rarely is it an indication of invasive bacterial disease. The observation of eosinophils in the superficial third of the mucosa should also be considered an indication of genuine colitis until we have data to the contrary.

Colitis

In reflecting upon the range of lesions seen in endoscopic or full-thickness colonic biopsies from dogs and cats with a history compatible with colitis, it seems reasonable to divide those biopsies into three broad histologic categories: those with no significant histologic lesions, those with convincing lesions of active colitis characterized by increased leukocytes and/or mucosal damage, and then a large group with more controversial "residual" lesions compatible with waxing and waning colitis captured during one of its quiescent intervals. Those residual lesions include one or more of mucosal fibrosis, cryptal atrophy or tortuosity, and increased leukocytes with no evidence of active epithelial injury or vascular changes appropriate to active inflammation. Considering the waxing and waning clinical signs in many examples of canine or feline colitis and the rapidity of colonic repair, we need to pay much more attention to when the biopsies were taken relative to the last "episode" of clinical disease when assessing colonic biopsies. Lesions of mature mucosal fibrosis and mucosal atrophy are not likely to be relevant if the biopsies were taken in the midst of an acute episode of classical colitis; on the other hand, they may be extremely significant as a footprint of previous inflammatory disease if the biopsies were taken, for example, 2 weeks after the last episode (which is often the case just because of scheduling appointments with a specialist).

Classification of Colitis

There is no official convention for the classification of colitis in dogs and cats. As the vast majority of cases have no demonstrated etiologic agent, colitis is usually classified based on the predominant type and location of the cellular infiltrate.[4,8-10] The shortcomings of such classifications are several. First, most of our biopsies capture only the mucosa and do not allow assessment of submucosa or muscularis propria. Second, because the normal colonic lamina propria is populated almost exclusively by lymphocytes and plasma cells, other infiltrating cell types have little chance of becoming "predominant" even when their increase may actually be greater and more directly related to the cause of the disease. For example, there is no agreement among pathologists about how many eosinophils it takes for colitis to be classified as "eosinophilic." This is further complicated by the fact that most biopsies are taken fairly late in the course of the disease, at which time the long-lived lymphocytes and plasma cells are almost certain to predominate even if their daily proliferation or recruitment is far less than the recruitment of eosinophils or other leukocyte types. Finally, and perhaps most importantly, there is a huge interobserver variation in how pathologists assess leukocyte numbers and other grading criteria even when using a pictorial guide.[5] Unfortunately, there is no obvious solution to any of these significant shortcomings. At the moment, all we can do is acknowledge that it is indeed a dilemma, not only when making the original diagnosis, but also when trying to compare the results of different studies.

Colitis can also be classified by etiology, but that is problematic because most of the agents appearing on such lists have not actually been proven to cause colitis. Almost all of them are part of the normal flora or at least are "common" isolates from clinically healthy dogs or cats. The common assumption that the isolation of such agents, the demonstration of their DNA via PCR testing, or the presence of their toxins somehow "proves" that they are causing disease has no credibility.[1,2]

Box 29-2 is a simple histologic classification that reflects the reality of what is seen by veterinary diagnostic laboratories receiving samples from primary care and specialty private veterinary clinics. Those interested in more refined grading schemes should see previously published studies.[4,8] These patterns are not mutually exclusive, in that the predominant leukocyte type may shift as the disease progresses, and a disease that is initially just mucosal may progress to submucosal or transmural colitis. Nonetheless, the classification proposed here is still useful for the vast majority of cases.

Idiopathic Lymphoplasmacytic (and Eosinophilic) Mucosal Colitis

This is garden-variety chronic episodic colitis in dogs and cats, probably accounting for at least 90% of all diagnoses made on routine colonic biopsies. The histologic diagnosis is based on seeing cryptal separation by a combination of edema, fibrosis, and a mixture of leukocytes that creates more than four layers of leucocytes separating adjacent crypts from one another and from the muscularis mucosa (Fig. 29-35). Ulceration is not a common feature, but when seen may take the form of shallow active ulceration, or, more commonly, superficial epithelial flattening and basophilia indicating recent ulceration in the midst of healing. Lesions are typically diffuse and uniform so that all colonic biopsies look essentially identical. A diagnosis of eosinophilic colitis can be made if eosinophils appear in the superficial half of the mucosa.

Box 29-2 Colitis Classified by Histologic Pattern

Mucosal colitis
- Lymphoplasmacytic
- Eosinophilic
- Granulomatous

Ulcerative colitis

Submucosal and transmural colitis

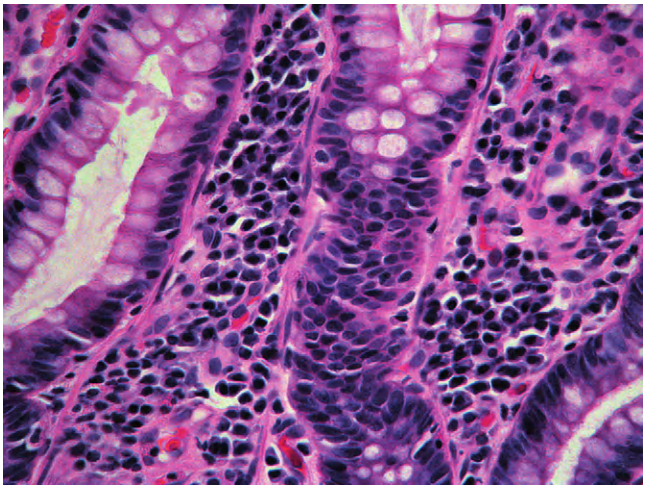

Figure 29-35 Traditional lymphoplasmacytic mucosal colitis with an increase in mononuclear leukocytes separating adjacent crypts, mucosal edema, and subtle fibrosis. This is by far the most common pattern of colitis in dogs and cats, with no proven etiologic implications. Hematoxylin and eosin stain.

Granulomatous Mucosal Colitis

Mucosal colitis in which the predominant leukocytes are macrophages is more or less limited to histiocytic ulcerative colitis (HUC) of Boxer dogs and to histoplasmosis. HUC is a distinct disease syndrome with characteristic histologic lesions seen in young Boxers and French Bulldogs. It is a chronic, progressive, and eventually transmural disease characterized initially by shallow microscopic erosion and ulceration of the colonic surface and by an accumulation of large epithelioid macrophages containing PAS-positive cytoplasmic vacuoles between the muscularis mucosa and the base of the colonic crypts (Figs. 29-36 and 29-37). Over time, the number of macrophages increases dramatically, with extension into submucosa and spread via lymphatics to occupy large portions of the draining colonic lymph nodes.[11,12] The granulomatous proliferative disease is usually more obvious than the ulceration. In the early disease, the patchy deep mucosal granulomatous infiltrates can be missed if one is looking only at shallow endoscopic biopsies. For many years, this disease was considered idiopathic and invariably fatal. More recently, the observation that most cases responded to antibiotic treatment with enrofloxacin stimulated a resurgence of interest in this disease.[13] Subsequently, fluorescence in-situ hybridization (FISH) in colonic biopsies from affected dogs and subsequent genomic analysis identified specific strains of *Escherichia coli* capable of adhering to, invading, and replicating within colonic epithelium. These strains were not found in colonic biopsies from healthy dogs and clinical response to treatment was accompanied by disappearance of the organisms.[14] Why the disease is limited almost exclusively to Boxers and related French Bulldogs remains an intriguing mystery worth solving.

Histoplasmosis frequently causes diffuse granulomatous colitis either alone or as part of systemic disease. The colonic lesions are usually diffuse and large numbers of organisms can be found in macrophages throughout the mucosa. The infected cells are usually most numerous in the deep third of the mucosa, and may extend through submucosa and even muscularis propria. The diagnosis is seldom problematic because the organisms are numerous and their morphology is distinctive.

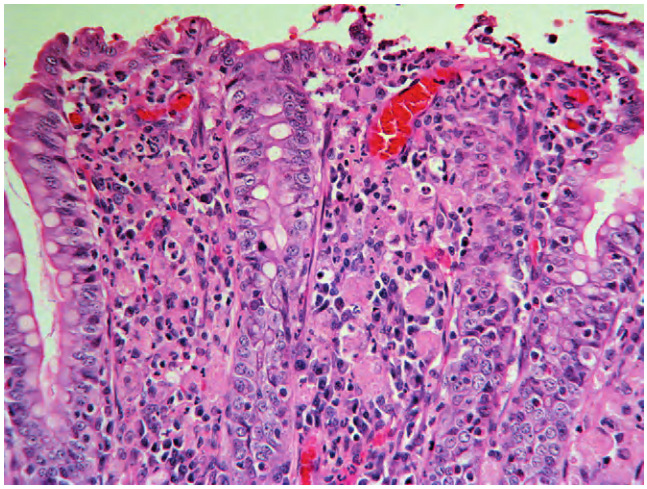

Figure 29-36 Early histiocytic ulcerative colitis in a young Boxer dog. The early lesion is usually found deep in the mucosa, associated with epithelial basophilia and flattening as evidence for ongoing superficial ulceration. Hematoxylin and eosin stain.

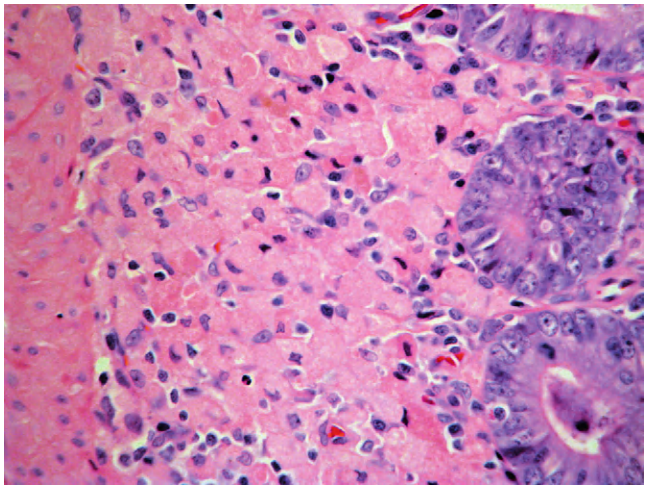

Figure 29-37 More advanced histiocytic ulcerative colitis in a Boxer. There is extensive replacement of mucosal architecture by proliferating histiocytes, including spread through the muscularis mucosa and into the submucosa. Hematoxylin and eosin stain.

Ulcerative Colitis

Ulcerative colitis may be seen as part of several specific etiologic diseases like HUC of Boxers, protothecosis, trichuriasis, and salmonellosis. The vast majority, however, have no proven etiology.

Colonic ulceration not associated with any proven infectious agent occurs under two different histologic settings. The more prevalent is where ulceration occurs without any concurrent increase in mucosal leukocytes. This is particularly prevalent in cats. In other cases, ulceration is accompanied by mucosal changes identical to those seen in idiopathic mucosal colitis described above. It is not clear whether those cases with ulceration alone have a different pathogenesis, prognosis, or response to treatment when contrasted to those examples with concurrent inflammation. It seems worthwhile to at least document the existence of these two different histologic patterns as a stimulus for further research.

Trichuriasis can cause patchy or diffuse ulcerative colitis in dogs with particularly heavy burdens in which the infection spreads beyond the usual cecal location. The worms embed themselves in shallow tunnels in the superficial epithelium and in most cases do not penetrate into the lamina propria. Only with particularly heavy infestations is there ulceration with resulting hemorrhage and mixed fibrinous and neutrophilic inflammation. In response to the ongoing shallow ulceration there is sometimes dramatic cryptal hyperplasia and depletion of recognizable cryptal goblet cells. Perhaps as a result of deep ulceration, worms can occasionally be found embedded within the submucosa and within colonic lymphoid follicles.

T. foetus is a cause of significant, diffuse shallow chronic ulcerative colitis in young cats, especially those in crowded communal husbandry settings. The shallow ulceration is accompanied by increased superficial mucosal neutrophils, and a diffuse increase in lymphocytes and plasma cells throughout the lamina propria. There is compensatory cryptal hyperplasia. The characteristic crescent-shaped protozoa (5×7 μm) are seen along the surface of the surviving colonic mucosa of all affected cats, but only in about half of the histologic sections from any one cat.[10] Their detection is greatly enhanced by FISH.[15]

Submucosal and Transmural Colitis

Biopsies in which the principal inflammatory lesions are found in the submucosa are infrequent, but important because they carry strong etiologic and prognostic significance. The most common of

these is the colonic form of FIP infection, but this is also the usual pattern seen with pythiosis and occasional cases of idiopathic vasculitis and intestinal ganglioneuritis.

The colonic form of FIP is usually seen as acute severe segmental-to-diffuse hemorrhagic colitis with no other clinical evidence of FIP. The classical lesion is a necrotizing submucosal vasculitis resulting in profound submucosal edema and hemorrhage (Figs. 29-38 and 29-39). As is typical for FIP in other tissues, leukocyte recruitment is variable and ranges from primarily neutrophilic to primarily granulomatous, with many cases having a mixture of virtually every leukocyte type. The key to the diagnosis is the vascular necrosis and the presence of a relatively normal overlying mucosa. Coronavirus can be demonstrated within macrophages and other leukocytes within the submucosa and in the adjacent colonic lymph node via immunohistochemistry, confirming the etiologic diagnosis. There are not enough reported cases accompanied by subsequent postmortem assessment to know the prevalence of microscopic lesions in other tissues. In the largest retrospective study, most cats initially diagnosed with FIP on the basis of intestinal lesions eventually died with clinical signs of systemic FIP.[16]

The fungus *P. insidiosum* causes characteristic necrotizing and granulomatous lesions anywhere in the GI tract of dogs. Lesions tend to be large, multifocal caseous nodules that are easily seen macroscopically. Lesions may be mucosal, submucosal, or transmural, but the submucosal lesions are probably the most prevalent. The fungi are numerous within such lesions, but they are difficult to see with H&E stain.[17] They are readily seen with any of the special fungal stains. As this disease has strong geographic predilections and is relatively common within those specific subtropical habitats, the lesions are usually quite familiar to pathologists working in those areas.

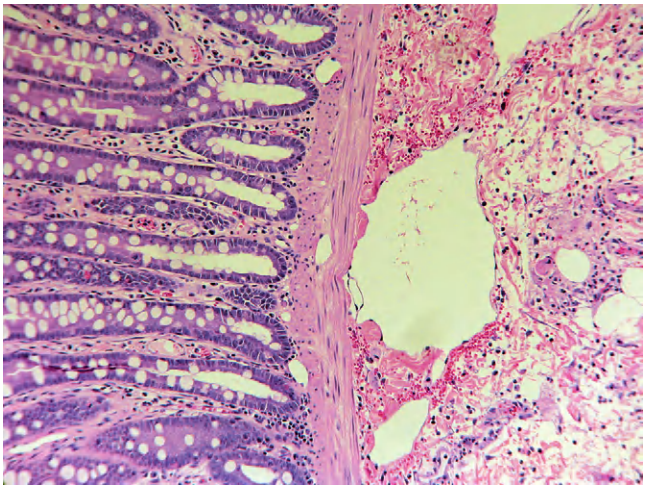

Figure 29-38 The colonic form of FIP in a young cat with acute onset of hemorrhagic diarrhea. In the early stages, there is a destructive submucosal vasculitis causing massive submucosal edema with fibrin and hemorrhage. The overlying mucosa often is almost completely normal. The magnitude of the cellular infiltration and the exact composition of that cellular mixture vary from case to case (and perhaps over time). Hematoxylin and eosin stain.

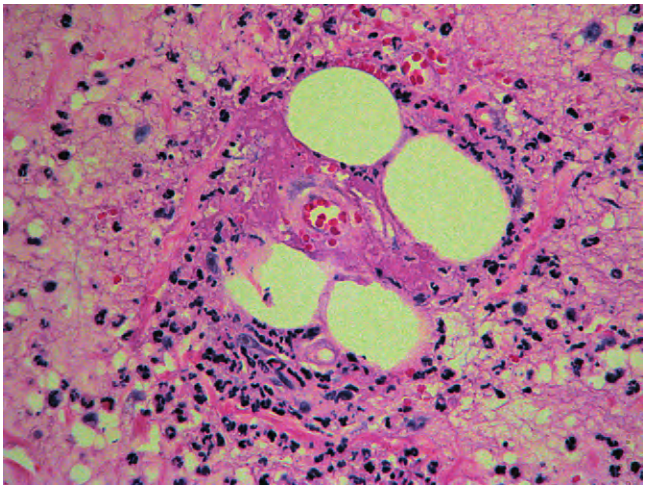

Figure 29-39 Colonic submucosa in a cat with acute hemorrhagic diarrhea. Severe edema, hemorrhage, and mixed pyogranulomatous submucosal inflammation are all suggestive of FIP, but the most specific lesion is neutrophilic leukocytoclastic submucosal vasculitis. Hematoxylin and eosin stain.

Colonic Neoplasia

Tumors affecting the colon and cecum of dogs and cats include virtually all of those documented for the stomach and small intestine. Because the histologic appearance and almost all aspects of the behavior of these tumors are the same regardless of their location within the GI tract, there is no point in repeating all of those details here. There are a few neoplasms, however, that are either substantially more prevalent within the large intestine or that have significant differences in appearance or behavior. Those tumors that occur exclusively or predominantly in the large intestine include rectal papillary adenoma (rectal polyp), rectal plasmacytoma, papillary colonic carcinoma, and cecal GIST in dogs.

Rectal papillary adenoma (rectal polyp, rectal carcinoma in situ) is the most common of the large intestinal tumors of dogs (Table 29-2), but is not seen in cats. It is detected as a focal, solitary sessile or pedunculated proliferation of rectal mucosa that protrudes into the rectal lumen to cause episodic hematochezia and dyschezia, but not diarrhea. All are found in the distal 10 cm of the large intestine. A similar lesion seen more proximally is more likely to be a papillary colonic carcinoma, with a vastly different prognosis. Unlike most neoplasms, there is no apparent increase in prevalence with age and any dog older than approximately 2 years of age can be affected. There is no proven link to diet or any other husbandry factors.[18,19]

Table 29-2 Relative Prevalence of Large Intestinal Tumors in Dogs and Cats*

Colonic Neoplasm	Dog	Cat
Carcinoma	80	134
Lymphoma†	46	80
Mast cell tumor	1	0
Rectal plasmacytoma	97	0
Leiomyoma‡	7	1
Leiomyosarcoma§	15	8
Rectal papillary adenoma	582	0

*Based upon 183,178 canine and 50,232 feline surgical biopsies from Canadian private veterinary hospitals, interpreted by a single pathologist, 1995-2009 inclusive.
†Tumors limited to the large intestine, based on surgical assessment or imaging.
‡Predominance of endoscopic samples probably underestimates true prevalence.
§Not reviewed to distinguish from gastrointestinal stromal tumor.
Source: Histovet Surgical Pathology, Guelph, Ontario, Canada.

Most samples submitted for histologic evaluation are the result of attempts at complete excision per rectum. Particularly large samples, or those arising too far from the anus, may be submitted as full-thickness samples following exploratory surgery. There is remarkably little variation in the qualitative histopathology among such samples. There is abrupt proliferation of hyperchromatic, jumbled but otherwise quite mature columnar rectal epithelium causing a two- to fourfold increase in the thickness of the epithelium. The hyperchromatic and jumbled cells cover villus-like extensions of lamina propria that extend as papillary projections into the rectal lumen (Fig. 29-40). A characteristic feature is that the transition from normal rectal mucosa rich in goblet cells to this hyperchromatic and jumbled epithelium devoid of goblet cells often occurs in the superficial half of the rectal mucosa. The deep half of the mucosa often remains histologically normal. There is no invasion into the lamina propria or into the submucosa. There is often some degree of mechanical or even ischemic necrosis along the surface of the lesion secondary to abrasion from feces or previous prolapse.

Surgical excision is curative in the vast majority of cases. It is essentially impossible to determine whether the few postoperative recurrences are because of incomplete excision or additional, independent polyps.

The only significant differential diagnosis is well-differentiated and early papillary colonic carcinoma. Between 1% and 2% of the diagnoses of rectal papillary adenoma/rectal polyp must subsequently be amended to papillary carcinoma on the basis of postoperative recurrence and subsequent submucosal invasion. We do not know whether this represents progression of rectal polyp to true carcinoma, or whether it was simply a mistaken initial diagnosis. The diagnosis of true carcinoma is most reliably made by seeing invasion through the muscularis mucosa and into the submucosa, but many samples are not deep enough to allow that distinction. Even shallow samples of carcinoma may, however, allow observation of invasion across the basement membrane and into the lamina propria, a behavior not seen in otherwise identical papillary adenomas. It is also helpful to remember that most colonic carcinomas arise in the more proximal colon. Rectal papillary adenomas, by definition, are limited to the distal 10 cm of the intestine.

Dysplastic repair following rectal mucosal ulceration could be confused with a portion of a rectal papillary adenoma if the sample was limited to a tiny endoscopic biopsy. Dysplastic repair should be primarily a cryptal phenomenon, giving rise to tortuous cryptal proliferation accompanied by fibrosis and increased leukocytes. It should not create a macroscopic, intraluminal mass.

Plasmacytoma is the second most common tumor of the canine large intestine. Although these tumors may occasionally occur anywhere in the mucosa or submucosa throughout the GI tract, the majority occur as a focal, solitary, and discrete nodule of atypical plasma cells within the submucosa of the rectum that can be easily detected by digital palpation.

Microscopically, they are exactly the same as the plasmacytomas more commonly found in nonintestinal locations like the ear canal, gingiva, lip, and digital skin. The tumor is often found only in the submucosa, with seemingly hesitant extension into the deep half of the overlying lamina propria. It is formed by solid packets of pleomorphic round cells with various degrees of plasmacytoid maturation. The plasmacytoid maturation is often most obvious at the periphery of the tumor. As in all plasmacytomas, the presence of scattered very large cells with hyperchromatic convoluted nuclei, or even multinucleation, is a strong diagnostic clue. The cells are typically arranged in solid endocrine-like packets of 10 to 20 cells surrounded by a delicate fibrovascular stroma (Fig. 29-41). In 10% to 15% of cases, there are islands of hyalinized homogenous pink material, identified as Aλ-amyloid, among the tumor cells.

Most tumors have discrete local growth amenable to surgical cure. A small proportion exhibits invasion into more proximal submucosa or outwardly into muscularis propria. Metastasis to regional lymph node is seen only rarely. The prognostic significance of such spread is unknown.

Differential diagnoses are malignant lymphoma and mast cell tumor. Immunohistochemical labeling for immunoglobulin is definitive for plasmacytoma, but is rarely required.

Most papillary colonic carcinomas closely resemble gastric and small intestinal carcinomas in their histologic appearance and behavior. They originate from epithelial cells in the crypts, invade across the muscularis mucosa and into the submucosa, and spread by direct extension and intralymphatic permeation through the

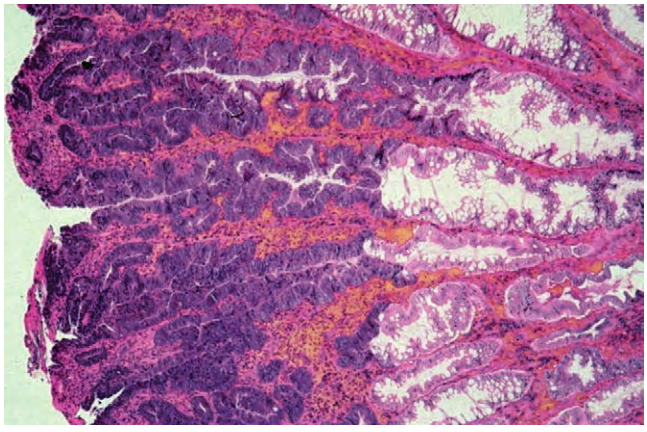

Figure 29-40 Canine rectal polyp. Transition from normal mucosa into the intraluminal papillary proliferation of hyperchromatic and slightly jumbled mature colonic epithelium is typical, and predictive of surgical cure. The absence of propria or submucosal invasion by the hyperchromatic epithelial cells is critical to distinguishing this from an early papillary colonic carcinoma. Hematoxylin and eosin stain.

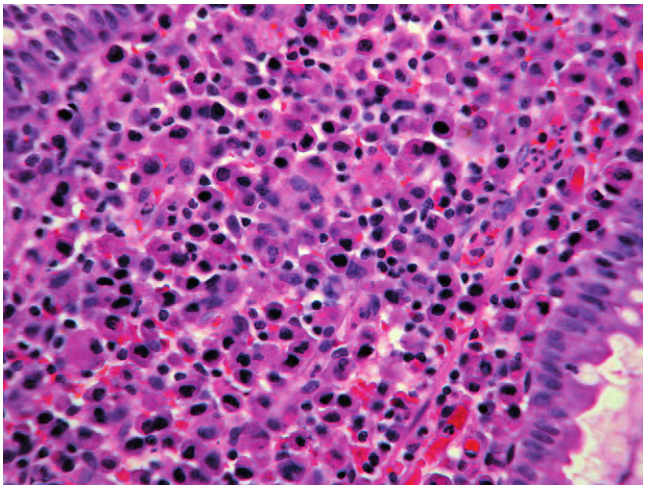

Figure 29-41 Canine rectal plasmacytoma, forming a discretely expansile mass of pleomorphic, atypical plasma cells with frequent nuclear gigantism and convolution. Hematoxylin and eosin stain.

muscularis propria. They then implant throughout the peritoneal cavity, and can also spread by lymphatic and venous dissemination to liver, lung, and any other location. They are often quite well-differentiated mucus-producing tubular carcinomas, and traditionally induce substantial scirrhous reaction. In the colon, however, approximately 25% of carcinomas are, at the time of initial diagnosis, extremely well-differentiated intraluminal papillary tumors that are seen rarely if ever in stomach or small intestine. If sampled just by shallow endoscopic biopsies, these can be mistaken for hyperplastic polyps (especially in dogs and especially if they occur in rectal mucosa where they overlap grossly and histologically with harmless rectal polyps). The key to the diagnosis of carcinoma is that these well-differentiated hyperchromatic columnar epithelial cells invade across the basement membrane and into the lamina propria (Fig. 29-42). In biopsies that are deep enough, one can usually detect at least some invasion into the submucosa. There is no information about whether these solitary discrete papillary carcinomas have a different prognosis from transmural invasive carcinomas.

GIST is a specific histologic entity with a predilection for the muscularis propria and submucosa of the canine cecum. GISTs can occur throughout the GI tract, including adjacent mesentery. To date, GIST has not been described in cats. There are only three studies describing the histologic appearance of GIST in dogs, especially the histologic criteria for distinguishing these tumors from smooth muscle tumors.[20-22] These retrospective studies, with a total of 165 canine intestinal tumors previously classified either as leiomyoma or leiomyosarcoma, reclassified 93 of the 165 as GIST based on immunohistochemical labeling. Making the distinction with ordinary histologic stains is clearly not reliable. The distinction is based on a panel of three immunohistochemical reactions: smooth muscle actin (SMA), desmin, and c-kit (CD117). GISTs are uniformly negative for expression of S-100 and desmin, and about half express c-kit. More importantly, virtually all of the smooth muscle tumors express SMA and two-thirds express desmin. None express c-kit.

In two studies, 41 of 101 tumors affected the cecum. All 41 of the spindle-cell tumors affecting the cecum were reclassified as GIST, making anatomic location alone a powerful predictor of the diagnosis.[21,22]

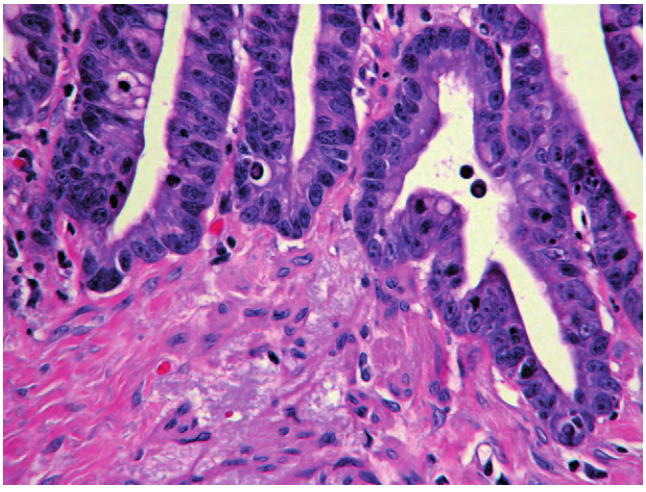

Figure 29-42 Papillary colonic carcinoma in a dog, with characteristic invasion of hyperchromatic and slightly jumbled epithelial cells across the basement membrane and into the lamina propria. Especially when these tumors occur in rectum, the invasion is essential to distinguishing these carcinomas from the much more prevalent entity of rectal polyp. Hematoxylin and eosin stain.

These tumors usually begin within the muscularis propria or in the submucosa, appropriate to their suspected origin from interstitial cells of the autonomic ganglia. They exhibit a wide range of histologic appearance with a wide range in mitotic activity and the degree of invasiveness. They are easily identified as pleomorphic spindle-cell tumors, but distinguishing whether they represent leiomyoma, leiomyosarcoma, or GIST requires immunohistochemistry. Traditional cytologic criteria of malignancy (e.g., mitotic index or nuclear pleomorphism) have little impact on biologic behavior. In one study, surgical excision of small intestinal or cecal tumors in 73 dogs resulted in 80% of these dogs being tumor-free at 1 year, and 62% tumor-free at 2 years.[21] A second and smaller study reported that 13 dogs with surgically excised GISTs that survived the immediate perioperative period had a mean survival of 37.4 months. Five dogs with excised leiomyosarcomas had a mean survival of 7.8 months. The difference was not statistically significant.[22] There are no adequate studies reporting the efficacy of chemotherapy alone or as adjunct treatment.

It will take some time to sort out what parts of the older literature pertaining to alleged smooth muscle tumors can be transferred to the GIST classification (observations like the great majority are behaviorally benign, and the great majority are clinically silent).

PANCREAS

Thomas Van Winkle

While the pancreas may be sampled routinely during necropsy examination, surgical biopsies are infrequently taken from this organ. Many of the major diseases of the pancreas, such as exocrine pancreatic insufficiency (EPI), diabetes mellitus (DM), and acute necrotizing pancreatitis (ANP), do not generally require histologic examination to either make or confirm the diagnosis. Pancreatic biopsy is useful in the diagnosis of neoplasms of the pancreas and to determine whether pancreatic enlargement is caused by inflammation or neoplasia. Many of the microscopic lesions seen in the pancreas are incidental findings and are not associated with serious clinical problems.

Pancreatic Atrophy

Atrophy of the pancreatic acinar cells can occur as a primary condition[1] or be secondary to chronic inflammation and fibrosis, starvation, or duct obstruction.[2,3]

Primary Pancreatic Acinar Atrophy Associated with Exocrine Pancreatic Insufficiency

Severe atrophy with loss of the majority of the pancreatic acini is an inherited condition in some canine breeds (German Shepherd dog, Rough-Coated Collie, and perhaps English Setter) that is caused by immune-mediated destruction of acinar cells and is associated with EPI.[1] It may occasionally be seen in other breeds. Before the pathogenesis was understood, this lesion was usually only observed in the later stages. Early lesions associated with subclinical disease are characterized by infiltration of lymphocytes, and fewer plasma cells and macrophages, at the border of normal and disorganized atrophic parenchyma and extending into the normal parenchyma. Lymphocytes may also be present within acinar and ductal epithelium and lymphoid follicles may be present. The lymphocytes

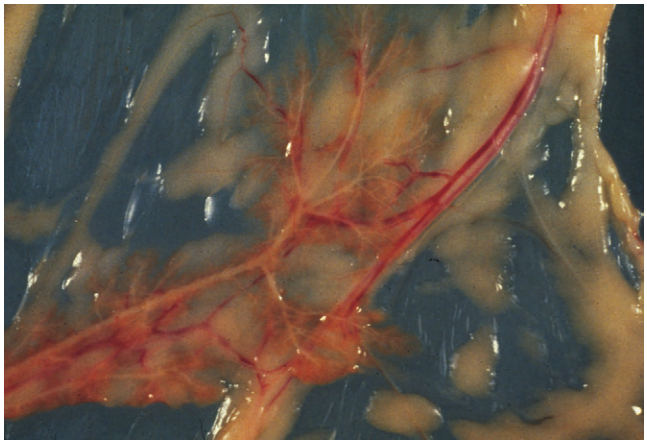

Figure 29-43 Severe pancreatic atrophy (canine); only pancreatic ducts, blood vessels, and adipose tissue remain.

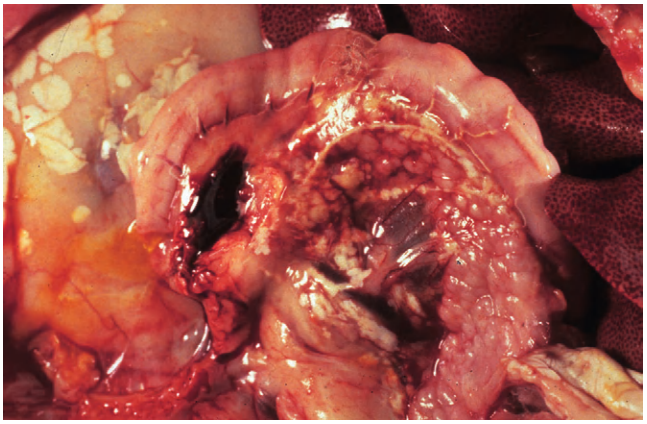

Figure 29-44 Acute pancreatitis (canine) with coagulation necrosis and hemorrhage of the pancreatic parenchyma. Cross-section of pancreas and duodenum (*below*).

are mostly $CD3^+$ T cells with $CD8^+$ cells more common than $CD4^+$ cells. There is multifocal destruction and loss of adjacent pancreatic acinar cells with individual cell necrosis associated with the lymphocytic infiltration. This stage has been called atrophic lymphocytic pancreatitis.

In later stages, dogs develop clinical EPI and have severe atrophy of the exocrine pancreatic tissue. Grossly, often only pancreatic ducts and adipose tissue are seen (Fig. 29-43). Histologically, only ducts, a few disorganized or normal acini, scattered lymphocytes, and islets remain, with extensive replacement of the pancreatic parenchyma by adipose tissue, but there is only limited fibrosis. Islets are usually normal histologically.

Secondary Pancreatic Atrophy

Mild pancreatic acinar atrophy is common in dogs and cats that are anorexic, starved, have specific nutritional deficiencies, or have maldigestion syndromes.[2,3] In these animals there is a generalized decrease in the size of the acinar cells, increased cytoplasmic basophilia, and zymogen granules are decreased. Cytoplasmic vacuoles may be present in acinar cells in some cases and apoptosis may occur in some conditions. Blockage of pancreatic ducts also leads to focal, regional, or diffuse decrease in acinar cell size and zymogen content. Ducts may be blocked by inflammation, fibrosis, or neoplasia. Experimental duct ligation leads to necrosis, duct dilation, acinar atrophy, secondary inflammation, and periductal fibrosis. Subsequently ductular hyperplasia may occur. Chronic pancreatitis may also lead to acinar cell atrophy associated with fibrosis. Rarely, the atrophy is sufficiently severe to lead to EPI.[4]

Pancreatitis

Pancreatitis is a broad term that includes all of the responses to acute and chronic damage to pancreatic acini and ducts associated with inflammation including edema, hemorrhage, necrosis, inflammatory cell infiltration, vascular dilation, and eventual fibrosis and atrophy. These lesions may be focal, multifocal, regional, or diffuse and vary from mild to severe. In the condition that is usually referred to clinically as *acute pancreatitis* or *acute necrotizing pancreatitis*, necrosis is primary and predominates and the lesion is perhaps better termed "acute pancreatic necrosis".[2] Mild to moderate acute and chronic pancreatic inflammation are common and of uncertain clinical significance in the cat[5,6] and dog.[7,8]

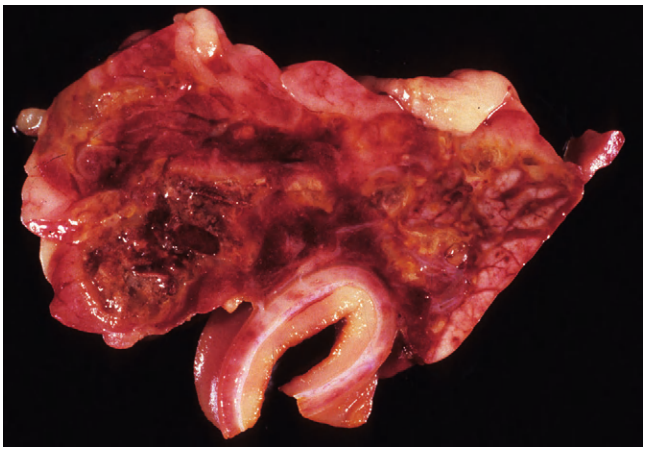

Figure 29-45 Acute pancreatitis (feline) with white plaques of peripancreatic fat necrosis and mineralization (saponification).

Acute Pancreatitis

In acute pancreatitis (acute necrotizing pancreatitis or acute pancreatic necrosis), necrosis usually predominates and is accompanied by varying degrees of inflammation in dogs[2,3,9,10] and cats.[2,3,11,12] Separation of the pancreatic lobes and lobules by edema occurs, and this is associated with early acute injury to the pancreas. Histologically, edema may appear as clear spaces or pale eosinophilic fluid separating cells, lobules, or lobes. Hemorrhage is also associated with acute injury and may be focal, multifocal, or diffuse.

In moderate to severe acute pancreatitis, focal, multifocal, confluent, or diffuse swollen, friable, and yellow-tan to red areas are seen grossly (Fig. 29-44). Multiple white plaques of fat necrosis and mineralization (saponification) in the peripancreatic fat (Fig. 29-45) are commonly associated with acute necrosis and inflammation of the pancreas. Areas of saponification also may be present throughout the abdominal fat and are occasionally seen in the subcutaneous or thoracic adipose tissue. The abdominal cavity may contain a serous to serosanguineous effusion with fat droplets and there may be fibrinous adhesions between the pancreas and the small intestine, colon, mesentery, or omentum. In very severe cases of acute pancreatitis, the adjacent wall of the duodenum may be necrotic and inflamed.

Histologically, in early acute pancreatitis, coagulation necrosis of the pancreatic parenchyma (Fig. 29-46) is often seen peripherally

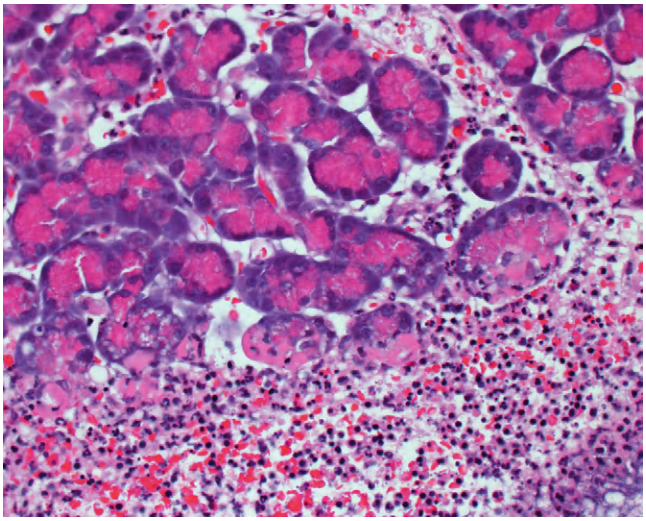

Figure 29-46 Acute pancreatic coagulation necrosis in a dog (*bottom*) showing infiltration of neutrophils and hemorrhage.

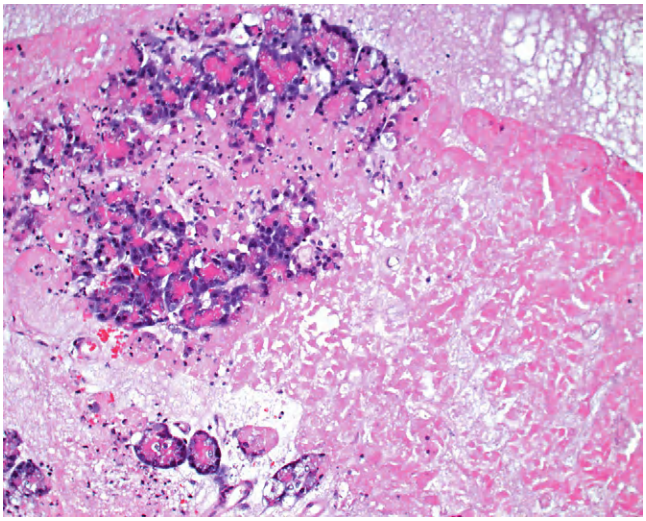

Figure 29-47 Acute coagulation necrosis of all but a few pancreatic acini (canine).

in the lobules in mild disease, but may involve the entire pancreas when severe (Fig. 29-47). Liquefactive necrosis may accompany or follow coagulation necrosis. Necrosis is often accompanied by peripancreatic fat saponification (Figs. 29-48 and 29-49). Infiltrates of neutrophils frequently accompany both pancreatic necrosis and peripancreatic fat necrosis (Figs. 29-48 and 29-49) and exacerbate injury to the pancreas by the release of enzymes. Septa between lobules are usually expanded by hemorrhage, fibrin, neutrophils, and macrophages. There may be local destruction of small blood vessels associated with hemorrhage, and thrombi are common in small veins and arteries in severe disease (Fig. 29-50) leading to further ischemic damage to the pancreas. Thrombi may extend into the portal vein from the pancreas.[13]

Occasionally, in both dogs and cats, neutrophils may predominate in acute pancreatitis without extensive necrosis. They may be seen in the parenchyma, in the interlobular septa, or in the

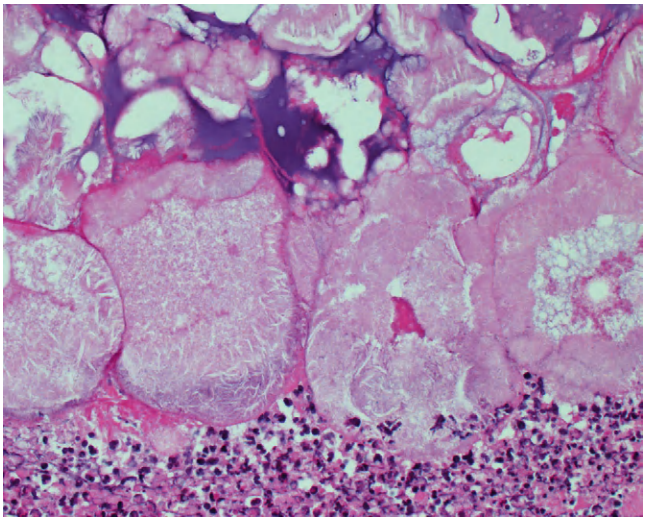

Figure 29-48 Peripancreatic fat necrosis and mineralization (*upper left*) surrounded by inflammatory cells (feline).

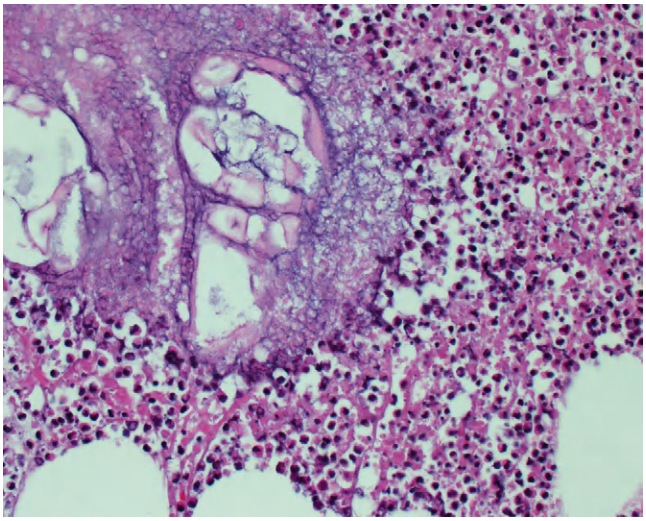

Figure 29-49 Necrotic and mineralized fat (*above*) and viable and necrotic neutrophils (*below*).

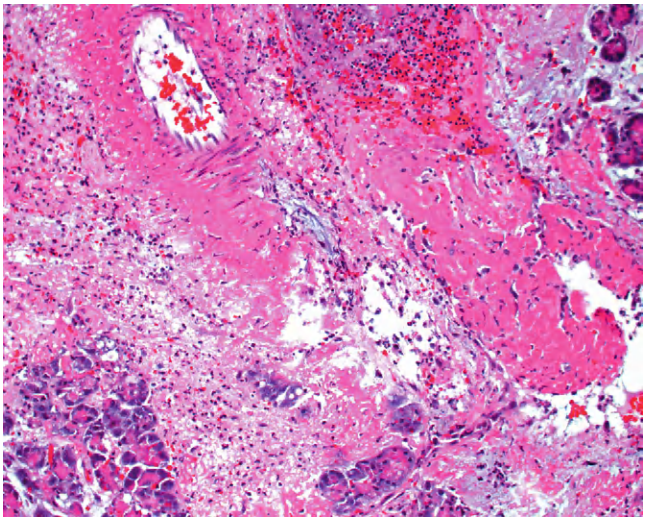

Figure 29-50 Acute pancreatitis with necrosis of arterioles (*upper left*) and venous thrombus (*upper right*).

pancreatic ducts. Suppurative ductal inflammation occurs in young cats,[11] but less commonly in dogs.

Abscesses and/or pseudocysts may occur in acute necrotizing or suppurative pancreatitis and may be found in the pancreas or adjacent to it.[14] These two conditions may be difficult to distinguish clinically and pathologically. Abscesses are localized collections of pus, which consist of neutrophils and necrotic tissue debris, and they are usually sterile. Pseudocysts are focal nonepithelial lined collections of fluid containing pancreatic enzymes, necrotic debris, and, in some cases, red blood cells and inflammatory cells. With time, both may develop peripheral granulation tissue and eventually an outer rim of mature fibrous connective tissue. Measurement of intralesional pancreatic enzymes may be necessary to distinguish abscesses from pseudocysts.[14]

Fibrosis and infiltrates of lymphocytes and plasma cells are seen in some dogs and cats with acute necrotizing pancreatitis, presumably because of previous bouts of necrosis and inflammation.

Acute multifocal pancreatic necrosis with minimal inflammation has been reported in association with canine parvovirus, canine distemper virus, and feline herpesvirus infections.[3] Pancreatic necrosis and inflammation can also be seen with toxoplasmosis and feline infectious peritonitis, although it is rarely clinically relevant. Pancreatic necrosis and inflammation has been produced experimentally in cats and naturally in dogs with zinc toxicity.[3]

Chronic Pancreatitis

Chronic pancreatic inflammation may be the result of acute pancreatitis or be a chronic process not preceded by clinical evidence of an acute injury. Some degree of inflammatory cell infiltration of the pancreas with age is common and of undetermined significance.[5,7,8] The pancreas may be grossly normal or small, firm, irregular, and nodular (Fig. 29-51). Peripancreatic fat saponification, pseudocysts, abscesses, and fibrous adhesions to adjacent abdominal structures may be present. Histologically, there are varying degrees of acinar atrophy and fibrosis (Fig. 29-52) with scattered or clustered lymphocytes and plasma cells (Figs. 29-53 and 29-54) and occasionally macrophages and neutrophils. Hyperplasia of ducts is relatively common in chronic disease and some ducts may be dysplastic. Lesions may be focal, multifocal, or regional, and mild to moderate lesions are common in dogs and cats without obvious clinical pancreatic disease.

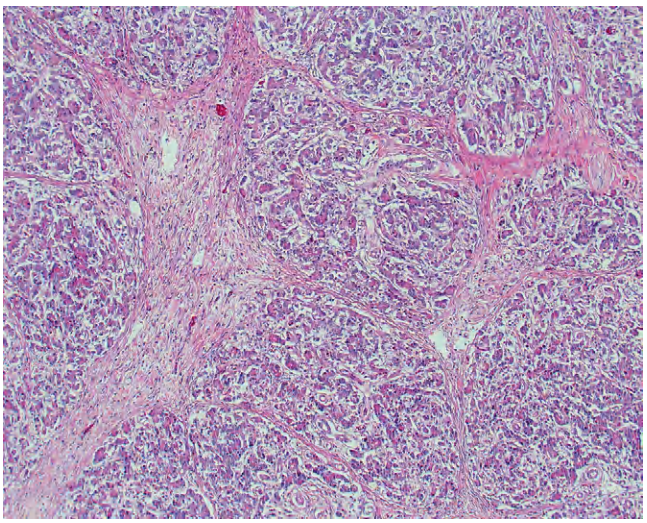

Figure 29-52 Chronic pancreatitis (feline). Atrophic acini are surrounded by variably thick bands of collagen with scattered neutrophils.

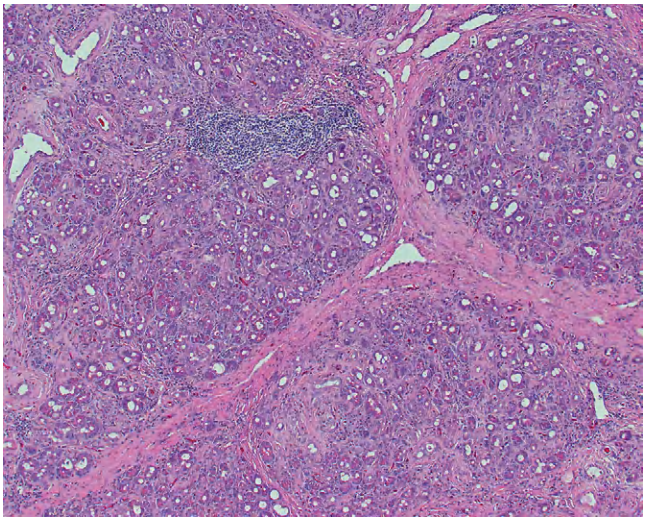

Figure 29-53 Chronic pancreatitis (feline). Atrophic acini with bands of collagen and foci of lymphocytes.

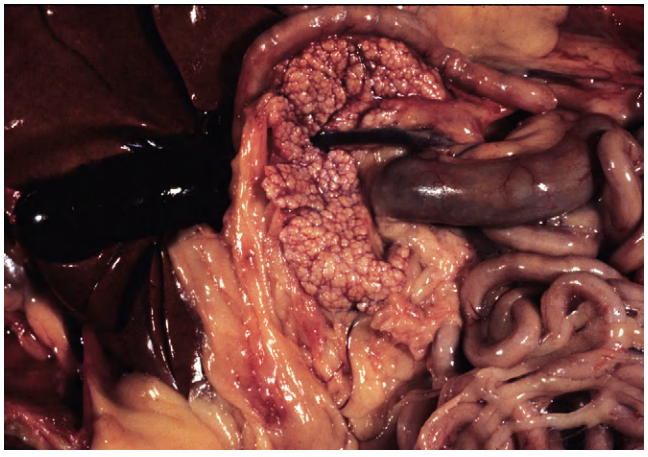

Figure 29-51 Chronic pancreatitis (feline). The pancreas is small firm and nodular.

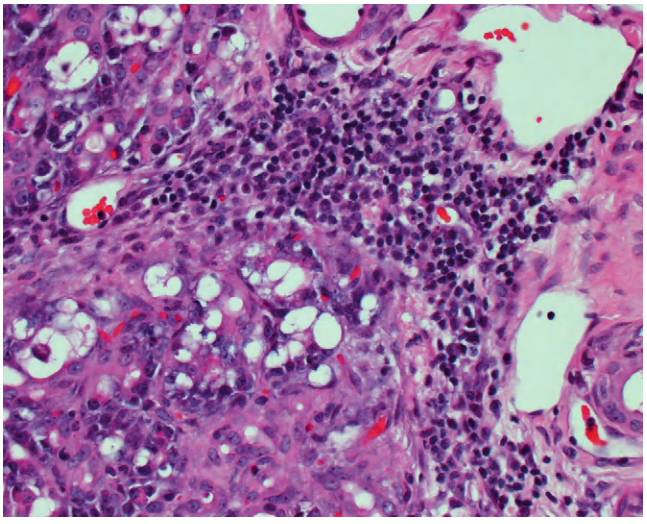

Figure 29-54 Chronic pancreatitis with acinar atrophy, vacuolated acinar cells, fibrosis, and clusters of lymphocytes and plasma cells (feline).

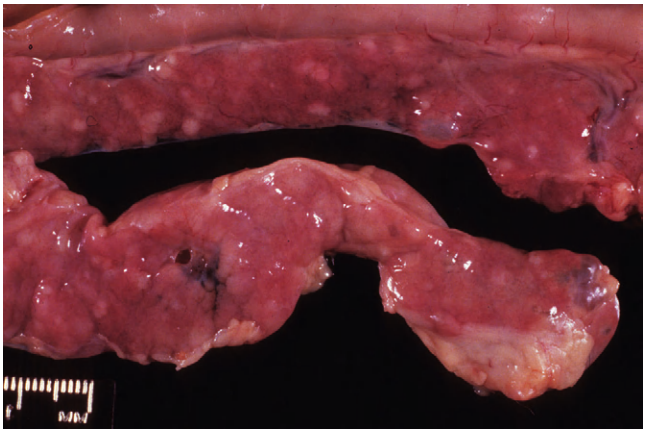

Figure 29-55 Pancreatic nodular hyperplasia (feline). Small, tan nodules of hyperplasia are scattered throughout the pancreas. A focal ductal cyst is also present.

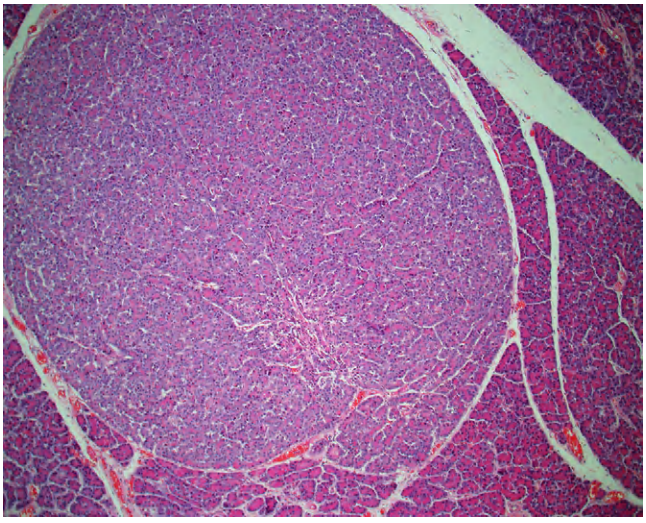

Figure 29-56 Pancreatic nodular hyperplasia (feline). An unencapsulated focal collection of well-differentiated acinar cells.

Incidental Findings and Lesions of Unknown Significance

Ectopic or Accessory Pancreatic Tissue (Pancreatic Choristoma)

Small masses of normal pancreatic acinar tissue are seen rarely in ectopic sites in the abdomen. Common sites are the serosa or muscular wall of the duodenum, mesentery, stomach, spleen, liver, and gallbladder. Islets are not always identified in ectopic pancreatic tissue.

Cysts and Ductal Dilation

Cystic ducts and acini and dilated pancreatic ducts are incidental findings in older dogs and cats. Many of these animals also may have mild to moderate chronic pancreatitis and nodular hyperplasia.

Vacuoles in Acinar Cells

Clear cytoplasmic vacuoles are seen sporadically in acinar cells, particularly in the cat (see Figs. 29-54 and 29-55). Epithelial vacuoles may also be seen in hyperplastic and dysplastic nodules.

Fat Infiltration

In older animals the pancreatic lobules may be surrounded and infiltrated by normal adipose tissue. This is particularly common in overweight animals. Fat infiltration is also common in severe pancreatic atrophy in dogs.

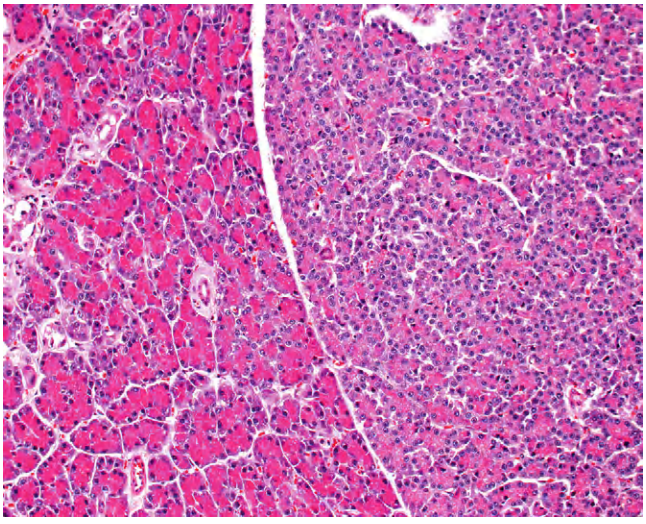

Figure 29-57 Pancreatic nodular hyperplasia (feline). The cells in the nodule (*right*) are more basophilic and contain fewer cytoplasmic zymogen granules.

Hyperplasia and Neoplasia

Nodular Hyperplasia

Small (1- to 10-mm diameter) tan or tan-pink, slightly firm nodules are common in the pancreas of dogs and cats and increase in number and frequency with age (Fig. 29-55). Histologically, even smaller nodules are common. The nodules are usually not encapsulated by fibrous tissue and do not compress the adjacent pancreatic parenchyma (Fig. 29-56). They are usually composed of clusters of well-differentiated cells that form acini and contain variable amounts cytoplasmic zymogen granules (Fig. 29-57). Nodules of less-well-differentiated cells with larger nuclear to cytoplasmic ratios and scant amphophilic cytoplasm containing clear cytoplasmic vacuoles without zymogen granules have been described in cats.[5] Nodules composed of ductular epithelial cells are less common in dogs and cats (Fig. 29-58).

Adenomas

Pancreatic adenomas are rare and are composed of well-differentiated acinar or ductular epithelial cells that are encapsulated and compress the adjacent parenchyma (Fig. 29-59). They are grossly similar to nodules of hyperplasia, and the two lesions may be difficult to distinguish histologically.

Carcinomas

Carcinomas of pancreatic acinar or ductular epithelial origin occur in cats and dogs.[2,3] They are usually firm and tan to pink in color, and may contain yellow-tan areas of necrosis, gritty white areas of mineralization, or red areas of hemorrhage. They are sometimes accompanied by inflammation and necrosis of the adjacent pancreas and by necrosis and mineralization of peripancreatic fat, which can

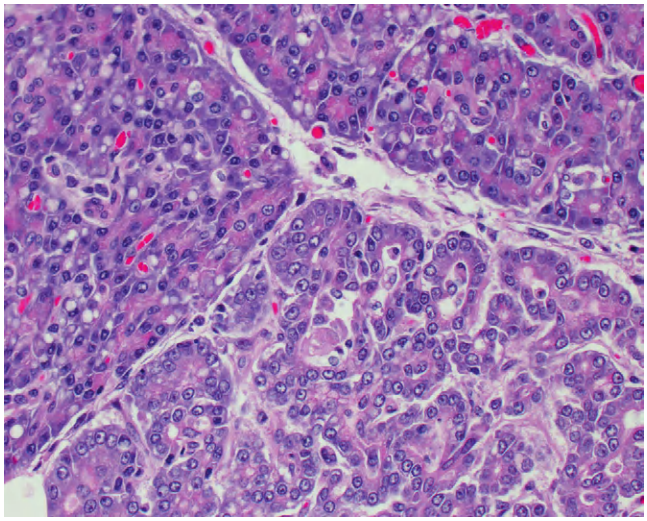

Figure 29-58 Pancreatic nodular hyperplasia (feline). Nodule of ductular origin (*lower right*). Some normal acinar cells contain cytoplasmic vacuoles.

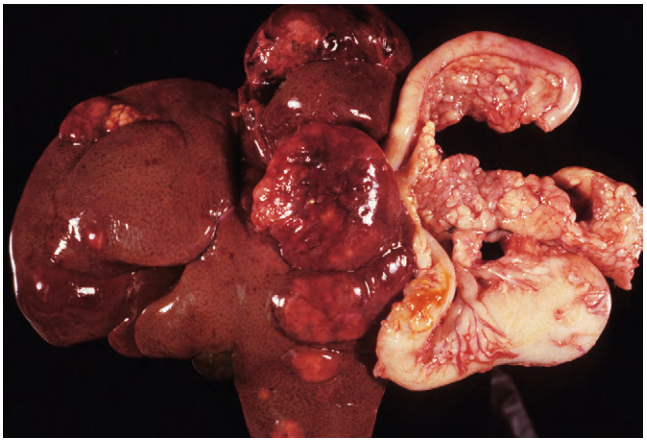

Figure 29-60 Pancreatic carcinoma (*lower right*) with multiple liver metastases.

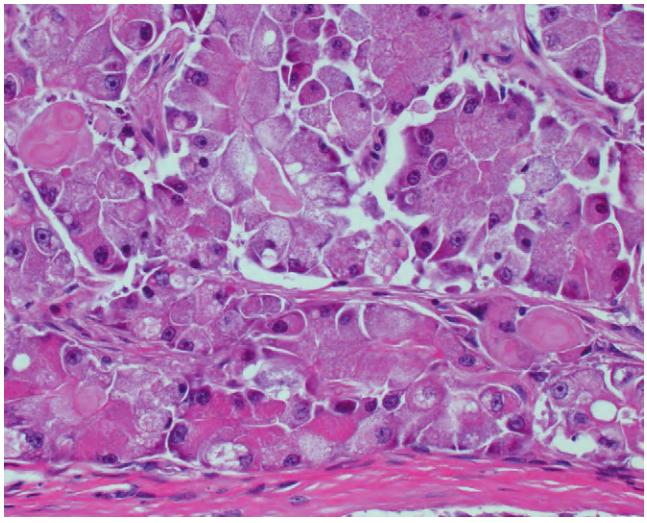

Figure 29-59 Pancreatic acinar adenoma composed of well-differentiated acini bordered by a fibrous capsule (*bottom*).

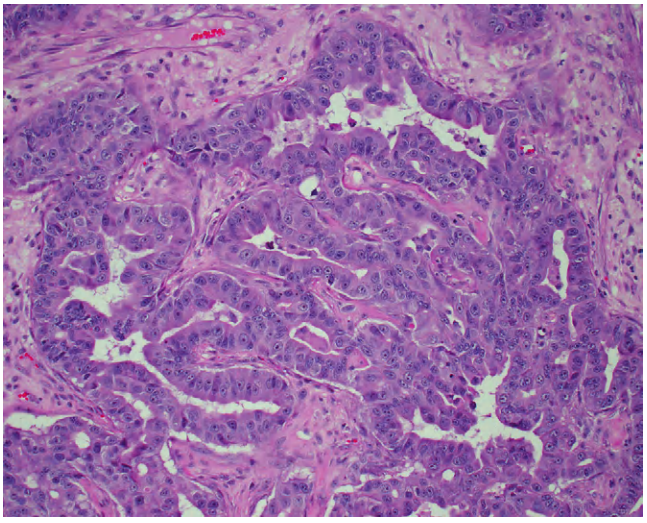

Figure 29-61 Pancreatic ductal carcinoma (feline).

mask the neoplasm, grossly. Carcinomas may present as a single nodule or coalescing nodules that may extend into the adjacent mesentery or invade the duodenum or liver (Fig. 29-60). The cells form ducts, tubules, or acini or have a solid pattern. The neoplastic cells exhibit a broad range of morphologies, from relatively well-differentiated acinar or ductular cells (Fig. 29-61) to poorly differentiated anaplastic polygonal cells with large nuclear-to-cytoplasmic ratios, scant amphophilic to basophilic cytoplasm, and numerous mitotic figures. In anaplastic tumors it may not be possible to determine if the tumor is of exocrine or endocrine (islet) origin by routine light microscopy. Islet cell tumors may be positive for insulin, glucagon, or somatostatin and are usually positive for chromogranin by immunohistochemistry. Carcinomas may spread into the adjacent duodenum, stomach, and liver, and also spread throughout the abdomen (carcinomatosis). Pancreatic carcinomas frequently elicit a desmoplastic response with cells surrounded by fibroblasts and collagen (Fig. 29-62). In poorly differentiated tumors that have spread into adjacent organs, it may be difficult to determine whether

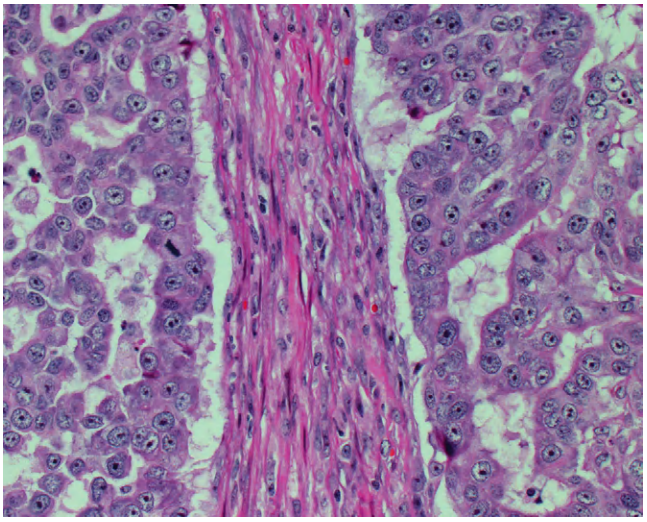

Figure 29-62 Pancreatic ductal carcinoma with desmoplasia (feline).

the carcinoma is of pancreatic, biliary, gastric, or intestinal origin by light microscopy.

Other Primary Neoplasms

Nonepithelial primary tumors of the pancreas are rare and include fibromas, fibrosarcomas, liposarcomas, and nerve sheath tumors.[3]

Metastatic Neoplasms

Metastatic neoplasms that may involve the pancreas include hemangiosarcoma, lymphoma, malignant melanoma, a variety of carcinomas, and osteosarcomas.[3,18]

HEPATOBILIARY

John M. Cullen

Normal Liver Histology

Abnormal histology of the liver can be best appreciated when the normal histologic appearance is well understood. There are a number of models that describe the structural unit of the liver.[1,2] In this section, the standard lobule is used as the structural unit of the liver. The liver is a three-dimensional structure and can be envisioned as a tightly packed cluster of grapes with each grape representing a lobule. From the two-dimensional microscopic perspective the "typical" lobule is outlined by a hexagon of portal tracts about 1 mm in diameter with a central vein (terminal hepatic venule) at its center, although some lobules form imperfect hexagons (Fig. 29-63). Portal tracts usually contain a branch of the portal vein and one or two branches of the hepatic artery, as well as a bile duct. In addition, the portal tract contains abundant connective tissue as well as lymphatics and nerves. However, there is normal variation in the number of bile ducts and hepatic artery branches. Usually, the portal vein profile is larger than the surface area of the bile ducts and the hepatic arteries. There is a distinct border between the portal tract connective tissue and the initial surrounding row of hepatocytes, termed the *limiting plate*. Between the portal tract and the central vein the hepatocytes are arranged in radial plates that are one or occasionally two cells thick. Normal hepatocytes have abundant cytoplasm that is more than three to four times the surface area of nucleus and the cytoplasm may be vacuolated to various extents. Frequently, there is a mild to moderate coarse, irregular, clear vacuolation caused by the presence of stored glycogen. Hepatocytes may vary in size in response to systemic or localized factors. Blood oxygen is highest in the periportal regions of the lobule where blood from the portal veins enters the sinusoids and lowest in the centrilobular areas. Centrilobular hepatocytes may become smaller than normal when blood oxygen levels become too low (e.g., during anemia or chronic congestion) or hepatocyte oxygen demands increase (e.g., during heat stroke). Centrilobular hepatocytes may become enlarged where there is induction of drug metabolizing enzymes as these enzymes are in the highest concentration in these hepatocytes. In older cats, the centrilobular hepatocytes often contain brown granular lipofuscin pigment. Mitotic activity of hepatocytes is rarely seen in the normal liver.

Hepatic plates are separated by vascular sinusoids formed by specialized endothelial cells, evident only by their flattened nuclei along the sinusoid, and characterized by fenestrations that are evident only at the ultrastructural level. The relationship between hepatocytes and sinusoids is viewed two-dimensionally under the microscope, but is ideally envisioned in three dimensions. The portal tracts can be viewed as tree trunks and the finest branches of the distributing portal veins and the hepatic arterioles as branches that extend into the hepatic parenchyma where they open into the sinusoids. These small caliber vessels can occasionally been detected histologically. There are no divisions between normal lobules and there is ready flow of blood between them.

The sinusoids also contain Kupffer cells, actively phagocytic cells that sit on the endothelial cells within the flow of sinusoidal blood. The number and size of these cells can vary with systemic and local inflammation or other stimuli, but they are usually evident histologically due to their abundant cytoplasm. Hepatic stellate cells reside between the hepatocytes and the endothelial cells, in the space of Disse. In normal circumstances these cells can be identified histologically, because they contain lipid vacuoles with stored retinoids. They are usually more prominent in cats than in dogs. It is important to "census" the normal structures as the initial step in the slide review process because the absence of a normal structure can be clinically significant. Pathologists are trained to search for abnormalities, but may overlook the absence of a normal structure, and consequently a diagnosis, if a consistent search pattern is not used during the examination.

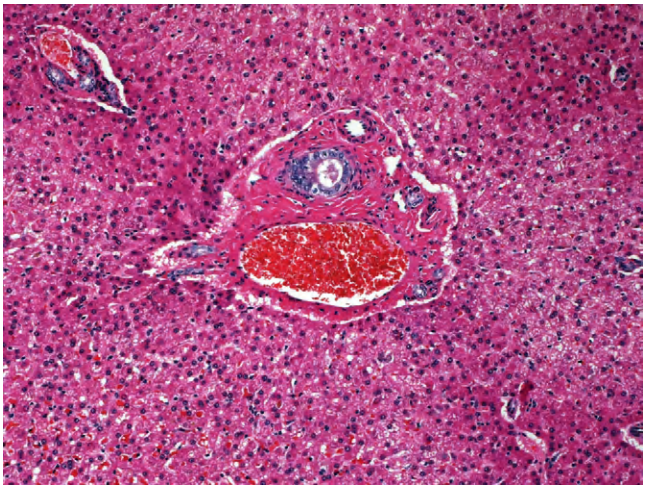

Figure 29-63 The normal portal tract contains a portal vein, hepatic artery, and bile duct gathered within a connective tissue sleeve that is bordered by a uniform row of hepatocytes, termed the *limiting plate*.

Gross Assessment of Liver Pathology

Gross examination of the liver may take place during laparotomy or postmortem examination. Table 29-3 summarizes the main gross pathologic changes and possible diagnoses. These disorders are described in detail in the following sections.

Optimal Liver Biopsy Collection

Consultation with the pathologist is often a useful first step in the biopsy procedure; particularly when there is a clinical indication for special handling of the specimen. The optimal size of the biopsy is determined by balancing the need for sufficient tissue to enable diagnosis and the clinician's concern for the patient. Disorders with diffuse and uniform appearance require the least amount of tissue to make a diagnosis. Other disorders, particularly chronic inflammation, can vary from lobe to lobe and even within a lobe and require multiple sections for accurate assessment of the

Table 29-3 A Gross Morphologic Approach to Liver Pathology

Gross Appearance	Possible Diagnoses
Uniformly small liver	Vascular anomaly Starvation Massive necrosis
Uniformly small, firm liver	Lobular dissecting hepatitis
Uniformly small liver with nodules	End-stage fibrosis with nodular regeneration (cirrhosis)
Uniformly enlarged liver	Infiltrative disease Round cell neoplasia Lymphoma Myeloid neoplasia Enlarged hepatocytes Glycogen Steatosis (lipid) Storage diseases Expanded sinusoids Acute congestion Amyloid Acute congestion Amyloid Expanded hepatocytes Lipid Glycogen storage products Expanded sinusoids Acute congestion Round cell tumor Expanded hepatocytes Lipid Glycogen storage Expanded sinusoids Acute congestion Amyloid
Normal-size liver: altered color	Anemia Bile retention Iron/hemosiderin Chronic passive congestion Hemochromatosis Copper Hemosiderin-CPC Copper bile
Normal-size liver: foci	Small white foci ~1 mm Gout/septicemia/viral Larger white/red foci Focal necrosis/acute toxicity Focal inflammation Granulomas Abscesses Metastasis Biliary hyperplasia Congenital biliary anomalies Focal inflammation Granulomas, abscesses Metastasis/biliary hyperplasia Biliary anomalies
Single lobe affected	Torsion other vascular accidents Portal streaming of toxic insult? Portal streaming/toxicity?
Nodular liver	Single nodule Nodular hyperplasia Biliary cysts Hepatic or biliary adenomas Primary carcinomas Multiple nodules Regenerative nodules/end-stage liver Nodular hyperplasia (dogs) Metastasis

health of the liver. Wedge biopsies provide a more accurate view of most liver disorders than needle biopsies,[3] but it is disappointing, at the least, for the pathologist to receive a single wedge of liver after the patient has undergone a laparotomy. Despite the apparent normality of liver at surgery, histologic evaluation is frequently useful. Multiple small wedges from several lobes are preferred over a larger section from a single lobe. Needle biopsies can be sufficient for many approaches, but multiple biopsies from more than one liver lobe are desired. In any event, properly collected and handled tissue is essential for optimal microscopic evaluation. Once collected, the liver tissue should be handled as little as possible to avoid physical distortion or loss of tissue. This is particularly true of needle biopsies. Small or fragmented biopsies can be placed into embedding bags or plastic cassettes with a screen mesh. In most circumstances, the tissue should be placed immediately into 10% neutral buffered formalin. Tissue should not be more than 0.5 to 1 cm at its greatest thickness and the ratio of formalin to tissue should be 10:1. If immunohistochemistry (IHC) is to be performed, the tissue should be processed within 48 hours to avoid overfixation.

If electron microscopy is required, sections should be cut with a scalpel into 1-mm pieces and then placed into an appropriate fixative such as Trump's. Electron microscopy can be useful in certain storage disorders, mitochondrial abnormalities or infectious diseases. Frozen sections are required for certain antibodies applied in IHC, particularly those used to identify various tumor cell types, as formalin fixation can destroy relevant antigens. Frozen sections can also be used for microbiology, genetic studies, and some special stains (e.g., lipid stains) more effectively than formalin-fixed samples. Frozen sections are also useful for evaluations of hepatic metals such as iron and copper. Formalin-fixed liver is also suitable for this purpose if the sample is sufficiently large (i.e., bigger than a needle biopsy)[4] and, in cases of storage disorders, analysis of stored material may be possible.

Liver biopsies are stained routinely with hematoxylin and eosin (H&E), but evaluation is often enhanced by a battery of special stains. Some pathologists advise that a particular set of stains is done on all samples as part of the routine evaluation, but this step varies with pathologists and financial constraints. Table 29-4 lists histochemical stains and their targets.

Table 29-4 Selected Special Stains Used in Diagnostic Histopathology of the Liver

Material Stained	Stain Name(s)	Stain Appearance
Amyloid	Congo red	Green under polarized light
Glycogen	Periodic acid-Schiff (PAS)	Purple (removed with diastase treatment)
Lipid	Osmium	Black
	Oil red O	Red
Connective tissue/ collagen	Sirius red	Deep red
	Masson's trichrome	Blue
Reticulin	Reticulin stain (Gordon and Sweet)	Black
Iron	Perl's Prussian blue	Deep blue
Copper	Rhodanine	Orange brown
Lipofuscin	Schmorl	Blue-green
	PAS (diastase resistant)	Magenta
	Acid-fast	Red

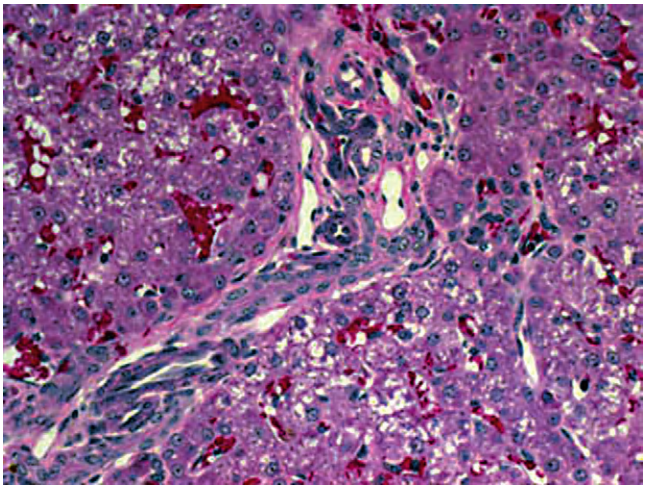

Figure 29-64 Portal tracts lack a normal portal vein profile and contain an increased number of small-caliber arterioles in cases of portosystemic shunts, as well as other conditions that lead to hypoperfusion of the liver via the portal vein. Lymphatics may also be dilated.

Circulatory Disorders

Congenital Vascular Anomalies

Normal liver function is dependent on a close interrelationship between hepatocytes and blood from the portal vein. Congenital abnormalities that lead to inadequate portal vein flow into the liver are manifested grossly as microhepatica, because of reduction in the size of hepatocytes and smaller lobules. Loss of sufficient nutrition, growth factors, and oxygen all contribute to the abnormalities of the hepatocytes. In addition to congenital vascular anomalies, starvation and anemia are should be considered when the liver is smaller than normal.

Congenital Portosystemic Shunts

A congenital portosystemic shunt is an abnormal vascular channel that allows a portion of the blood within the portal venous system to bypass the liver and to drain into the systemic circulation. Shunts occur most commonly in the dog, but are also described in cats.[5] A congenital shunt can be either intra- or extrahepatic in location, but is almost always limited to a single vessel.[5] Extrahepatic congenital shunts can occur between a variety of sites within the portal drainage and the systemic venous system. Extrahepatic shunts occur more often in small breeds of dog. Typically, intrahepatic portosystemic shunts involve failure of closure of the fetal ductus venosus at birth. These shunts, like the ductus venosus, are most often located in the left side of the liver. This anomaly occurs most often in large breed dogs. Regardless of the site of the shunt, affected animals are typically stunted and frequently develop signs of hepatic encephalopathy. The liver is small and microscopically displays hepatocellular and lobular atrophy.[5] There is an increase in the profiles of hepatic arterioles within the portal areas, presumed to relate to a compensatory increase in systemic arterial blood flow, in response to the inadequate portal flow. There is also sometimes a proliferation of small caliber bile ducts. Portal vein profiles are smaller than normal or absent (Fig. 29-64). Changes in the central and sublobular veins are often overlooked or misinterpreted. Dogs have a spiral smooth muscle surrounding the hepatic veins that can contract to restrict blood flow from the liver. This muscle constricts in response to various pharmacologic agents and presumably in shock. In some instances, dogs with hypoperfusion of the portal vein, regardless of the cause, have constricted smooth muscle, leading to a small-caliber hepatic vein with prominent smooth muscle (Fig. 29-65). This change has been misinterpreted as "arterialization" of hepatic veins. Surrounding lymphatics are also often distended. Variable numbers of lipogranulomas, collections of vacuolated and pigmented macrophages, can be found in the parenchyma or within the portal areas. Portal vein pressure is normal in congenital shunts and ascites does not occur. At postmortem examination abnormal vascular anastomoses are often difficult to identify without the benefit of antemortem imaging studies to localize the shunting vessel. The histologic appearance of congenital portosystemic shunts and other vascular anomalies of the liver have considerable overlap as the liver has a stereotypical response to inadequate portal perfusion. Clinical data, such as the presence or absence of shunt vessels and the determination of portal vein pressure, may be needed to achieve a final diagnosis.

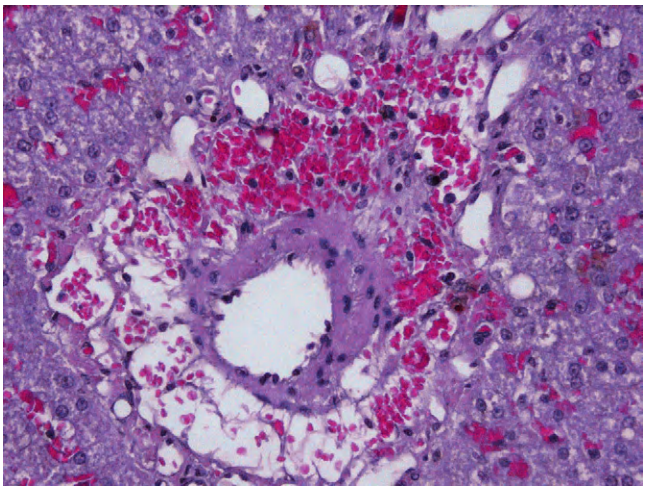

Figure 29-65 The spiral smooth muscle that surrounds sublobular veins can contract in cases of hepatic hypoperfusion, among other causes, increasing the prominence of the muscle, which can resemble an artery.

Disorders Associated with Portal Hypertension

Portal Vein Hypoplasia (Microvascular Dysplasia, Noncirrhotic Portal Hypertension)

Portal vein hypoplasia is a congenital vascular anomaly that occurs in dogs and occasionally in cats that is characterized by abnormally small extrahepatic or intrahepatic portal veins, diminished hepatic perfusion by portal vein blood flow and the potential for portal hypertension.[5] There is considerable discussion surrounding the preferred terminology for this condition and there are several synonyms associated with this condition.[6] Recently, the term *portal vein hypoplasia* has been recommended to identify this condition.[7] Typically, affected animals have small livers, and the microscopic changes include portal vein hypoperfusion, small or absent portal veins, proliferation of hepatic arterioles, and hepatocyte atrophy. Lipogranulomas, constricted hepatic veins, and distended perivascular lymphatics may also be present. This disorder resembles portosystemic shunting histologically, but affected animals often have portal hypertension and resultant ascites. Portal fibrosis and biliary hyperplasia occur in about half of the cases. Because of the histologic similarities between portal vein hypoplasia and congenital portosystemic shunts, clinical procedures (e.g., imaging to determine the presence of a shunt vessel) are often required to make a final diagnosis.

Intrahepatic Arteriovenous Fistulas

Intrahepatic arteriovenous fistulas arise from a direct communication between the hepatic artery and the portal vein and occur in dogs and cats. The size of the vessels involved affects the degree of injury. Arteriovenous fistulas may be single or multiple and occur anywhere within the liver. Affected portions of the liver contain dilated, tortuous, pulsating vessels.[8] Several histologic abnormalities are present in the hepatic artery branches, including partial elastosis, intimal hyperplasia, and smooth muscle hyperplasia with areas of degeneration and scattered disorganized elastin fibers and areas of degeneration (Fig. 29-66). Portal vein branch abnormalities include prominent dilation, with abnormal, thickened walls. The liver adjacent to the fistula has the typical appearance of portal hypoperfusion. Arterial shunting of blood may lead to portal hypertension or reversal of the direction of portal blood flow, and subsequent development of acquired portocaval shunts and ascites.

Portal Vein Obstruction

Obstruction of the portal vein may occur by thrombosis or by compression from local inflammation (e.g., acute pancreatitis or abscess formation) or neoplastic processes that surround the vein. In the affected livers, the portal vein profiles may be reduced in diameter as a consequence of restricted flow, or may contain thrombi or emboli. Depending on the cause of the obstruction, tumor emboli or inflammatory aggregates may also be found in portal vein branches.

Impaired Hepatic Perfusion

Ischemia

Reduced blood flow to the liver leads to hepatocyte atrophy or necrosis. The rate and magnitude of blood flow or oxygen content determines the balance between necrosis and atrophy. Hepatocytes are resilient and only sudden drops in perfusion lead to acute necrosis. Acute necrosis is evident first in the centrilobular areas, as the oxygen-rich blood enters at the periportal region and progressively loses its oxygen as it travels along the sinusoid toward the central vein. Sudden loss of perfusion from shock, ruptured chordae tendineae, or hemolysis can produce generalized centrilobular necrosis (Fig. 29-67). This lesion is histologically very similar to acute hepatotoxicity and clinical data are often needed to clarify the pathogenesis. Random foci of ischemic necrosis are more likely attributed to localized disruption of blood flow, which can follow fibrin deposition within sinusoids during DIC.

Infarction of the liver is uncommon because of its dual blood supply from the hepatic artery and the portal vein. Infarcts most often occur at the distal edges of the lobes where the perfusion fields dwindle. Affected areas are sharply delineated and dark red or pale. Histologically, coagulative necrosis of hepatocytes is evident.

Disturbances of Outflow

The most common cause of impaired outflow of blood from the liver is posthepatic and occurs in chronic passive congestion of the liver caused by cardiac disease. Histologically there is distention of

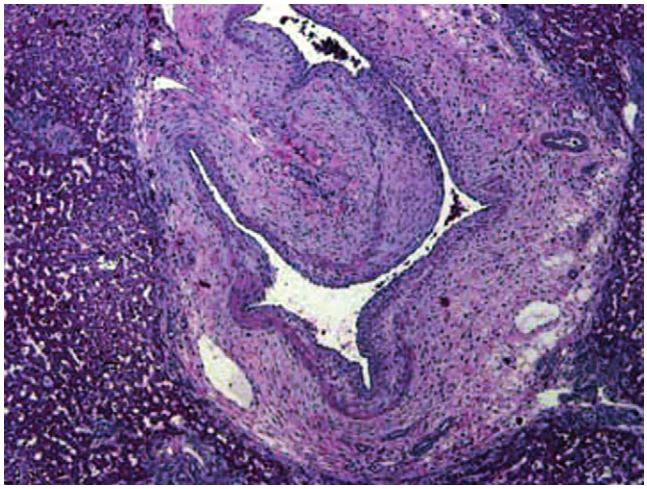

Figure 29-66 A hallmark of intrahepatic arteriovenous fistulas is the presence of a large distended vein with an altered wall formed in response to the increased and abnormal blood flow.

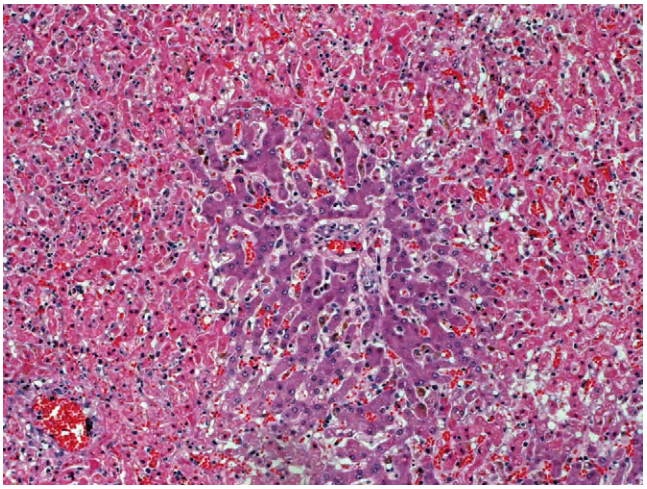

Figure 29-67 Acute centrilobular necrosis can occur in cases of sudden significant loss of oxygen delivery to the liver from acute anemia, blood loss, or cardiac decompensation.

hepatic veins, atrophy of centrilobular hepatocytes, and an abundance of hemosiderin within Kupffer cells. With chronicity, fibrosis emanating from the central veins can become prominent. Intrahepatic causes of outflow disorders are uncommon in cats and dogs.

Incidental Vascular Disorders

Peliosis Hepatis

Peliosis hepatis is defined as a random distribution of blood-filled cystic spaces in the hepatic parenchyma (Fig. 29-68). Grossly, these areas appear as variably sized dark blue-black foci within the liver that vary from pinpoint to several centimeters in size. Peliosis hepatis occurs in older cats and occasionally in dogs. Peliosis hepatis can be mistaken for a vascular tumor (e.g., hemangioma, hemangiosarcoma).

Biliary Disorders

Congenital Biliary Cystic Disease

Solitary Biliary Cysts

Solitary biliary cysts are uncommon in dogs and cats. They are thin walled and contain pale fluid. Histologically, the cysts are lined with a flattened single layer of biliary epithelium. It is not known if they are an acquired or a congenital disorder.

Congenital Cysts

Congenital biliary cystic diseases are a complex and potentially confusing collection of conditions of dogs and cats. In general they can all be attributed to abnormal development of the primordial biliary ductular system. The biliary tree arises from the ductal plate, an embryonic structure consisting of a two-cell-thick sheath of hepatoblasts that surround the primitive portal tract. Some cells in the ductal plate mature into the bile duct system, whereas others undergo apoptosis. Disturbances in development of this cell population give rise to a variety of biliary developmental abnormalities. Congenital biliary cystic disease is characterized by dilation of portions of the biliary tree and associated fibrosis. Similar lesions are frequently found in the renal tubules as well. Although the pattern of lesions and inheritance in domestic animals is not as clearly separated as it is in man, the WSAVA Liver Study Group[7] has proposed the following classification for congenital lesions of the biliary tree:

1. Congenital dilation of the large and segmental bile ducts (similar to Caroli disease)
2. Juvenile polycystic disease/congenital hepatic fibrosis
3. Adult polycystic disease (including von Meyenburg complexes)

Caroli Disease

Caroli disease is thought to be caused by an early defect in the formation of the bile duct system, affecting the larger-caliber bile ducts. In man, the disorder is characterized by saccular dilations of the larger intralobular, lobar, or common bile ducts, and cystic renal lesions may occur concurrently. Affected dogs have similar lesions, although the common bile duct was not abnormal.[9] Involved bile ducts often contain inspissated mucus, bile, and mineralized concretions. Histologically, the cystic bile ducts are lined by columnar epithelium and the portal tracts are fibrotic with bridging between portal tracts and proliferation of bile ducts within the areas of fibrosis. Acquired shunts may develop in affected dogs because of the extensive hepatic fibrosis.

Juvenile Polycystic Disease/Congenital Hepatic Fibrosis

Juvenile polycystic disease/congenital hepatic fibrosis can occur in dogs and cats.[10] This disorder is characterized primarily by microscopic abnormalities of the bile ducts. Typically there is formation of prominent portal-to-portal bridging fibrotic tracts within which there are abnormal, often irregular, mildly dilated biliary ducts (Fig. 29-69). The abnormal ducts are typically tortuous and may have small papillary projections into their lumina. Portal vein profiles may be reduced in area or absent, and arteriolar proliferation may be present. Portal vein hypertension can occur. Typically, this condition is recognized early in life, particularly when portal hypertension arises, but in other cases congenital hepatic fibrosis is only an incidental finding at postmortem.

Adult Polycystic Disease

In adult polycystic disease, the liver contains multiple unilocular or multilocular biliary cysts containing clear fluid that range from a few millimeters to several centimeters in diameter (Fig. 29-70).

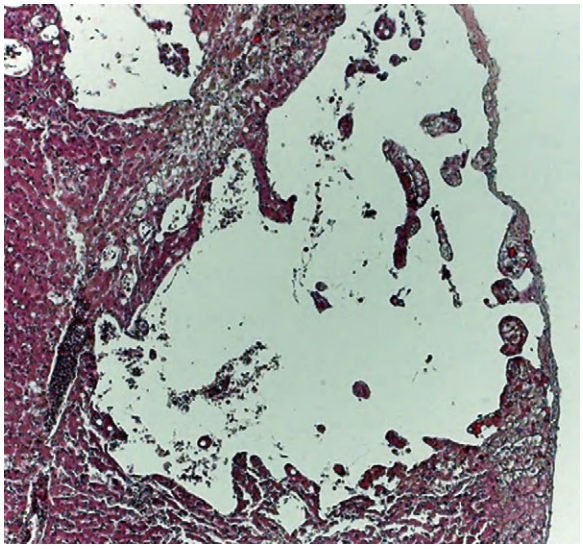

Figure 29-68 Peliosis hepatis is identified as a distended vascular space, usually a few millimeters in diameter, which may be lined by endothelium.

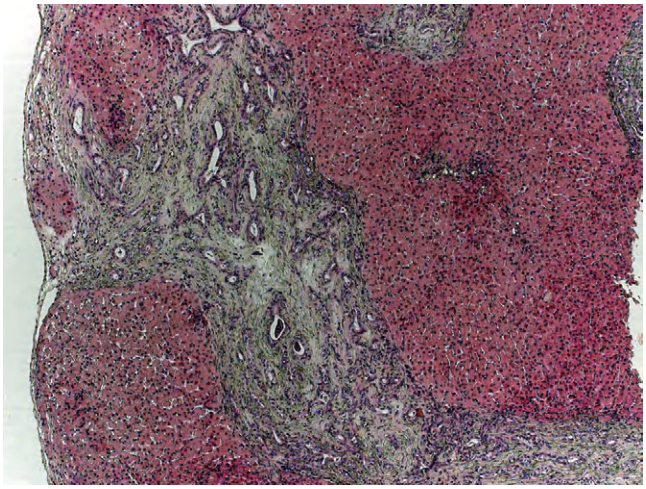

Figure 29-69 Congenital hepatic fibrosis in dogs or cats is characterized by portal-to-portal bridging fibrous bands of connective tissue that contain abundant, often abnormal, biliary ducts.

Hepatocytes are usually compressed at the margins of the cysts, or may, on occasion, be entrapped by expanding cysts. The stroma of the cyst wall consists of fibrovascular tissue with moderate amounts of collagen. Cysts are lined by normal biliary epithelium that may be simple cuboidal to flattened (Fig. 29-71). Another feature of affected livers is the presence of von Meyenburg complexes: discrete, usually subcapsular, fibrotic areas with small caliber bile ducts that typically have an irregular outline. They are usually smaller than a lobule. It is believed that some forms of this disorder have epithelial cells with a secretory phenotype and the production of fluid over time leads to the large cysts, while other forms do not secrete fluid and remain as the smaller von Meyenburg cysts. This would explain why cysts are not found in neonates despite the congenital nature of the disorders.

The well-known biliary and renal cystic disorder of Persian cats does not have a phenotype that allows consistent classification. Affected cats with renal cysts may develop biliary lesions typical of either juvenile polycystic disease or adult polycystic disease or a combination of the two. Other breeds of cats can develop congenital hepatic fibrosis and cysts; this may also occur in dogs.

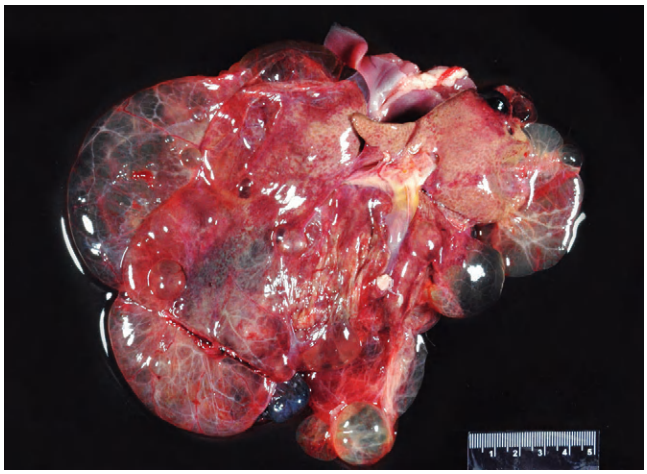

Figure 29-70 Polycystic biliary disease produces multiple cysts throughout the parenchyma of the liver. They are usually filled with clear to straw-colored fluid.

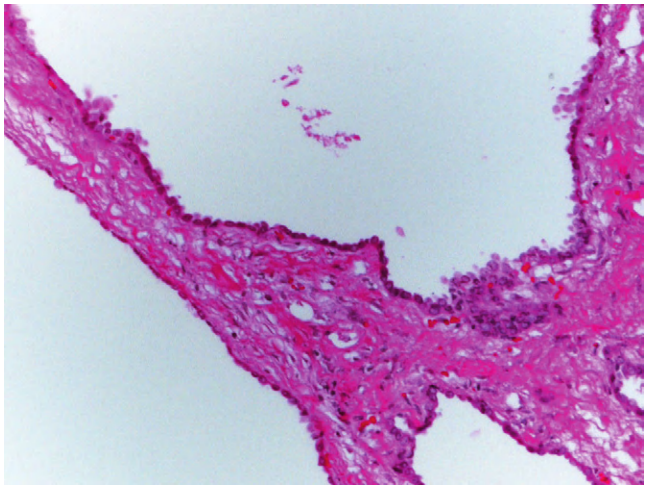

Figure 29-71 Congenital biliary cysts are lined by a single layer of cuboidal to flattened biliary epithelium.

Debate continues regarding the nature of multicystic biliary lesions in the canine liver. It is likely that the majority of these lesions are congenital ductal plate disorders, rather than neoplasms. Multicystic lesions in the kidney are recognized as congenital disorders and the multicystic biliary lesions found in dogs with simultaneous renal cystic disorders are similar to lesions previously diagnosed as biliary adenomas.

Cholestasis

Impaired bile flow accompanied by the accumulation in the blood of components normally secreted in the bile (e.g., bile acids, conjugated bilirubin, cholesterol) is termed *cholestasis*.[11] Cholestasis is characterized microscopically by the presence of bile in the hepatic parenchyma recognized as bile plugs in the canaliculi, phagocytosed bile in Kupffer cells or other macrophages, and, on occasion, as bile granules in the cytoplasm of hepatocytes. Cholestasis is easily recognized in cytologic preparations and frozen sections, but detectable bile is often reduced in the paraffin wax embedding procedure. Bile detection can be enhanced by using special stains (e.g., Hall's stain). In dogs, bile is rarely apparent histologically in hepatocellular cytoplasm.

Intrahepatic Cholestasis

Intrahepatic cholestasis is associated with a wide spectrum of liver diseases. In general, microscopic lesions apart from the cholestasis are related to the primary hepatic disease, but cholestasis may be the only histologic abnormality.[12] In acute cases, bile plugs in canaliculi and Kupffer cells may be evident, but this change is not specific for intrahepatic cholestasis (Fig. 29-72). Over time, bile plugs are less evident in canaliculi, but bile may be present somewhat longer in Kupffer cells.

Extrahepatic Cholestasis

Extrahepatic cholestasis can be associated with extraluminal compression of cystic or common bile ducts by tumors or local inflammatory processes. Intraluminal obstruction can arise from a variety of agents including choleliths, intraluminal neoplasia, parasites, or mucus plugs from gallbladder mucoceles. Regardless of the mechanism, the result is stasis of bile and dilation of the bile ducts proximal to the obstruction.

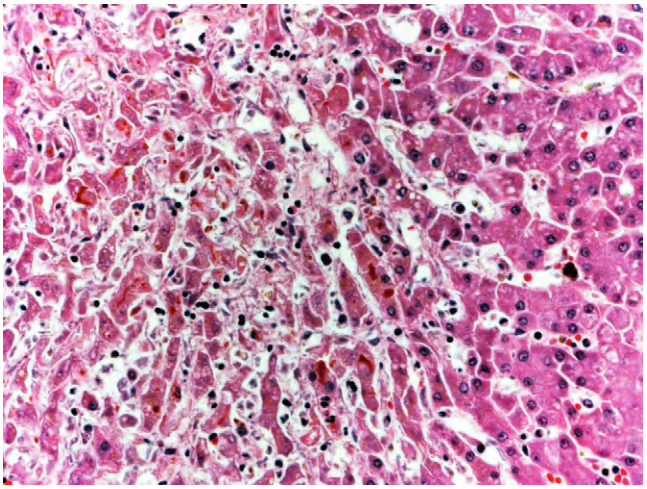

Figure 29-72 Acute intrahepatic cholestasis is characterized by the presence of bile plugs in the canaliculi that lie between adjacent hepatocytes.

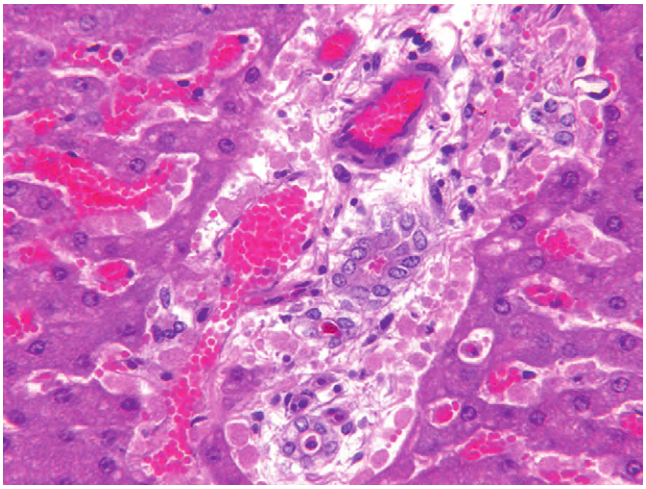

Figure 29-73 Acute extrahepatic cholestasis is characterized by portal tract edema, a light infiltrate of inflammatory cells, usually including neutrophils and degeneration or necrosis of biliary epithelium.

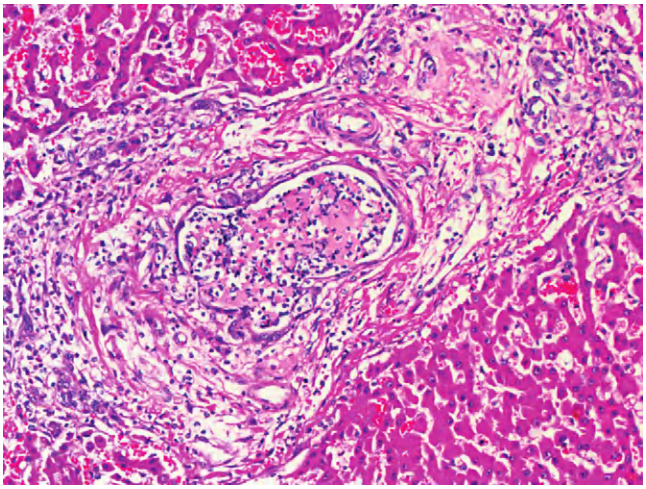

Figure 29-74 Neutrophilic cholangitis is characterized by the presence of degenerate or necrotic neutrophils within the lumen or within the wall of affected bile ducts.

The characteristic microscopic lesions of acute extrahepatic cholestasis in the dog are portal tract edema and infiltration of neutrophils around the interlobular bile ducts (Fig. 29-73). Biliary epithelium may be degenerate or necrotic, but more often the epithelium has a reactive morphology with variable cell swelling and mild basophilia creating a somewhat disorganized appearance. In acute cases, centrilobular bile plugs are present and in severe cases, canalicular plugs can extend to the periportal region of the lobule. As cholestasis becomes more chronic, portal tracts expand as a result of fibrosis, bile duct proliferation, periductal concentric fibrosis, and an increase in pigment-laden (lipofuscin and bile) macrophages, lymphocytes, plasma cells, and neutrophils. With increasing chronicity, the bile plugs become less evident and portal-to-portal bridging fibrosis with biliary hyperplasia and eventual biliary fibrosis may develop in cases of persistent obstruction.[12]

Inflammation

Cholangitis

Cholangitis may be classified as neutrophilic, lymphocytic, destructive, or chronic (associated with liver fluke infestation).

Acute Neutrophilic Cholangitis

Neutrophilic cholangitis (suppurative/cholangiohepatitis) is the most common type of cholangitis in dogs and cats, and more common in cats overall. The most likely pathogenesis of this lesion involves bacterial translocation from the intestine. Histologically, there is neutrophilic infiltration of the lumen or epithelium of the bile ducts (Fig. 29-74). In acute cases there is more edema around the bile duct and it extends into the portal tract. Neutrophils may also be found within the portal connective tissue, and neutrophilic inflammation may extend through the limiting plate leading to hepatocyte necrosis and, on occasion, to hepatic abscesses, at which point the diagnosis of cholangiohepatitis is appropriate.

Chronic Neutrophilic Cholangitis

Chronic neutrophilic cholangitis can be difficult to discern microscopically. The chronic stage is associated with a variable number of mixed inflammatory cells, neutrophils, lymphocytes, and plasma cells in the portal tracts (Fig. 29-75). Fibrosis and bile duct proliferation may be evident. Neutrophils persist, even in low numbers, in the lumina of the bile ducts.

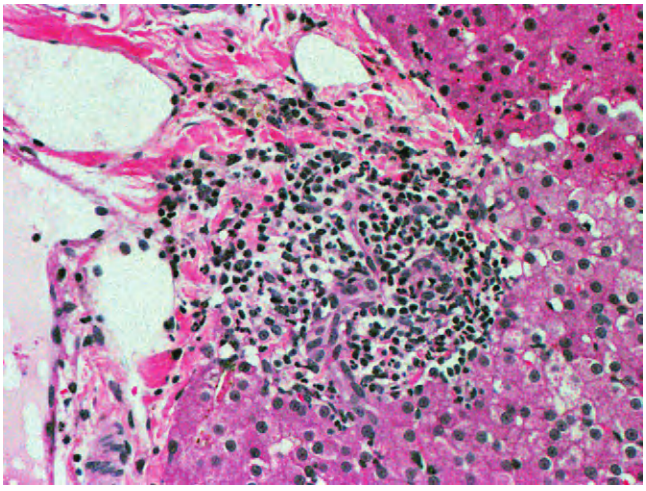

Figure 29-75 Chronic neutrophilic cholangitis retains the presence of neutrophils within the lumen of the bile ducts, but there may also be a significant number of mononuclear inflammatory cells and concentric peribiliary fibrosis may be evident.

Acute and chronic neutrophilic cholangitis occur in varying intensity and distribution. Some cases are uniform and diffuse and readily diagnosed, but in others there is an irregular distribution with only limited numbers of portal tracts affected and multiple biopsies may be required to confirm the diagnosis.

Lymphocytic Cholangitis

Lymphocytic cholangitis is characterized by infiltration the portal tracts by small lymphocytes, often associated with variable portal fibrosis, reactive biliary epithelium, and bile duct proliferation.[13] Lymphocytic cholangitis is a relatively common hepatic disease in cats; the pathogenesis is unknown. Lymphocytic infiltrates centered on bile ducts or present in the biliary epithelium are evident, but in severe cases these infiltrates can bridge portal tracts (Fig. 29-76). Lymphoid follicle formation may occur. Centrilobular areas of the

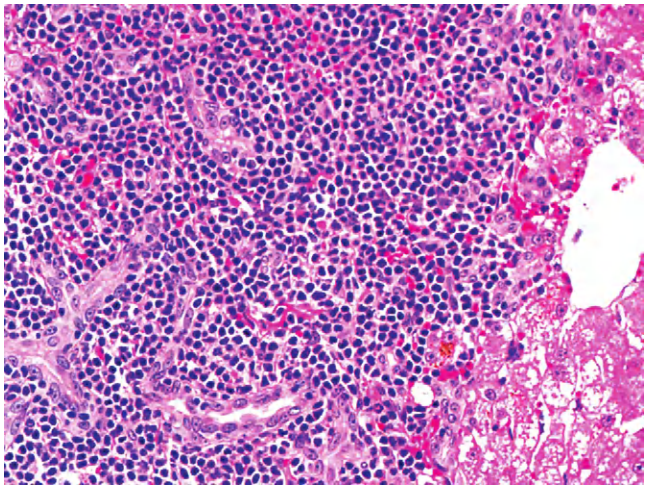

Figure 29-76 Feline lymphocytic cholangitis is recognized by the intense lymphocytic infiltration of the portal tracts and associated biliary hyperplasia.

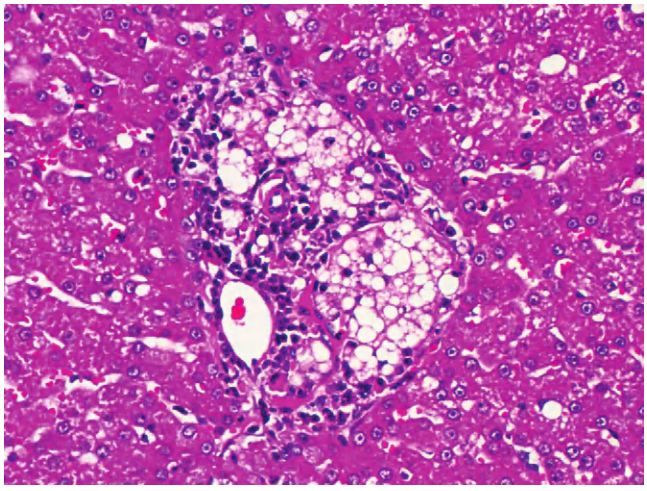

Figure 29-77 In destructive cholangitis the bile ducts are not evident within the portal tract and there is mononuclear cell infiltration with pigmented macrophages.

lobule are not affected. Apart from lymphocytes, occasional plasma cells and eosinophils may be present. The principal differential diagnosis for this disorder is lymphoma, and it can be difficult to discern the correct diagnosis on the basis of histologic evidence alone.

Destructive Cholangitis

Destructive cholangitis is characterized by necrosis or absence of biliary epithelium in smaller portal areas with infiltration of neutrophils and/or eosinophils and pigment laden macrophages (Fig. 29-77).[14] In chronic forms portal fibrosis may develop. The cause is unknown, but destructive cholangitis may result from an idiosyncratic reaction to drugs, particularly sulfonamides. Other toxic insults and viral infection (e.g., canine distemper) also may be associated with destruction of biliary epithelium. It is not known if destruction and loss of the bile ducts is always permanent or recovery can occur.

Chronic Cholangitis Associated with Liver Fluke Infestation

Several species of fluke can inhabit the bile ducts of cats and, less frequently, dogs. Chronic fluke-associated cholangitis results in dilated, fibrotic larger bile ducts. Histologically there are papillary projections and marked periductal and portal fibrosis with a slight to moderate inflammation within the ducts and portal areas (Fig. 29-78). Inflammatory cells within the lumina of the bile ducts are typically neutrophils and macrophages, while the portal inflammatory cells are usually neutrophils, lymphocytes and plasma cells. Eosinophils may be present, but usually only in small numbers. Typically there is no evidence of the adult flukes or eggs, but they may be present in a small proportion of cases.[7] Cholangiocarcinomas have been reported in dogs and cats with chronic cholangitis caused by chronic fluke infestation.

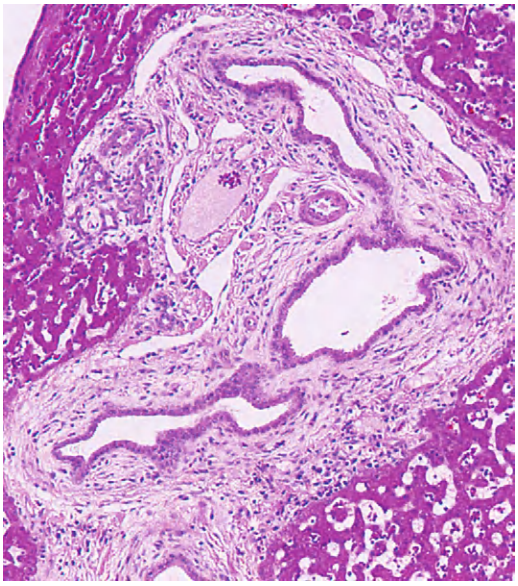

Figure 29-78 Fluke-associated cholangitis has a prominent dilation of bile ducts, an extensively thickened layer of connective tissue surrounding the duct, and, often, proliferation of the lining biliary epithelial cells. A moderate mononuclear cell infiltration is common.

Diseases of the Gallbladder

There are several disorders of the gallbladder that may be related, representing different stages of a single entity or separate disorders. These include cystic mucinous hyperplasia, gallbladder mucocele, and gall bladder infarction.

Cystic Mucinous Hyperplasia

Cystic mucinous hyperplasia of the gallbladder is characterized by prominent hyperplasia of the gallbladder epithelium. Well-differentiated hyperplastic epithelium forms numerous papillary projections that contain mucin and impart a honeycombed appearance to the mucosa. This change is common in older dogs, but uncommon in cats, and is of no clinical significance.

Gallbladder Mucocele

The accumulation of dark, gelatinous to semisolid bile-stained material, presumably abnormal bile or gallbladder epithelial secretions is characteristic of gallbladder mucocele. This disorder occurs in dogs and there is evidence of breed predisposition (e.g., Shetland Sheepdogs).[15] The gallbladder and, occasionally, the cystic and common bile duct, may become distended with this material and cause extrahepatic cholestasis. Histologically there are fine strands of hyperplastic biliary epithelium that extend into the intraluminal material.

Inflammatory changes are variable and may depend on the degree of injury or vascular compromise to the gallbladder wall caused by the expanding material within the gallbladder (Fig. 29-79). Inflammation can be negligible when affected gallbladders are removed early, but fibrin, neutrophilic infiltrates and acute necrosis can be evident where the gallbladder has ruptured. Adjacent liver parenchyma may display biliary hyperplasia and mild to moderate inflammatory infiltrates within the portal tracts, sometimes with reduced portal vein profiles.

Gallbladder Infarction

Gallbladder infarction occurs in dogs and appears to be distinct from cholecystitis (see "Cholecystitis" section below) in that inflammation is not reported to be significant.[16] Rather, there is acute full-thickness necrosis of the gallbladder wall, and on occasion, evidence of thrombi or degenerative changes in the cystic artery or its branches. Gallbladder rupture can be associated with infarction.

Cholecystitis

Neutrophilic Cholecystitis

Neutrophilic cholecystitis is typically associated with ascending bacterial infection from the intestine. It is common in cats and rare in dogs. Neutrophilic cholecystitis may occur in concert with neutrophilic cholangitis or as a single entity. Histologically there are neutrophils in the gallbladder lumen, as well as in the epithelium and muscularis of the gallbladder. In the acute stages only erosion and ulceration of the epithelium may be evident. Over time there is mixed inflammatory infiltration of neutrophils, lymphocytes, and plasma cells, and, in some cases, fibrosis.

Lymphoplasmacytic and Follicular Cholecystitis

This diagnosis is warranted when the lymphoplasmacytic infiltrate within the mucosa of the gallbladder exceeds the normal background content of these cells. The cause is unknown. Occasionally lymphoid follicles may be present in apparently normal gallbladder mucosa so it can be difficult to distinguish a true inflammatory condition if there is only a small amount of tissue to evaluate.

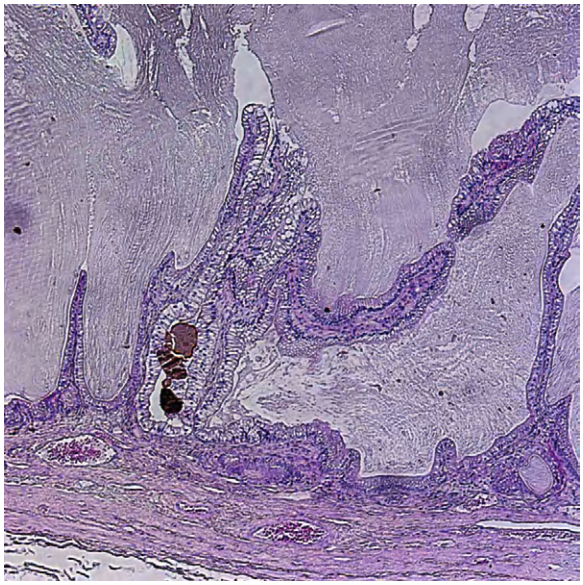

Figure 29-79 Gallbladder mucoceles are characterized by abundant, thick mucinous material within the lumen of the gallbladder. The mucosa is proliferative and may form papillary projections.

Parenchymal Disorders

Vacuolar Disorders

Cytoplasmic vacuolation of hepatocytes occurs for a variety of reasons, some physiologic and others as part of a disease process. Consequently, the diagnosis of vacuolar hepatopathy is vague and often uninformative.[17] In young animals, particularly those with abnormal growth, storage disorders may cause vacuolation of hepatocytes and possibly Kupffer cells. In older animals the vacuoles almost always contain lipid or glycogen. Identification of the contents can help determine pathogenesis, particularly in storage disorders. There are distinct syndromes involving either glycogen or lipid; however, there are circumstances in which both substances are present and their relationship to the disease state of the patient is unknown. The physiologic mechanisms that lead to glycogen or to lipid accumulation are, for the most part, different. Some disorders associated with vacuole formation are discussed later.

Hepatocellular Steatosis (Lipidosis or Fatty Liver)

Abnormally increased lipid within hepatocytes is termed *hepatocellular lipidosis* or *fatty liver*. Hepatic steatosis may be part of a normal physiologic response or, in more advanced cases, a form of reversible injury. Hepatocellular steatosis can occur in a variety of disturbances of normal lipid metabolism or disease syndromes in small animals.

Regardless of pathogenesis, the gross appearance of hepatocellular lipidosis is highly characteristic. Lipid accumulation imparts a pale yellow appearance to the liver. With increasing amounts of lipid the liver becomes progressively yellow and enlarges leading to hepatomegaly. The cut surface of the liver can develop a greasy texture and the liver becomes friable. Microscopically, lipid appears as clear, round, distinct cytoplasmic vacuoles. There are two microscopic forms of hepatic lipidosis, macro- and microvesicular.

Macrovesicular steatosis is the most common form of lipid encountered and is characterized by vacuoles that are larger than the hepatocyte nucleus and tend to displace the nucleus to the periphery of the cell (Fig. 29-80). Typically there are only one or two vacuoles per hepatocyte. Microvesicular steatosis is characterized by multiple fine vacuoles that are smaller than the nucleus and that fill the cytoplasm without displacing the nucleus (Fig. 29-81).

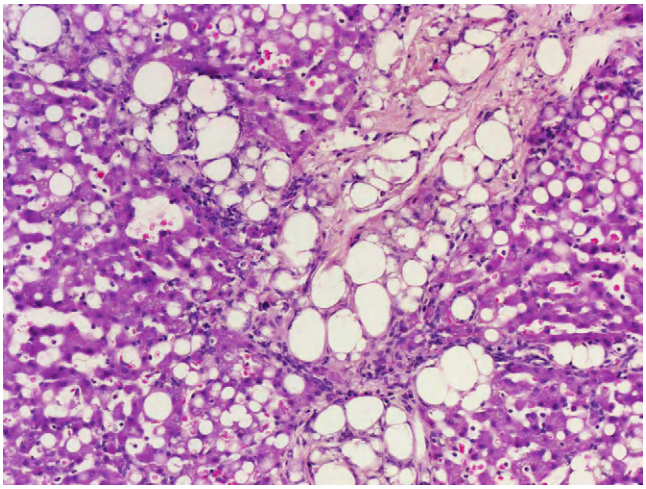

Figure 29-80 The macrovesicular form of steatosis or fatty liver has large, round, well-delineated and clear vacuoles that are larger than the hepatocyte nucleus and tend to displace the nucleus.

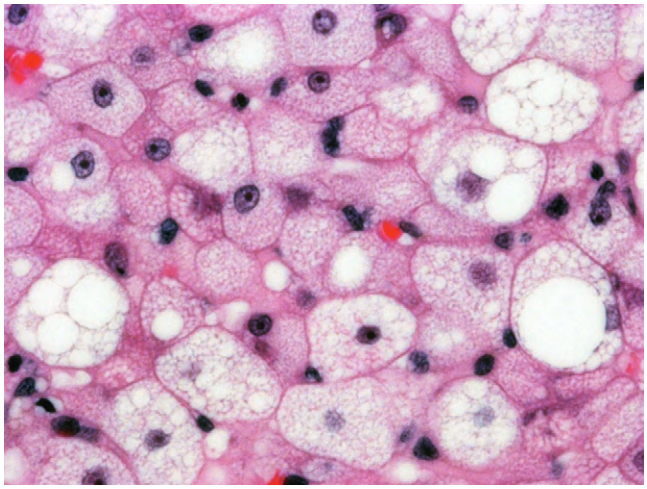

Figure 29-81 Microvesicular steatosis is recognized by the presence of multiple fine vacuoles that fill the hepatocyte cytoplasm but do not displace the nucleus.

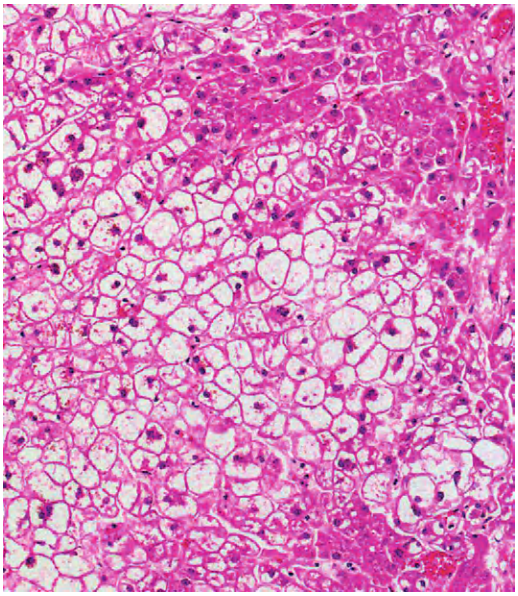

Figure 29-82 Excessive hepatocellular glycogen accumulation occurs most often in the presence of excess exogenous or endogenous corticosteroids, although there are other causes. Affected hepatocytes have ballooned profiles with empty cytoplasm or just wispy strands of eosinophilic cytoplasm evident.

In man and rodents microvesicular lipidosis is associated with injury to mitochondria and more severe liver dysfunction than macrovesicular lipidosis, but this has not been thoroughly investigated in dogs or cats. Microvesicular steatosis is seen most often in uncontrolled diabetes mellitus in dogs and in juvenile hypoglycemia of small-breed dogs in which the vacuoles are very small and may be diffuse or centrilobular. Mixed microvesicular and microvesicular lipidosis is common in the syndrome of feline hepatic lipidosis.

In paraffin wax–embedded and H&E-stained sections, lipid appears as a clear space because lipids are removed during processing. Other substances (e.g., glycogen and products of some storage disorders) can also appear as clear vacuoles, so it is desirable to identify the contents of clear vacuoles. Lipid can be identified by staining frozen tissue with lipid stains (see Table 29-4).

The lobular distribution of lipid vacuoles can vary from centrilobular to periportal, or, in extreme cases, the pattern is termed *massive*, involving all hepatocytes within the lobule. In mild cases, lipids may only accumulate in specific portions of each lobule, typically the centrilobular regions, leading to an enhanced lobular pattern. Lipid within hepatocytes should be distinguished from lipid between hepatocytes, as hepatic stellate cells can accumulate lipids, particularly in cats, and appear as cells with large single clear vacuoles that bulge into the sinusoidal space. Focal lipid accumulations, usually with foamy macrophages that also contain pigment are common in older dogs and are termed lipogranulomas.

Lipid accumulation in hepatocytes is often nonspecific; however, evaluation should include the lobular distribution and possible contributing factors, as well as the type of lipid vacuoles.

Glycogen Accumulation

Glucose is normally stored within hepatocytes as glycogen and is often present in large amounts after eating. Abnormal hepatic accumulation of glycogen is most often encountered in dogs as a result of glucocorticoid hepatopathy; however, other metabolic perturbations involving glucose regulation, including diabetes mellitus and the glycogen storage diseases, can produce similar changes. Disturbances of adrenocortical function involving steroids other than glucocorticoids, excessive progestins, and treatment with D-penicillamine are also reported to cause glycogen vacuolation.

Glucocorticoid-induced hepatocellular degeneration is a specific disorder of dogs characterized by excessive hepatic accumulation of glycogen. Excessive amounts of endogenous or exogenous glucocorticoids cause extensive swelling of hepatocytes from the accumulation of glycogen. In severe cases of glucocorticoid hepatopathy, the liver is enlarged and pale. Hepatocytes are prominently swollen with clear cytoplasm and diaphanous strands of eosinophilic cytoplasm with a central nucleus (Fig. 29-82). The distribution can be diffuse, zonal, or involve individual cells. Glycogen is notoriously difficult to detect in such livers, but PAS staining with or without diastase (which digests glycogen and distinguishes glycogen from nonglycogen carbohydrates) may be used. Special stains may help to identify glycogen accumulation in mild cases but, should it be necessary, frozen sections collected immediately at the time of biopsy are more useful. Other hepatic changes associated with glycogen accumulation are margination of neutrophils in sinusoids and occasional foci of extramedullary hematopoiesis.

Glycogen storage diseases type Ia and type II also lead to glycogen accumulation within hepatocytes, and such disease generally presents in young dogs.

Storage Diseases

A variety of inherited metabolic disorders, usually enzyme deficiencies, lead to excessive retention of storage of materials in hepatocytes and Kupffer cells. These materials often produce clear vacuoles, although they can have many morphologic appearances. Vacuoles can, alternatively, contain granular or hyaline material or, in some instances, cytoplasmic yellow-brown material (Fig. 29-83). The appearance varies with the type of substances retained. These changes are usually nonspecific, and water- or lipid-soluble materials are often lost in routine tissue processing. In such cases the liver can be evaluated using frozen sections, plastic-embedded sections, or electron microscopy. The histologic appearance of the vacuoles is generally insufficient to make a definitive diagnosis. Identification of the storage product, the enzyme deficiency, or the defective gene

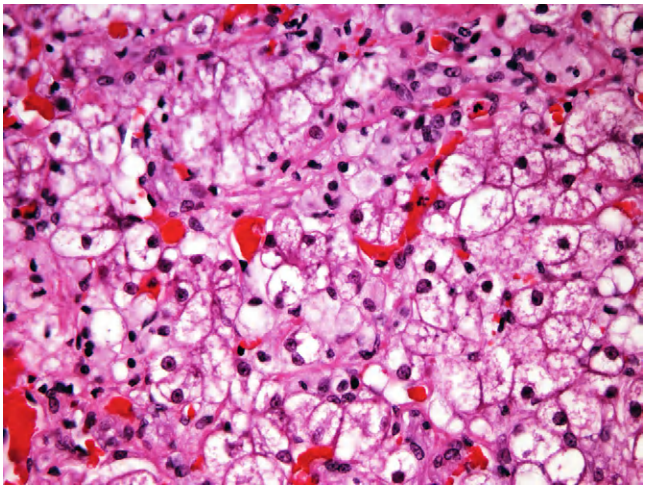

Figure 29-83 Inherited storage disorders can lead to hepatocellular and/or Kupffer cell vacuolation. In some disorders the vacuoles may appear clear, as in this kitten.

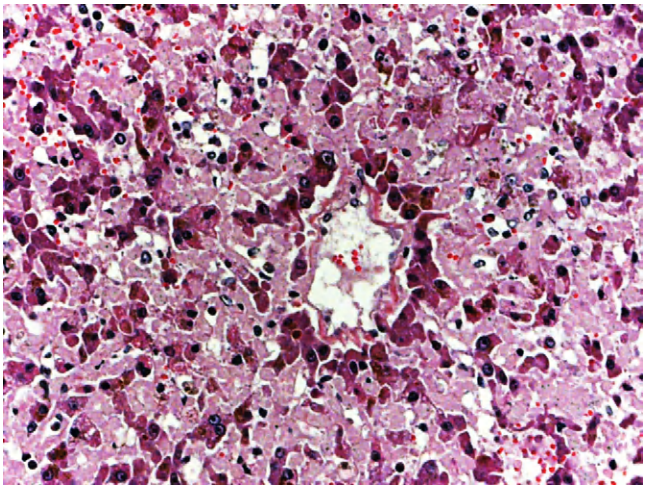

Figure 29-84 Amyloidosis. Amyloid can be recognized by its uniform pale and eosinophilic appearance. It can be deposited in the sinusoidal spaces, as seen in the left of this image, and is associated with hepatocellular atrophy.

is required. Some storage disorders (e.g., copper and cholesterol esters) may lead to necrosis, inflammation, and cirrhosis.

Amyloidosis

Hepatic amyloidosis occurs in dogs and cats. Amyloidosis is not a single disease entity, but a term used for various diseases that lead to the deposition of proteins that are composed of β-pleated sheets of nonbranching fibrils. Secondary or reactive amyloidosis is most common in dogs and cats and occurs as a consequence of prolonged inflammation. Inherited or familiar amyloidosis occurs in Shar Pei dogs and Abyssinian, Siamese, and other oriental breeds of cats. Histologically, all forms of amyloid appear as bright eosinophilic amorphous deposits that are usually found along the sinusoids in the space of Disse, but can be found in the portal tracts and within blood vessel walls (Fig. 29-84). The diagnosis can be confirmed with Congo red staining, which imparts an apple-green fluorescence when viewed under polarized light. As amyloid impairs blood flow or the access of hepatocytes to blood, hepatocellular atrophy is common, although affected livers are often enlarged as a result of the accumulation of amyloid.

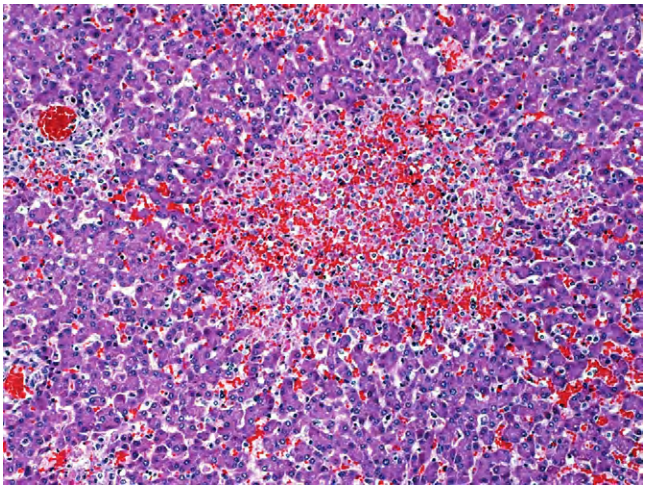

Figure 29-85 Neonatal puppies are susceptible to herpes virus infections that cause multifocal random necrosis, but little inflammation in the liver and other organs.

Inflammatory Disorders of the Liver

Acute Hepatitis

Regardless of the cause, acute hepatitis is characterized by hepatocellular necrosis or apoptosis, inflammation, and possibly regeneration. The pathologist should communicate the pattern and extent of necrosis and describe the type of inflammation present. If possible, the etiology and the age of the lesion should be identified.

Acute Viral Hepatitis

Viral infections of the liver typically occur in conjunction with systemic involvement. The most clinically significant hepatic infections are discussed next.

α-Herpes Viruses

Herpes virus infections in dogs and cats typically affect neonatal animals. Hepatic lesions are multifocal necrosis with scant inflammation. Necrosis may involve the portal tracts and the connective tissue surrounding the central and sublobular veins (Fig. 29-85). Infrequent intranuclear inclusions of hepatocytes and biliary epithelium, which are small and eosinophilic, are diagnostic but difficult to identify.

Infectious Canine Hepatitis

Infection with canine adenovirus 1 (CAV-1) is the exception to the typical pattern of random distribution of lesions with infectious disease. The virus kills endothelial cells as well as hepatocytes and it may be that this vascular component produces local ischemia and the generalized centrilobular injury and necrosis superimposed on the random foci of hepatocellular necrosis (Fig. 29-86). The diagnostic feature associated with infection is the presence of prominent basophilic intranuclear inclusions with a clear rim of marginated chromatin in infected hepatocytes and endothelial cells, and, occasionally, in biliary epithelial cells (Fig. 29-87). Foci of necrosis are acute and coagulative, rimmed with apoptotic hepatocytes. Inflammation in the parenchyma and the portal tracts is typically minimal.

Coronavirus (Feline Infectious Peritonitis)

FIP can affect the liver and other tissue sites. In the liver there is a characteristic vasculitis, as well as a perivenular and subcapsular inflammatory lesion that may consist of pyogranulomatous

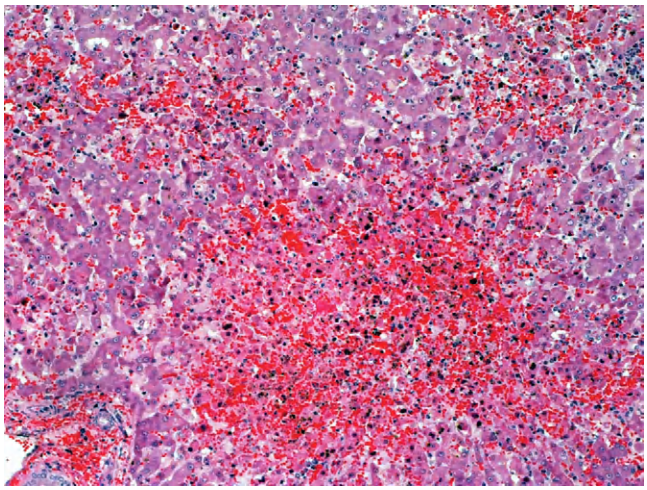

Figure 29-86 Infectious canine hepatitis. Typically, infection with canine adenovirus I produces foci of necrosis with a centrilobular to bridging distribution and variable inflammation.

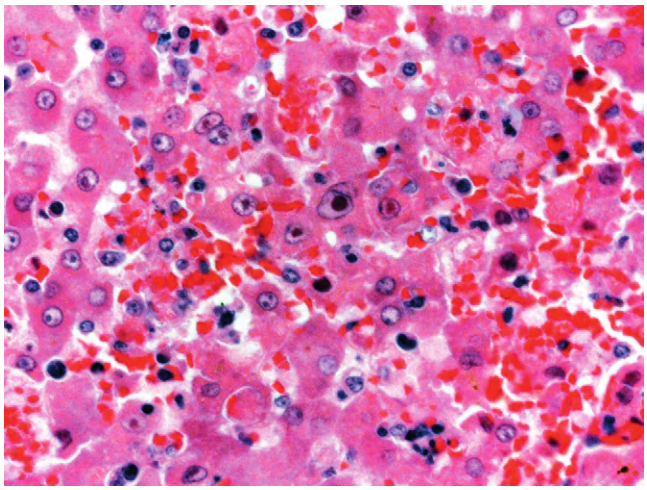

Figure 29-87 Infectious canine hepatitis. Prominent basophilic intranuclear inclusions are readily found within hepatocytes.

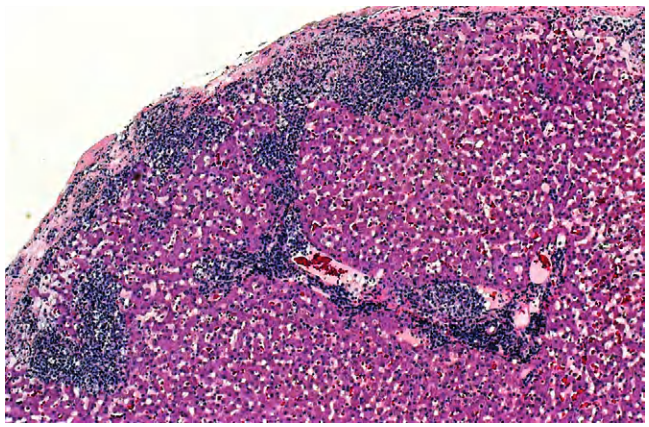

Figure 29-88 Feline infectious peritonitis. The characteristic lesion of this disease is perivascular inflammation composed of lymphocytes, macrophages, and neutrophils in varying proportions. Capsular injury and fibrin accumulation are also typical.

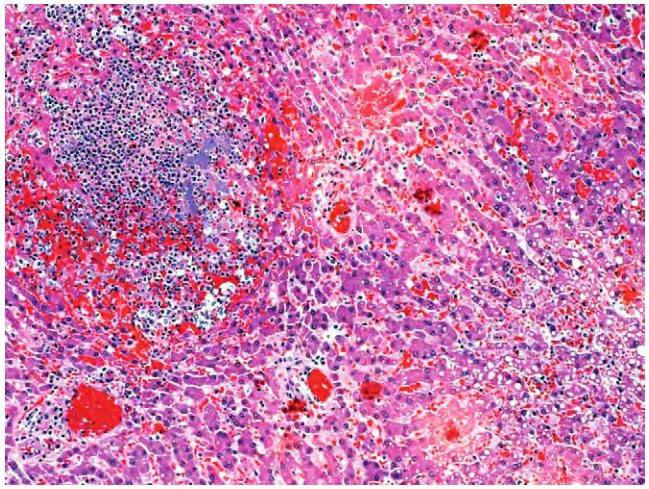

Figure 29-89 Various bacteria that can cause bacteremia may shower the liver and produce a random distribution of hepatocellular necrosis and associated inflammation, usually with neutrophils predominating.

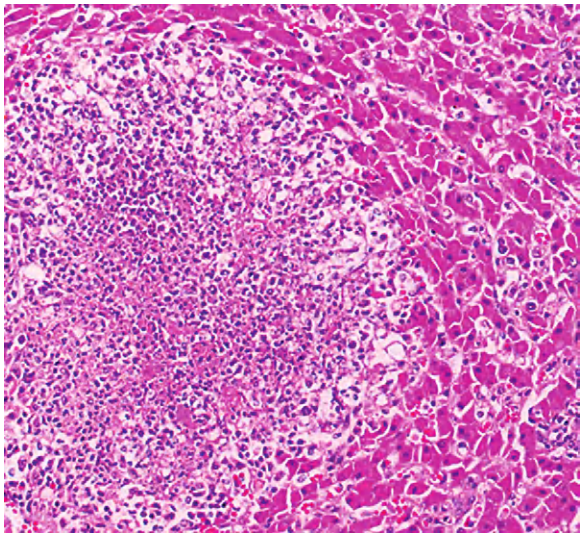

Figure 29-90 *Yersinia pseudotuberculosis* infection in a cat. Bacterial infections that produce septicemia often produce multiple, randomly distributed foci of necrosis and suppuration.

inflammation composed of foci of necrosis and infiltration of macrophages and degenerate neutrophils rimmed with lymphocytes, although in other cases lymphocytes and plasma cells may predominate (Fig. 29-88). Inflammation and necrosis usually also involve the liver capsule, which has prominent adherent fibrin with infiltrations of neutrophils and macrophages. The hepatic lesions can be similar in the effusive and the noneffusive forms of the disease.

Acute Bacterial Hepatitis

Most bacteremias involve the liver, and the range of bacteria that can produce septicemia and hepatic disease in dogs and cats includes *Salmonella* spp., *Leptospira* spp., *Clostridium piliforme*, *Francisella tularensis*, *Nocardia asteroides*, *Streptococcus* spp., and various mycobacteria and enteric organisms such as *E. coli*. Acute infections can produce random multifocal areas of necrosis with neutrophilic infiltration (Figs. 29-89 and 29-90). Culture is usually needed to distinguish the etiology. Some bacterial infections have somewhat distinctive changes. *Leptospira* infections, depending on the serotype, can produce prominent cholestasis, individualization of

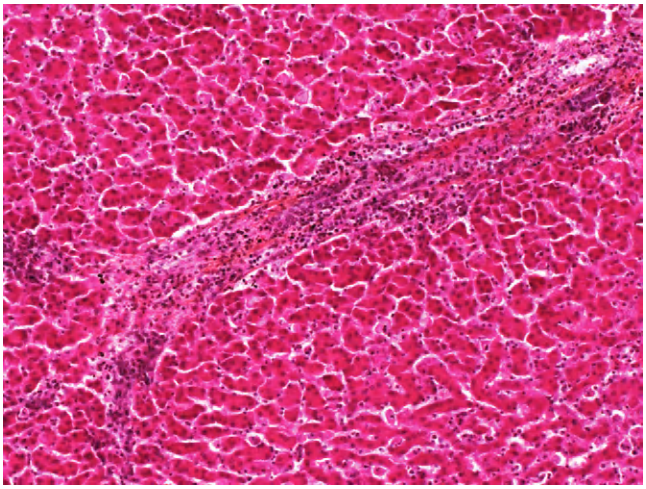

Figure 29-91 Leptospirosis can produce a pattern of hepatocyte individualization with mild lymphocytic portal infiltration.

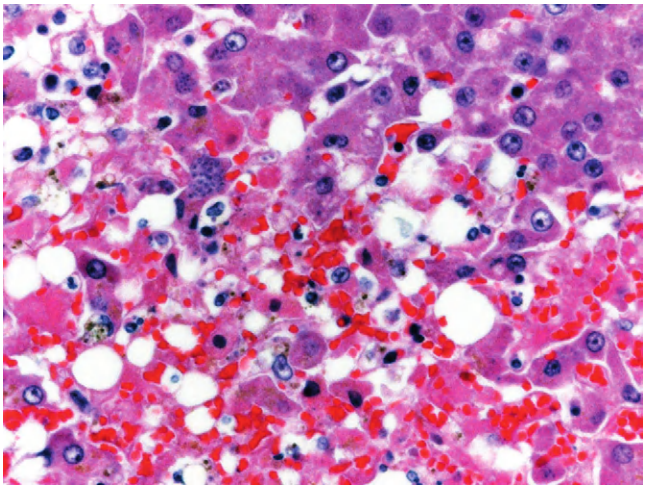

Figure 29-92 *Toxoplasma gondii* infection in a cat. Infection with *Toxoplasma* spp. and other protozoa typically produce multiple, randomly distributed foci of necrosis and a mixed inflammatory infiltrate. The presence of cysts with 1- to 2-μm basophilic merozoites is characteristic.

hepatocytes, increased hepatocellular proliferation, mixed inflammatory reactions in portal tracts, and scattered individual necrotic hepatocytes (Fig. 29-91). *C. piliforme* infections have slender elongated bacilli arranged in tangles within the cytoplasm of viable hepatocytes at the margins of the foci of random necrosis. The organisms are readily identified with silver stains. Mycobacterial infections are generally more chronic and produce granulomatous inflammation. Acid-fast bacilli within the lesion, although several forms of acid-fast stain may be required, are diagnostic. Infection with *Helicobacter canis* has been associated with multiple foci of necrosis and mixed inflammatory infiltrates in one young dog.[18] Silver stains are necessary to identify the organisms in the tissue. *Bartonella* spp. have been described in a variety of inflammatory hepatic lesions, including granulomatous hepatitis.[19]

Acute Protozoal Hepatitis

Apicomplexa protozoa, including *Toxoplasma gondii*, *Neospora caninum*, *Sarcocystis canis*, and *Sarcocystis neurona*, can infect the liver of dogs, usually as part of a neurologic or systemic disease process.[20] As in most infectious diseases, there is a random pattern of lesions in the liver. Hepatic infection with *T. gondii* is characterized by a random, diffuse to confluent pattern of lesions with a central area of necrosis surrounded by in a modest mixed inflammatory infiltration of neutrophils, macrophages, and other mononuclear cells (Fig. 29-92). Cysts containing bradyzoites and free tachyzoites may be found within and adjacent to these lesions. Hepatic lesions caused by *S. canis* do not occur in all infections, but include multifocal and portal inflammation, which may involve the limiting plate, with neutrophils, mononuclear cells, giant cells, and foci of necrosis within which intrahistiocytic schizonts and free merozoites can be found.

Hepatic Toxicity

As the recipient of all of the blood flow from the digestive tract, the liver is centrally positioned to protect the body from endogenous and ingested injurious substances. Consequently, it is also the most common site of toxic injury. Such injury often produces a characteristic distribution of acute coagulative necrosis within the hepatic lobule, most often centrilobular (Fig. 29-93). This pattern of toxin-induced injury is attributed to the higher content of cytochrome P450 enzymes in this area of the lobule. Hepatic metabolism of

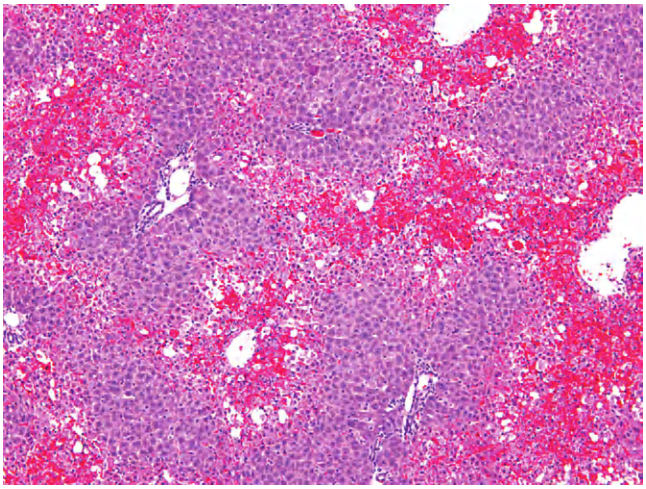

Figure 29-93 Acute centrilobular necrosis is characterized by extravasated blood cells and necrotic hepatocytes. This is a very common pattern for acute hepatic toxicities of many types and is also seen with acute hemolysis, blood loss, or cardiac decompensation.

many molecules destined for excretion usually goes through a three step process that involves oxidation of the parent molecule, conjugation with a polar molecule (often glutathione), and transport across the canalicular membrane into the bile. Hepatocellular injury can arise when the initial oxidation step leads to an excess of the oxidized (or bioactive) parent molecule. This bioactive form can bind to cellular proteins, RNA, and cell membrane lipids, causing acute toxicity, and in other circumstances bind to DNA and lead to carcinogenicity. Many naturally occurring and therapeutic hepatotoxins (e.g., acetaminophen, xylitol, aflatoxin B_1) produce centrilobular to massive necrosis, depending on the dose.[21-23] Cats are particularly sensitive to hepatic toxins such as acetaminophen and this is likely because of less robust antioxidant defenses and hepatic drug conjugation pathways compared with the dog.[24] Other types of toxins do not need hepatic metabolic activation and can cause injury directly, often producing random or periportal patterns of necrosis. However, drug- or chemical-induced acute necrosis in the

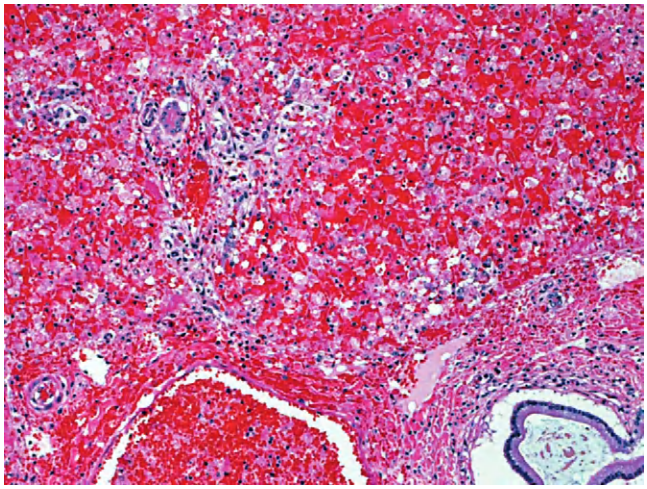

Figure 29-94 Massive necrosis involves the loss of all hepatocytes within a lobule. Several toxins, particularly in high doses, can produce this lesion.

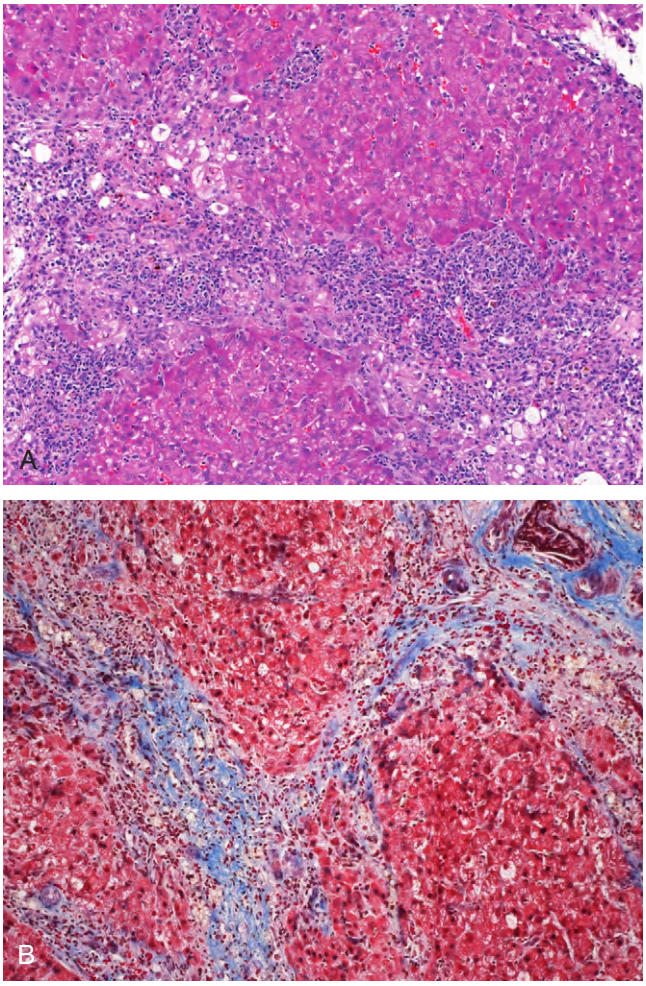

Figure 29-95 **A**, Chronic hepatitis. The hallmarks of chronic hepatitis are hepatocellular degeneration and death, fibrosis, usually in bridging bands with variable amounts of biliary hyperplasia and inflammation. Evidence of hepatocellular regeneration may be present. **B**, The connective tissue can be viewed more easily with special stains such as Mallory's trichrome that stains collagen blue.

periportal or midzone of the hepatic lobule is uncommon in dogs and cats.

Because the lobular model does not fully account for the three-dimensional anatomy of the liver, the pattern of acute necrosis more often irregularly bridges central areas with thick zones of necrosis. The degree and extent of necrosis can vary considerably from lobe to lobe and within lobes. Inflammation may be seen, but this is typically a nonspecific response to cell injury and death. The histologic appearance of acute toxic injury is heavily dependent on time, as a single insult can be nearly resolved in 3 to 4 days, depending on the severity of the initial insult. As a result, biopsies may fail to show significant lesions if the biopsy is obtained several days after a single exposure to a toxin, even though liver enzymes may still remain elevated. Centrilobular necrosis of the liver can also be caused by vascular disease, hypoxia, and some viruses, and must be distinguished from necrosis caused by toxins.

Massive acute necrosis is the most severe form of hepatic injury and affects all hepatocytes within the lobule (Fig. 29-94). This pattern can occur in dogs that have ingested toxic mushrooms such as *Amanita phalloides*,[25] blue-green algae, or as severe, possibly idiosyncratic, toxicities following drugs such as sulfonamides or trimethoprim sulfonamide in dogs and benzodiazepine in cats.[26,27] Chronic drug toxicity can produce lesions typical of chronic hepatitis with fibrosis, possibly bridging, and mononuclear cell inflammation.

Chronic Hepatitis

Chronic hepatitis is common in dogs, but rare in the cat. The pathogenesis remains unclear. Some cases have been associated with leptospirosis, *Bartonella* spp., and experimental and spontaneous CAV-1 infection, but this is a minority of cases.[7] Chronic hepatitis has also been reported in dogs treated with anticonvulsant drugs such as primidone, phenytoin, and phenobarbital, and in aflatoxicosis.[28] Approximately half of the cases of chronic hepatitis are linked to intrahepatic copper excess, but many cases are idiopathic.[29]

Histologically, chronic hepatitis is characterized by an inflammatory infiltration of mononuclear cells, lymphocytes, and macrophages, but other cell types, plasma cells, neutrophils, and eosinophils can be present in varying proportions (Fig. 29-95).[30] Other features include apoptosis or necrosis, regeneration, and fibrosis. The proportion and distribution of these components vary widely and it is appropriate for the pathologist to include in the diagnosis the activity and stage of the disease as well as the possible cause. The activity of the disease is determined by the amount of inflammation and extent of hepatocellular apoptosis and necrosis. The stage of the disease and the prognosis may be determined by the extent and pattern of fibrosis and the presence of architectural distortion. Early fibrosis may be seen as fine septa penetrating the parenchyma from the portal tracts or along the sinusoids. This is common in association with interface hepatitis (inflammation at the limiting plate). Fibrosis is usually the result of direct activation of hepatic stellate cells that are positioned in the space of Disse or related cells in the portal tract and connective tissue around the central vein. Increased connective tissue may be present or the collapse and condensation of the reticulin network because of hepatocyte injury and loss may give the appearance of increased fibrosis. The more advanced patterns of fibrosis may include portal-to-portal, portal-to-central and central-to-central bridging, or it may dissect the lobule. Other changes seen in chronic hepatic injury or hepatitis include regeneration and regenerative nodules of hepatic parenchyma, and proliferation of ductular structures at the periphery of the parenchymal

nodules and within fibrous septa. These ductular structures may represent biliary hyperplasia or, in cases of severe injury, proliferation of bipotential hepatic progenitor cells. Histochemical stains for connective tissue may be helpful in detecting the amount and pattern of fibrosis, particularly in early and mild disease.

Copper-Associated Hepatitis

Copper accumulation occurs in dogs and occasionally in cats. Progressive hepatic copper storage leading to inflammation and necrosis is well recognized in Bedlington Terriers because of a mutation in the COMM-D gene. Other breeds can also have elevated liver copper levels, but the disease process is not as well characterized.[31] Affected breeds with apparently familial disease include the West Highland White Terrier,[32] Skye Terrier,[33] and Dalmatian.[34] Chronic hepatitis and elevated liver copper has also be described in the Doberman Pinscher,[35] Labrador Retriever,[36,37] and American and English Cocker Spaniel, and likely occurs in other breeds.

Histologically, the pattern is similar in all affected dogs. Hepatocellular copper accumulation is first evident in centrilobular hepatocytes as intracytoplasmic granules. With progressive accumulation retained copper results in hepatocellular necrosis, inflammation with copper-laden macrophages forming small aggregates, and, finally, chronic hepatitis and cirrhosis (Fig. 29-96). Healthy dogs with normal livers may have copper levels of 400 to 500 mg/g dry weight, but some dogs can have higher liver copper burdens without significant liver disease.

Canine Idiopathic Chronic Hepatitis

Chronic hepatitis that is not associated with excessive copper retention remains a conundrum. The histology is typical of that described previously for chronic inflammation of the liver. Suggestions of breed predispositions to chronic hepatitis have been reported.[31] Drug toxicity, immune-mediated disorders, α_1-antitrypsin deficiency, and chronic infections may play a role, but the majority of cases are idiopathic.[29,38]

Granulomatous Hepatitis

Granulomatous hepatitis can result from the presence of any persistent antigen, including infectious agents such as mycobacteria, parasites, and fungi. Some cases do not have a clear etiology and novel infectious agents such as *Bartonella* spp. or atypical inflammatory responses or drug reactions have been suggested.

End-Stage Liver (Cirrhosis)

The terms *end-stage liver* and *cirrhosis* each have their adherents, but debate on the proper terminology remains. The WSAVA Liver Study group recommends the use of the term *cirrhosis* and supports the following definition for cirrhosis: a diffuse process characterized by fibrosis with conversion of normal hepatic architecture into structurally abnormal nodules and the presence of portal-to-central vascular anastomoses.[7] Bridging fibrosis is a regular feature, but fibrosis within the space of Disse also occurs and disrupts the interface between hepatocytes and the sinusoidal plasma. The pathologist should communicate to the clinician the extent and pattern of the fibrosis, the activity of the disease and, if possible, the likely etiology.

There are two morphologic categories of cirrhosis: micronodular cirrhosis with nodules less than 3 mm and regular in size, and macronodular cirrhosis with nodules greater than 3 mm and irregular in size. It is believed that micronodular cirrhosis develops from regular and diffuse injury and fibrosis. In contrast, macronodular cirrhosis develops from larger irregularly distributed areas of necrosis with secondary collapse and scarring (Fig. 29-97). In dogs, the histologic features also include proliferation of ductular structures and varying degrees of inflammation, bile stasis, lipidosis, and glycogen accumulation. Ascites and multiple acquired portosystemic shunts may develop when hepatic fibrosis disrupts hepatic blood flow leading to portal hypertension. Diminished hepatic function interferes with albumin synthesis, which can accentuate the formation of ascites. An idiopathic syndrome of hepatic fibrosis, unrelated to chronic injury has been reported in dogs and should be distinguished from typical cirrhosis.[39]

Cirrhosis is uncommon in cats. Affected cats may have diffuse hepatic fibrosis and disruption of the normal lobular pattern, usually as the result of chronic biliary disease, but rarely have nodules of regeneration. These cats may also have inflammation and proliferation of ductular structures.

Hepatocutaneous Syndrome (Superficial Necrolytic Dermatitis)

Hepatocutaneous syndrome is a disorder of dogs in which there is a combination of abnormalities in the liver and the skin, except in less-common cases where the skin disease is related to a

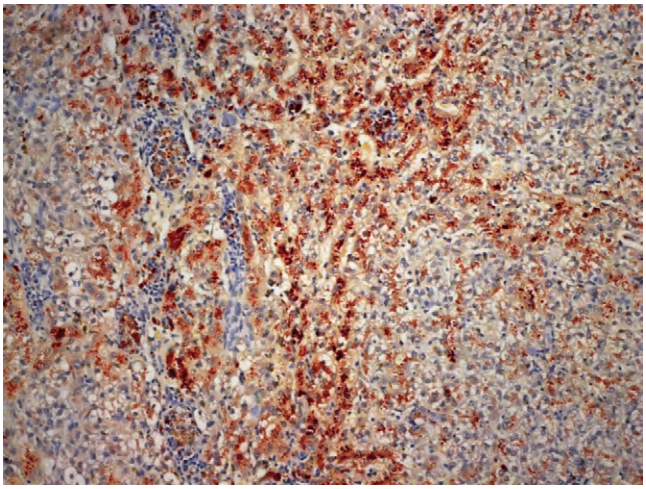

Figure 29-96 Retained hepatocellular copper can be seen more readily when special stains such as rhodanine are used, imparting an orange tint to the copper and associated binding proteins.

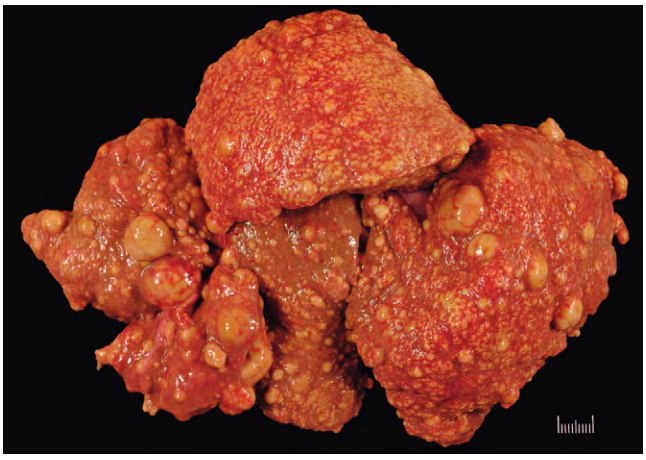

Figure 29-97 Macronodular cirrhosis. This condition is characterized by the formation of regenerative nodules that are greater than 3 mm in diameter. Irregular fibrosis is also evident.

glucagon-producing tumor of the pancreatic islet. Typically the hepatic lesion is a form of cirrhosis that has some atypical features. The liver, in this syndrome, is divided into multiple large confluent nodules, which are separated by prominent, enlarged hepatocytes containing clear vacuoles. Fibrous septa may be found between the nodules, although they may be less robust than in typical macronodular cirrhosis and in some cases nodules may only be separated by collapsed and condensed hepatic extracellular matrix. These septa usually contain proliferations of ductular structures and macrophages. Necrosis and inflammation are usually absent.

Lobular Dissecting Hepatitis

Lobular dissecting hepatitis occurs in young or young adult dogs as isolated cases or in groups of dogs from the same litter or kennel. Clinically, affected dogs deteriorate rapidly, but the histologic lesion is a form of cirrhosis. The liver usually has a normal size with a smooth capsular surface or may have some small nodules of regeneration. Microscopically, bands of fibroblasts (or myofibroblasts) and thin strands of extracellular matrix are seen between individual and small groups of hepatocytes that cause dissection of the original lobular architecture (Fig. 29-98).

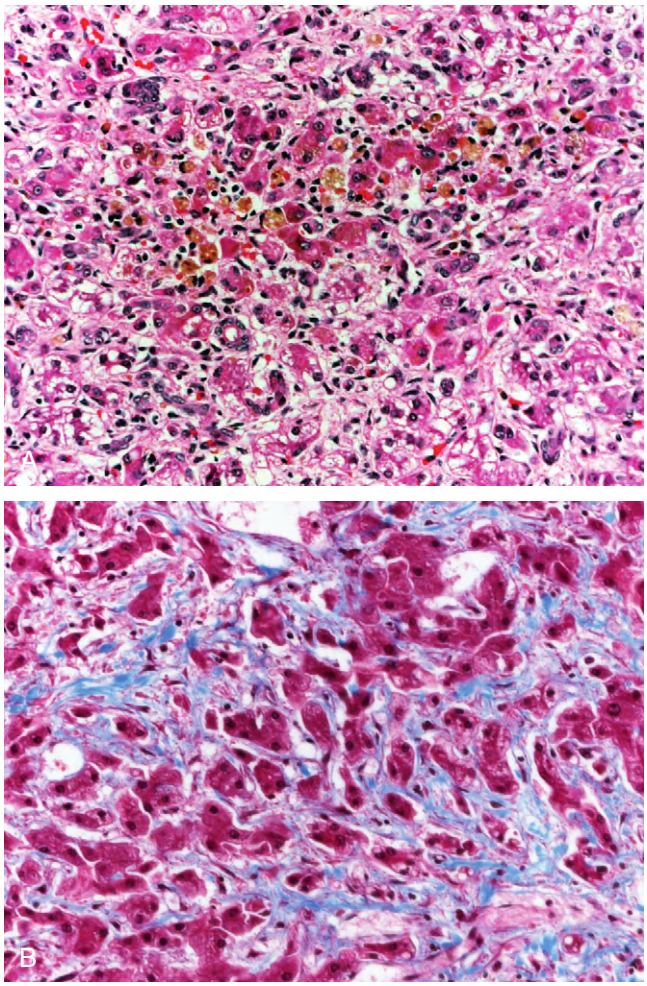

Figure 29-98 Lobular dissecting hepatitis. **A**, The normal lobular architecture is disrupted by the many fine fibrous septa that divide and distort hepatic plates. **B**, The presence of the fibrous septa can be more readily seen as blue linear material in this Mallory's trichrome stain.

Connective tissue stains demonstrate the pattern of connective tissue alterations. Inflammation is usually light and hepatocellular death is not a prominent feature. The cause is unknown.

Hepatic Abscesses

Hepatic abscesses can occur as single or multiple lesions in dogs and cats. Isolated organisms are predominately of enteric origin.[40,41] Abscesses contain central areas of suppuration and the surrounding hepatocytes may be necrotic, degenerate, or relatively normal, depending on the cause and maturation of the abscess.

Nonspecific Reactive Hepatitis

Nonspecific reactive hepatitis is not a disease, but is a recognizable response of the liver to a variety of extrahepatic disease processes, especially those involving the splanchnic bed or febrile illnesses. It may also be the residuum of an earlier hepatic disease. The importance of this diagnosis is the realization that the liver is responding to a systemic problem and that there is no primary liver disease, although there may be elevated liver-related enzymes and other clinical signs. The histologic pattern of nonspecific reactive hepatitis is characterized by an inflammatory infiltrate in portal areas and in the parenchyma. Hepatocellular necrosis is not usually evident (Fig. 29-99). Neutrophils may predominate in a proportion of the portal areas in acute extrahepatic diseases. There is slight to marked accumulation of inflammatory cells within the sinusoids and Kupffer cells may be prominent because of hyperplasia or hypertrophy. The central vein connective tissue may have similar changes to those in the portal tracts. The chronic form of nonspecific reactive hepatitis is characterized by infiltration of mononuclear cells, plasma cells and lymphocytes, and pigmented macrophages. The connective tissue around the central and sublobular veins, as in the case of acute disease, may mimic the changes in the portal tracts. This disorder has been termed *mild (neutrophilic* or *lymphocytic) cholangiohepatitis*, which is misleading, as the disease process does not involve the hepatic parenchyma or the biliary tree as a primary component of the disease process.

Eosinophilic Hepatitis

Eosinophilic hepatitis is of unknown cause. It can be regarded as a nonspecific reactive hepatitis particularly associated with allergic conditions and hypereosinophilic syndromes, and is more common in cats than dogs. Histologically, this condition may be present as part of a mixed inflammatory infiltrate in portal and perivenous areas and less frequently within the sinusoids. A distinct and less-common process of prominent eosinophilic hepatic inflammation is most likely associated with migrating nematode larvae or other parasitic infections. Rare drug reactions may involve an eosinophilic response, as can be seen in man.

Parasitic Helminths

The livers of dogs and cats can be infected with a variety of helminthes. Most cestode infections lead to cystic change grossly. There are no significant nematodes that infect the liver of dogs and cats, apart from *Calodium hepaticum* (formerly *Capillaria hepatica*) and these produce granulomatous reactions to the deposited eggs. Adults and eggs with typical polar caps can be seen within the lesions. Larval migration often produces tracts of acute necrosis at the early stages and encysted larvae provoke granulomas. Trematodes of clinical significance are discussed above under biliary disease.

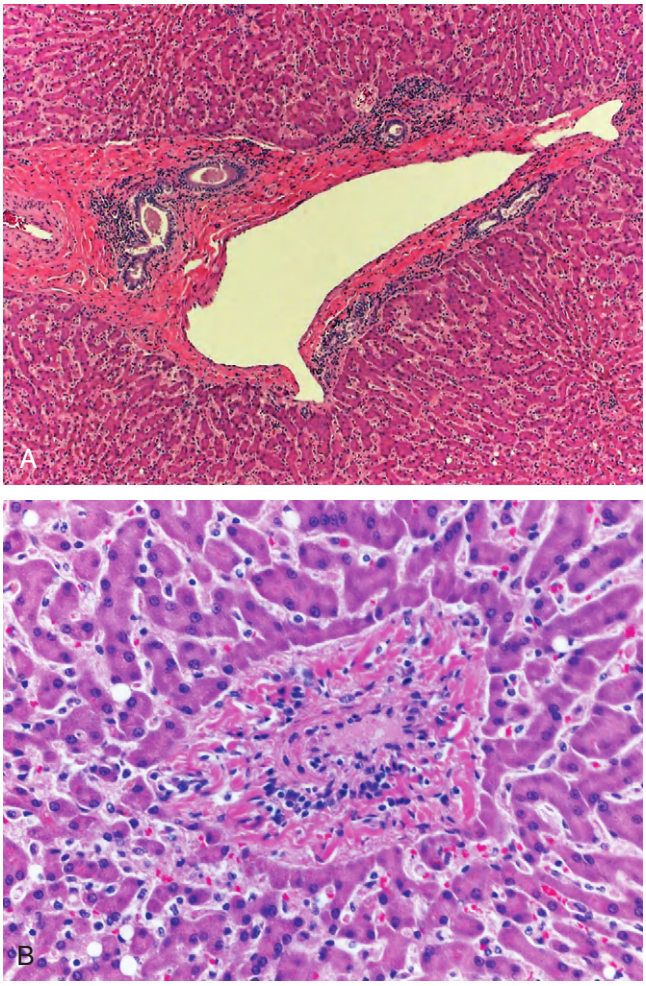

Figure 29-99 Nonspecific reactive hepatitis. This is a nonspecific response to extrahepatic inflammation or injury, usually in the gastrointestinal tract. **A**, Portal tracts contain a modest inflammatory infiltrate that may be composed of neutrophils or mononuclear cells (as in this case) depending on the type and duration of the condition. **B**, Similar changes can occur within the connective tissue surrounding the sublobular veins. Hepatocellular necrosis is not evident.

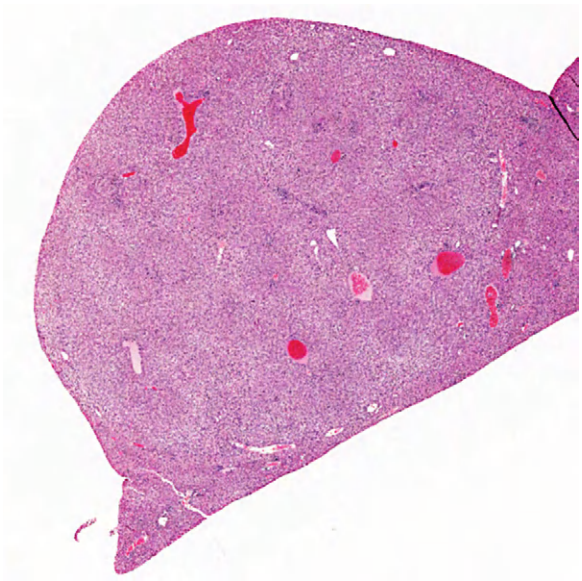

Figure 29-100 Nodular hyperplasia. Most older dogs have areas of nodular hyperplasia. Typically the remainder of the liver is completely normal and there are one or several expansile masses of well-differentiated hepatocytes present.

Proliferative Disorders of the Liver

Nonneoplastic Proliferative Lesions

Hepatocellular Nodular Hyperplasia

Hepatocellular nodular hyperplasia is common in older dogs, but rare in cats. The incidence of nodular hyperplasia in dogs is age-related, becoming evident at approximately 6 years of age, without predilection for either sex or breed.[42] The cause of these nodules is unknown. Nodular hyperplasia has no clinical impact, but because this change is readily detected with contemporary imaging techniques, the nodules should be distinguished from metastatic or primary hepatic neoplasms and regenerative nodules. Multiple hyperplastic nodules may occur, but often only a single mass is evident. Typically, the nodules are raised above the capsular surface and appear hemispherical. The color of the nodules can vary considerably, ranging from yellow to tan, to dark red when congested. The nodules vary in size with the smallest evident only microscopically and others as large as 3 cm in diameter. They are well demarcated from the normal parenchyma and usually compress adjacent parenchyma (Fig. 29-100). Hyperplastic nodules maintain a semblance of lobular architecture, but the lobular pattern is distorted, as portal tracts are separated by greater than normal and varying distances. Hepatocytes in nodular hyperplasia frequently contain lipid or glycogen vacuoles.

Regenerative Nodules

Regenerative nodules occur primarily in dogs and are not age related, but arise from the proliferation of hepatocytes in response to damage and loss. Often the source of the insult is unknown. They are typically multiple and often so numerous in macronodular cirrhosis that the affected liver resembles a cluster of grapes. The nodules can be smaller than 1 cm in diameter or up to several centimeters in diameter (see Fig. 29-97). Regenerative nodules are separated by septa of collapsed hepatic stroma, variable amounts of collagen and other newly synthesized extracellular matrix, proliferated bile ducts and variable inflammation, typically composed of mononuclear cells. Nodules are typically pale red-brown to darker mahogany, but may be pale when they contain lipid. Because these lesions result from the outgrowth of surviving hepatocytes, there is usually only a single portal tract apparent in sections. Hepatocytes in regenerative nodules are well differentiated. Regenerative nodules are readily distinguished from nodular hyperplasia since regenerative nodules occur in the presence of significant injury, fibrosis, and disruption of normal hepatic parenchymal architecture.

Neoplastic Lesions: Primary Hepatic Neoplasia

Primary liver tumors can arise from epithelial (e.g., hepatocytes, biliary epithelium of bile ducts or the gallbladder), neuroendocrine, or mesenchymal elements (e.g., connective tissue and blood vessels).

Hepatocellular Adenoma

Hepatocellular adenomas are benign neoplasms that are typically single, red or brown unencapsulated masses that compress adjacent parenchyma. They are usually spherical and can be less than 1 cm in diameter, or they may be quite large, involving the majority of a

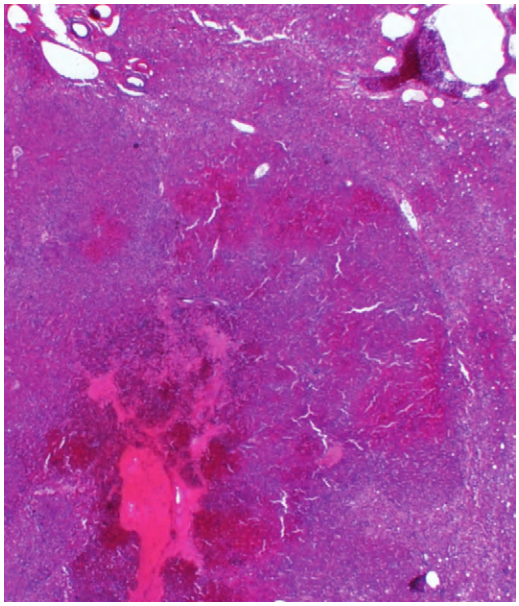

Figure 29-101 Hepatocellular adenomas are characterized by well-differentiated hepatocytes that form a uniformly expansile mass that compresses adjacent parenchyma. Central necrosis may occur, as it does in this case.

liver lobe. On occasion they may be pedunculated. Small to moderate areas of hemorrhage and necrosis may occur within the center of the tumor.

Macroscopic differential diagnoses for hepatocellular adenomas include nodular hyperplasia, regenerative nodules, hepatocellular carcinoma, and metastatic masses. Histologic examination is often needed to make a final determination. Histologically, hepatocellular adenomas are compressive masses composed of well-differentiated hepatocytes that form uniform plates up to two to three cells thick. Within the mass there is usually no more than a single portal tract (Fig. 29-101). Adenomatous hepatocytes tend to abut normal adjacent hepatocytes at right angles. Cystic areas of necrosis, hemorrhage, or serum, as well as foci of extramedullary hematopoiesis can be present. Hepatocellular adenomas can be difficult to distinguish from hepatocellular nodular hyperplasia in biopsies because of similarity between the level of differentiation of the hepatocytes in both lesions. Unlike adenomas, nodular hyperplasia retains normal lobular architectural elements, although the portal tracts are more separated than normal. In small biopsies it is nearly impossible to distinguish regenerative nodules from hepatocellular adenomas, as many microscopic features are identical, such as the degree of differentiation of the hepatocytes and the paucity of portal tracts. However, regenerative nodules arise in a background of hepatocellular injury and are typically multiple so an appropriate clinical history can aid in the correct interpretation. Hepatocellular adenomas are most likely underdiagnosed and often confused with well-differentiated hepatocellular carcinomas because diagnostic criteria have been imprecise but the advent of newer criteria should clarify this issue.[7]

Hepatocellular Carcinoma

Hepatocellular carcinomas are typically gray-white or yellow-brown masses that are subdivided into lobules by multiple fibrous bands. They are often quite friable. Hepatocellular carcinomas are often solitary, frequently involve an entire lobe, and are well demarcated, although these tumors can also form multiple nodules within the

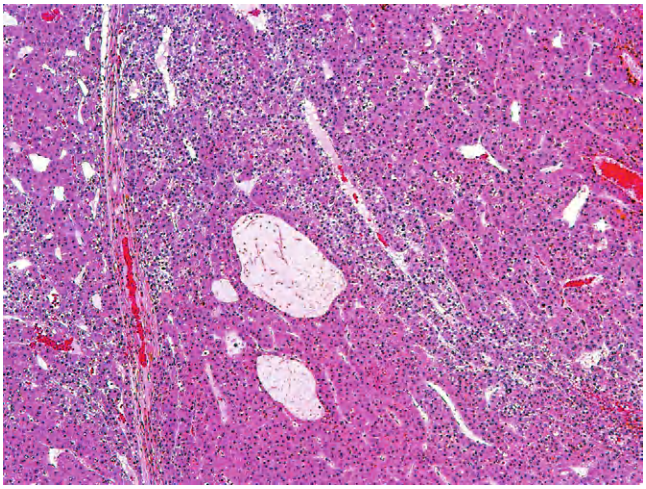

Figure 29-102 Hepatocellular carcinomas may have an irregular trabecular arrangement with intervening vascular channels.

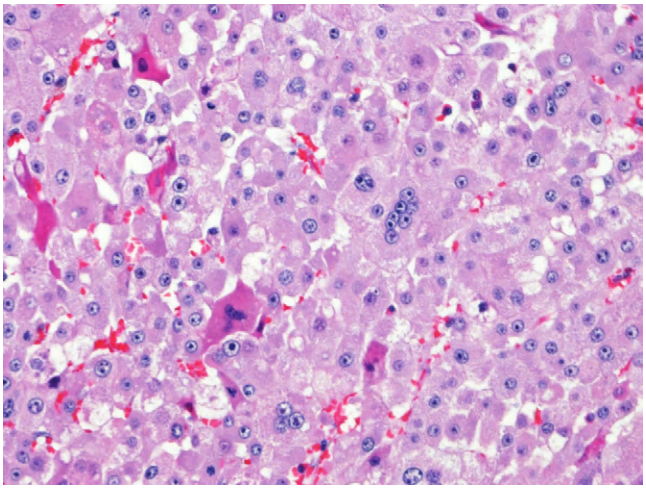

Figure 29-103 Varying sizes and shapes of neoplastic hepatocytes and their nuclei (pleomorphism) are a characteristic feature of hepatocellular carcinoma, as seen in this pulmonary metastasis of a primary hepatocellular carcinoma.

liver via intrahepatic metastasis or possibly multiple sites of origin.[43] Massive forms involving the entire liver can also occur.[43] Areas of necrosis and hemorrhage are common. Histologically, malignant hepatocytes can form trabecular, pseudoglandular, or solid patterns. All three patterns can be found in a single neoplasm. Trabeculae are variably thick with three or more cells forming a trabecula and there may be prominent vascular spaces between the trabeculae (Fig. 29-102). In the pseudoglandular pattern neoplastic cells line a space that may contain eosinophilic fluid. Solid variants are composed of sheets of neoplastic hepatocytes (Fig. 29-103). Neoplastic hepatocytes can range from well-differentiated to highly anaplastic spindle cells. Pleomorphic and giant cells can occur. Bile plugs may be found in canaliculi. Metastasis to a variety of sites may occur, particularly to lymph nodes within the anterior abdomen, lungs, and seeding into the tissues of the peritoneal cavity.[43,44] Intrahepatic metastasis is also possible. The rate of metastasis of hepatocellular carcinomas is an area of considerable debate. Early references suggest a relatively high rate of metastasis (more than 60%),[43] although most were reported to occur in the hepatic lymph node. Other reports

indicated a rate of metastasis half of this level.[44] More recent surveys are not available, but the conclusion of a consensus panel of veterinary hepatic pathologists was that metastasis of hepatocellular tumors to other organs was very uncommon. In the absence of metastasis, a clear indication of malignancy, the most useful criteria of malignancy are (a) invasion by malignant hepatocytes into local veins and through the interface between the tumor mass and the normal adjacent compressed normal hepatocytes; (b) prominent hepatocellular atypia, including pleomorphism, anisokaryosis, prominent nucleoli, and giant cells; and (c) increased mitotic index.

Cholangiocellular (Biliary) Adenoma

Cholangiocellular adenomas are benign tumors of biliary epithelium and are uncommon in dogs and cats. There is ongoing debate regarding the proper terminology for proliferative biliary lesions. In one new classification scheme[7] the majority of multicystic biliary lesions are interpreted as congenital biliary anomalies; however, there are pathologists who consider these lesions to be benign neoplasms. When multicystic disorders of the biliary and renal epithelium occur in the same animal, they are readily identified as developmental disorders. Given the similarity between lesions found only in the liver and those found in combination with renal cysts, it is likely that the majority of multicystic biliary lesions arise from congenital malformations. In keeping with the WSAVA classification, true adenomas of the biliary ducts are discrete, firm, gray or white masses comprised of well-differentiated biliary epithelium that forms narrow tubular or ductular structures lined with cuboidal epithelium and scant intervening connective tissue.[7]

Cholangiocellular (Biliary) Carcinoma

Cholangiocellular carcinomas occur in dogs and cats and usually arise from the intrahepatic ducts. Biliary epithelial malignancies may form a single mass or more often, multiple masses are scattered throughout the liver, possibly as a result of intraorgan metastasis. Tumor masses are pale gray to tan and unencapsulated. Cholangiocellular carcinomas can be distinguished from hepatocellular carcinomas by their firm texture, frequent presence of umbilication, and typically widespread distribution throughout the liver.

The tumors are composed of cells that retain a resemblance to biliary epithelium. Characteristically, well-differentiated carcinomas are organized into a tubules or acini lined by cuboidal to columnar epithelium. Well-differentiated tumors often contain mucin within the lumina of the tubules (Fig. 29-104). Bile pigment is not a feature of these tumors. In less-well-differentiated neoplasms some acinar arrangements can be detected among solid masses of neoplastic cells. Poorly differentiated carcinomas are composed of packets or cords and areas of squamous differentiation can occur. Tumor cells typically have a clear or pale eosinophilic cytoplasm. Nuclei remain round and mitotic figures are typically abundant. The epithelial components of the tumors are usually separated by abundant fibrous connective tissue (a scirrhous response) that is responsible for their firm texture. The growth pattern of this tumor is aggressive and the margins of cholangiocarcinomas are characterized by multiple sites of invasion into the surrounding hepatic parenchyma. Multiple sites of hepatic necrosis are also common in the adjacent parenchyma.

Metastasis to extrahepatic sites is common, particularly to the adjacent lymph nodes of the anterior abdomen, lungs, or by seeding into the abdominal cavity. Metastasis into the peritoneal cavity can produce variably sized nodules within the mesentery and on the serosal surface of the abdominal viscera.

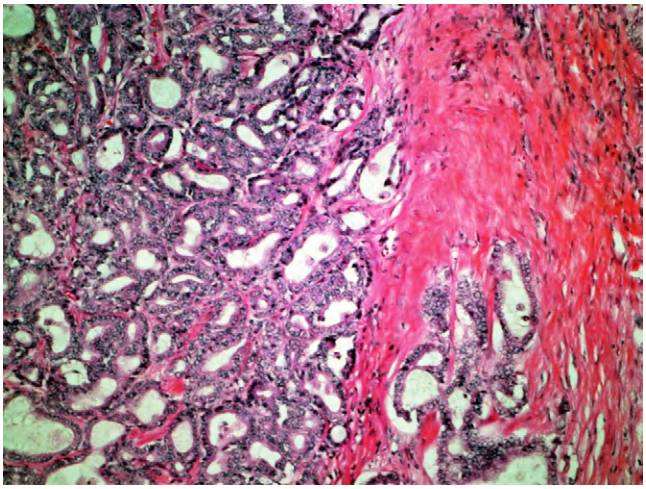

Figure 29-104 Biliary carcinoma is histologically typified by the presence of numerous small- to large-caliber tubular structures lined by cuboidal biliary epithelium. Dense connective tissue separates the tubular structures, imparting a firm texture to these masses.

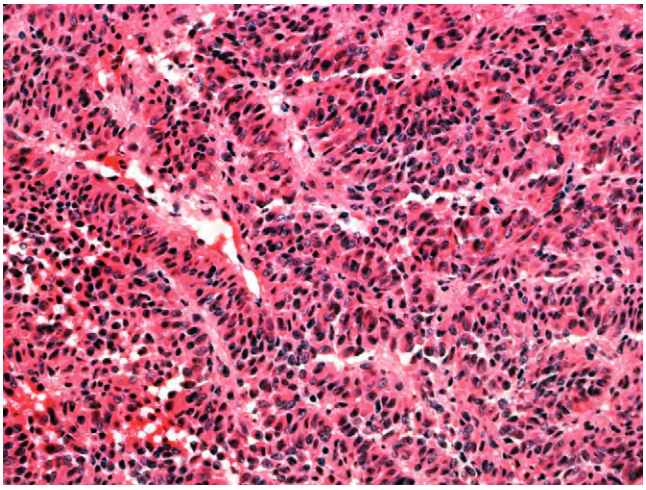

Figure 29-105 Hepatic carcinoid. These tumors are characterized by their ribbon or rosette conformation composed of small to elongated cells with dark basophilic nuclei.

Hepatic Carcinoids

Hepatic carcinoids are uncommon in dogs and cats, and most likely originate from neuroendocrine cells that lie within the hepatic parenchyma or biliary epithelium. These tumors have an aggressive course and frequently metastasize.[45,46] They may appear as a single mass, but multiple nodules can occur, probably secondary to intrahepatic metastasis. Cells tend to be small, oval to elongate or spindle-shaped, and form ribbons or rosettes. Neoplastic cells tend to be grouped into small islands separated by fine fibrovascular stoma (Fig. 29-105). Immunohistochemical detection of neuroendocrine markers such as chromogranin A or glucagon, among others, can be used to confirm the diagnosis.

Primary Hepatic Neoplasms of Mesenchymal Origin

Any of the cellular constituents of the liver can give rise to primary neoplasms. However, as a result of the relatively high frequency of metastatic spread of malignant tumors to the liver, a careful and

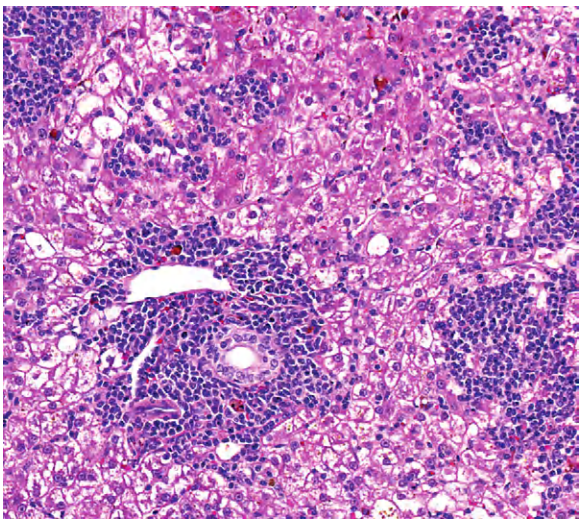

Figure 29-106 Lymphoma in the liver is manifested as dense lymphoid accumulations within and expanding the portal tracts, and occasionally involving the connective tissue around the central and sublobular veins. In advanced cases, neoplastic lymphocytes expand into the parenchyma.

thorough necropsy examination, as well as a thorough review of the history to check for, among other issues, the evidence of previous surgeries, must be performed to ensure that the tumor in question is indeed a primary mass. The most common primary mesenchymal neoplasm of the liver is hemangiosarcoma, but hemangioma, fibrosarcoma, leiomyosarcoma, and osteosarcomas are also recognized. Myelolipomas are discrete, nodular tumors with a thin capsule composed of lipocytes and myeloid elements that occur in cats.

Hematopoietic tumors, particularly lymphoma, occur in the liver. Lymphoma can infiltrate and enlarge the liver imparting a pale discoloration. Microscopically, lymphoma is characterized by infiltrates of neoplastic lymphocytes into the portal tract connective tissue and around the central and sublobular veins (Fig. 29-106). With advancing disease the neoplastic lymphocytes extend into the parenchyma. Usually there is no evidence of biliary proliferation in lymphoma that can help distinguish this tumor from feline lymphocytic cholangitis. Other hematopoietic neoplasms, including myeloid and erythroid neoplasia, malignant histiocytosis, and mast cell tumors can be found in the liver, although neoplastic cells are more likely to collect along the sinusoids, rather than within the portal tracts.

Metastatic Tumors

The liver is one of the two most common sites for metastasis for a large variety of malignant tumors. Distinguishing metastatic neoplasms from primary tumors can be difficult, particularly in the case of poorly differentiated epithelial tumors. For example, exocrine pancreatic and mammary tumors can resemble primary cholangiocarcinoma. It is important to ensure that a thorough postmortem examination is done, or when evaluating a biopsy, that the complete history is available to determine whether masses have been removed previously.

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CHAPTER 30

Nutritional Assessment and Management

MALNUTRITION

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Definition

Used broadly, the term *malnutrition* describes any nutritional disorder, including obesity caused by overnutrition, unbalanced nutrition as a consequence of one or more nutrient deficiencies, or cachexia caused by undernutrition.[1] Although there is no universally accepted definition for malnutrition, the World Health Organization describes it as "the cellular imbalance between supply of nutrients and energy, and the body's demand for them to ensure growth, maintenance, and specific function."[2] The term *undernutrition*, which is sometimes used interchangeably with malnutrition, is defined as "a state of energy, protein or other specific nutrient deficiency which produces a measurable change in body function, and is associated with a worse outcome from illness as well as being specifically reversible by nutritional support".[1] The terms *malnutrition* and *undernutrition* are used interchangeably in this chapter.

Isolated deficiencies of vitamins, minerals, and trace elements may occur in the absence of protein-energy malnutrition.[2] Suboptimal nutrition also occurs, in which an individual is not unhealthy, but will not function at his or her highest level. For example, it has been shown that an overnight preoperative fast in a healthy person results in postoperative insulin resistance and negative nitrogen balance.[3] Circumstances may also arise when an individual has an illness or trauma in which a substrate such as glutamate becomes limiting and is, therefore, a conditionally essential nutrient.[1]

Disease states may be accompanied by a loss of appetite or inability to eat, a decrease in the assimilation of nutrients, or nutrient losses that result in malnutrition. Malnutrition may also occur when an animal is being fed an insufficient amount of food for its energy needs, either because of poor feeding practices or a high energy requirement, such as in working dogs (Fig. 30-1). Feeding a poor-quality diet may result in energy deficiencies or specific nutrient deficiencies, such as thiamine. Animals fed homemade or vegetarian diets are known to be at higher risk for developing subclinical nutritional deficiencies or imbalances.[4]

Starvation in Healthy Animals

Starvation in an unstressed (i.e., not ill or injured) animal, also called *uncomplicated starvation*, initially results in utilization of the body's carbohydrate stores, especially hepatic glycogen. In dogs this reservoir may last for several days, compared with approximately 24 hours in humans.[5] Energy consumption then shifts primarily to fat and some protein metabolism. Both skeletal and visceral body proteins are used to provide gluconeogenic precursors, but liver structural proteins are used for gluconeogenesis before skeletal muscle.[6] As all body protein is functional, the primary adaptive shift is to fat utilization. Fatty acids are readily oxidized by the kidney and muscle tissues. Fatty acids are also converted to ketones in the liver which may then be used by the central nervous system. Several tissues, for example, adrenal medulla, red blood cells, and brain, have an obligate requirement for glucose, but the brain can adapt to ketone metabolism during periods of starvation. Glycerol resulting from the breakdown of triglycerides can be converted to glucose. Full adaptation to starvation with minimal protein oxidation can take up to 2 weeks in humans. At that time the respiratory quotient (RQ), a determination of the fuels being used by the body, is usually 0.6 to 0.7, indicating fat oxidation primarily.[7,8] If uncomplicated starvation lasts for longer than several days, metabolic rate is decreased as a consequence of a loss of tissue mass, a decreased metabolic rate of the remaining tissues, and decreased physical activity.[9]

Starvation in Ill or Injured Animals

Metabolism of the starved ill or injured animal is more complicated than in simple starvation (Table 30-1). Tumor necrosis factor (TNF) and interleukin-1 produced during injury or illness are associated with stimulation of proteolysis and inhibition of lipoprotein lipase activity. The counterregulatory hormones, cortisol and glucagon, and the catecholamines contribute to this process, eventually leading to insulin resistance and a tendency to develop hyperglycemia. Because of the metabolic shift, protein is catabolized at an increased rate and the adaptation to lipid metabolism is impaired.[7,8,10] The use of protein as an energy source often results in a persistent, marked nitrogen loss and net negative nitrogen balance. The increase in urinary nitrogen excretion can be approximately five times that of a patient in uncomplicated starvation. In humans, the RQ of 0.8 during this state indicates mixed fuel consumption, with

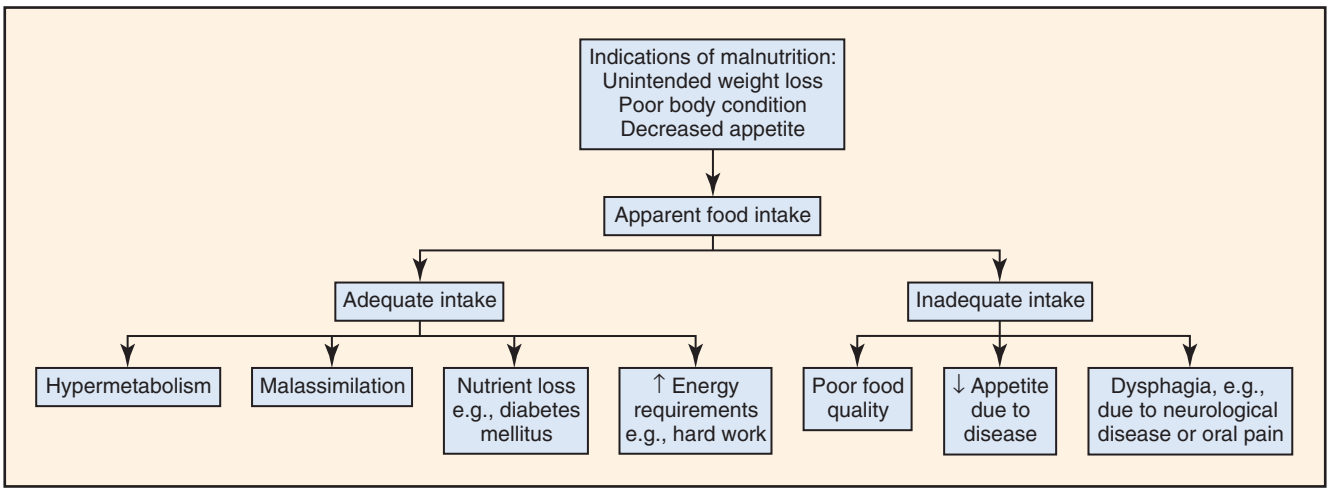

Figure 30-1 Causes of malnutrition.

Table 30-1 Comparison of the Metabolic Changes of Uncomplicated Starvation Versus Stressed Starvation of the Ill or Injured

Metabolic Parameter	Uncomplicated Starvation	Stressed Starvation
Inflammatory mediators	↑	↑↑↑
Primary energy sources	Glucose, fat	Glucose, amino acids, fat
Protein synthesis	↓	↓↓
Catabolism	↑ or ↓	↑↑↑

↑, increased; ↓, decreased.

Box 30-1 Complications of Malnutrition

Compromised wound healing
Immune suppression
Impaired muscle strength
Fatigue
Poor thermoregulation
Decreased respiratory function
Decreased gastrointestinal function
Decreased pancreatic function
Decreased water and sodium excretion
Increased tendency to develop edema
Increased morbidity and risk of secondary diseases
Increased risk of death

approximately 30% from amino acids, 40% from glucose, and 30% from fat.[7] It is the loss of body protein, not fat loss, that produces the complications of malnutrition during illness or injury.

Consequences of Malnutrition

Wound healing, which involves increased cellular activity and new protein synthesis, is compromised by malnutrition.[4] If the loss of lean body mass exceeds 10%, there may be decreased substrates for wound healing.[11] Specific micronutrients are also necessary for collagen synthesis and epithelialization, in particular, vitamins C and A, and zinc, copper, and manganese.[2] Malnutrition is also a predictor of postoperative complications after human abdominal surgery.[12]

Malnutrition affects the immune system in many ways, including decreases in the ratio of CD4:CD8 T cells, lymphokine and monokine production, complement C3, opsonic function, intracellular killing capacity of neutrophils, phagocyte dysfunction, antibody affinity, response of acute phase reactants to infectious challenge, and secretory immunoglobulin (Ig) A antibody response.[13,14] Seven days of starvation in cats results in immunosuppressive effects, including decreases in leukocyte and lymphocyte numbers.[15]

Other consequences of malnutrition include fatigue, impaired muscle strength and thermoregulation, and decreased respiratory, pancreatic, gastrointestinal, mental, endocrine, and cardiovascular functions.[1] As fat and lean components of the body are depleted, the extracellular fluid compartment stays the same or increases. The ability to excrete water and sodium may be reduced, increasing the tendency to develop edema.[1]

Morbidity and mortality rates are increased in malnourished patients. Postoperative mortality rates in human cancer patients approach 23% for the malnourished, but are only 4% in those in better nutritional condition.[16] Nutritional support in elderly patients reduces the mortality rate from 18.6% to 8.6% at 6 months.[17] Emaciated cats are significantly more likely to die within a year than those of optimal body condition.[18] Box 30-1 summarizes the consequences of malnutrition.

Assessment of Malnutrition

A number of methods have been used to assess nutritional status in humans, most of which include a combination of medical and dietary history, physical examination, anthropometric measurements, and laboratory data.[19] Many of the assessment protocols for humans use the body mass index (BMI), which is a ratio of weight in kilograms and the square of the height in meters, and anthropometric measurements such as mid-arm muscle circumference.[16] These methods are not practical in dogs because of extreme variations in body shape and size. A feline version of BMI has been developed for healthy cats and has been validated by dual-energy

X-ray absorptiometry for cats weighing between 3 and 9 kg of body weight.[20] The feline BMI uses the rib cage circumference in centimeters and the leg index measurement (LIM), which is the hind leg length from the middle of the patella to the dorsal tip of the calcaneal process in centimeters. The amount of body fat is then calculated using the equation:

$$\text{Percentage body fat} = [\text{rib cage}/0.762 - \text{LIM}] \div 0.9156$$

This measurement and calculation have not been validated in ill animals and feline BMI is not yet widely used in clinical practice.

The degree of weight loss can be difficult to assess if the animal's previous weight is unknown, and ascites may make weight loss assessment more difficult for the owner. Humans do not give reliable estimates of their own food intake[21]; the reliability of owners' assessment of the food intake of their pets has not been established.

Body condition scores (BCSs) provide a semiquantitative method for evaluating fat and lean body tissue percentages.[22,24] Scoring systems for dogs and cats have been developed using systems of 1 to 5 points, 1 to 6 points, and 1 to 9 points, with lower numbers representing thinner condition and higher numbers indicating obesity. In both dogs and cats, a BCS using a 9-point scale has shown good correlation (0.92 for dogs and 0.91 for cats) with percentage of body fat as determined by dual-absorption X-ray absorptiometry (DEXA).[23,24] This BCS system, using pictures and descriptions, shows good repeatability within and between observers. In dogs, a score of 4 or 5 out of 9 is optimal, depending upon the breed, and in cats a score of 5 is optimal. Unfortunately, the BCS systems do not take into account muscle wasting, and many ill animals may show loss of muscle that is disproportionate to the loss of fat because of the metabolic changes of stressed starvation. Consequently, a muscle mass scoring system has been developed that is based on palpation of skeletal muscle over the skull, scapulae, spine, and pelvis. Animals with no muscle wasting are scored as a 3, those with mild wasting are scored as 2, moderate wasting is scored as a 1, and a 0 score represents severe wasting.[25]

Multifrequency bioelectrical impedance has been used experimentally to assess body composition in healthy cats,[26] but has not yet been used in the clinical setting. Disturbances of water and electrolyte metabolism in the ill patient would limit the usefulness of this technique in the hospital setting.[16] Another method used in research settings for determination of body composition is DEXA, which has good accuracy but requires anesthesia and may not be practical for ill animals.[27]

Nutritional assessment in humans has included measurements of serum albumin and other proteins, including acute-phase reactants. These parameters may be affected by factors other than the metabolic changes of illness, including hydration status and changes in vascular permeability. Furthermore, normal serum albumin concentrations are maintained in starving people without stress, such as humans with anorexia nervosa,[16] and a study in elderly humans showed frequent discordance between serum albumin and clinical nutritional assessments. This may mean that changes in serum albumin seen in ill patients are more likely to be caused by the underlying disease.[28] Measurement of serum insulin-like growth factor 1 (IGF-1) concentrations in healthy dogs has shown correlation with nutritional restriction,[29] but IGF-1 is not yet performed in routine clinical practice and the association with nutritional restriction has not been examined in ill animals. Although there appears to be no reliable laboratory marker for assessment of nutritional status, the identification of specific nutrient deficiencies, such as folate, cobalamin, and iron, can be very useful. Box 30-2 summarizes the nutritional assessment for cats and dogs.

Box 30-2 History and Parameters for Initial Assessment of Undernutrition

Dietary history—type and amount, supplements
History of weight loss
History of decreased appetite
Body weight
Body condition score
Muscle mass score
Feline body mass index?
Possible disease causing malassimilation or nutrient loss?

Prevalence of Malnutrition

The prevalence of malnutrition in hospitalized human patients ranges from 13% to 78%.[30-32] The prevalence of malnutrition among cats and dogs is not as well documented. In a multicenter study of canine and feline BCSs using a 5-point scale, dogs had a mean BCS of 3.3 ± 0.7 and cats had a mean BCS of 3.2 ± 0.7.[33] The most commonly reported score for both species was 3, indicating ideal body weight. In another study of 276 hospitalized dogs that utilized a 9-point scale, the average BCS was 5.0 with a range of 1 to 9, and a normal distribution of scores.[34] Another study of small animal patients referred to an internal medicine service using the 9-point scale showed a median BCS for dogs of 6.5, although 20% of the dogs had a less-than-ideal BCS.[35] Of dogs, 34.7% had a history of decreased food intake and 45.8% had recent weight loss. Although many of the dogs had a good or even fat BCS, the history of weight loss and poor appetite was consistent with a risk of malnutrition and loss of functional lean body mass. For cats, the median BCS was 4.0, with 53.3% of the cats having a less-than-ideal BCS. Of cats, 53.3% had a decreased appetite and 56.7% had lost weight. In another study of canine cancer patients using a 9-point BCS scale, 55% of dogs were scored at 6 or higher, and only 4% were scored at 3 or less.[25] However, using the 3-point muscle-wasting score, 15% had moderate to severe muscle wasting and 20% had mild muscle wasting, consistent with the loss of lean body tissue.[25] The latter result emphasizes the importance of determining muscle mass scores in addition to BCSs.

Gastrointestinal Disease and Risk of Malnutrition

Human patients hospitalized with gastrointestinal disorders have among the highest rates of malnutrition.[2] The highest prevalence is in those people with inflammatory bowel disease (IBD), liver disease, and pancreatitis. The pathophysiologic mechanisms are manifold and include decreased intake, maldigestion, malabsorption, inflammation, increased nutritional requirements, and drug–nutrient interactions. Decreased appetite and reduced intake are obvious findings in many of the canine and feline gastrointestinal, pancreatic, and hepatobiliary disorders.

In humans it is noted that cobalamin is often deficient in cases of atrophic gastritis and disorders of the terminal ileum, and iron, folate, and magnesium deficiencies are common in patients with primary enteropathies.[16] Similarly, decreased cobalamin and folate have been reported in cats with gastrointestinal diseases,

including IBD, intestinal lymphoma, pancreatic inflammation, and cholangitis.[36,37] Iron-deficiency anemia may develop as a consequence of IBD in the dog.[38]

Reduced food intake and intestinal malabsorption may be present with many primary enteric diseases or secondary to cholestatic liver disease.[39] Fat malabsorption may result in deficiencies of fat-soluble vitamins A, D, E, and K, and zinc.[6,40] Pancreatic insufficiency classically presents with signs of malnutrition caused by maldigestion and decreased nutrient absorption. The reader is referred to Chapter 32 for more information on nutritional requirements in gastrointestinal, pancreatic, and hepatobiliary disorders.

Contribution of Hospital Practices to Worsening Nutritional Status

Ten percent to 60% of human patients lose weight during hospitalization.[16] Inadequate intake or fasting prior to anesthesia or diagnostic procedures may contribute to this weight loss. In one study, 20% of meals were missed, often because of fasting for investigative or therapeutic procedures.[41] In another study, estimated nutrient requirements were met in only 50% of patients because of inappropriate feeding instructions and failure to deliver prescribed nutrients.[42]

In a multicenter canine study it was found that a positive energy balance (>95% of calculated resting energy requirements) was achieved in only 220 (27%) of 821 "dog-days."[34] Reasons cited for patient negative-energy balance included poorly written feeding orders (22%), orders to withhold feed (34%), and, in many dogs (43%), a refusal to eat offered food. Anorexia in ill animals may arise as a consequence of the effects of cytokines such as pain and drug therapy. The reader is referred to Chapter 7 for more information on the mechanisms and management of anorexia.

In a study of enteral feeding prescribed by a nutrition support service, patients received 91% of their prescribed feedings.[43] Animals in this study received more than two-thirds of their goal calories on only 76 of 104 days, which may have resulted from continuous tube feedings rather than intermittent bolus feedings. The interruption of continuous feedings for procedures may have resulted in a smaller total intake than the use of intermittent bolus feedings.[43] Box 30-3 summarizes some of the causes of worsening nutritional status in hospitalized patients.

Box 30-3 Contributing Causes to Worsening Patient's Nutritional Status within the Hospital

- Animal's disease condition
  - Anorexia or decreased appetite
  - Nutrient malassimilation
  - Nutrient loss
- Hypermetabolism causing increased calorie requirements (uncommon)
- Lack of nutritional status assessment
- Delayed initiation of nutritional support
- Fasting for procedures
- Inappropriate diet, e.g., too low in calories or unpalatable
- Poorly written feeding orders or no feeding orders
- Incorrect calculation of caloric requirements
- Interruption of continuous feeding for procedures or to take animal out of cage

Management of Malnutrition

Management of malnutrition starts with appropriate assessment of the patient's nutritional status, including dietary history. Impairment of organ function occurs with starvation long before significant physical changes are observed, and nutritional deprivation is especially likely to be overlooked in the obese patient during hospitalization.[16] Initiation of nutritional support is indicated in patients meeting the criteria of acute weight loss of 5%; chronic weight loss of greater than 10%; anorexia for more than 3 days; or indications of decreased protein intake or malabsorption, poor body condition, weakness, or nonhealing wounds. Daily monitoring of the patient's nutritional status while hospitalized helps to ensure adequate intake. Patients should be weighed daily, although day-to-day fluctuations in weight may be greatly influenced by fluid balance. Energy requirements change as a consequence of illness, although in most patients requirements are not increased above resting energy requirements.[16]

Nutritional support in the starving and malnourished patient may induce a shift from the catabolic to the anabolic state. In the refeeding of a severely malnourished patient, a metabolic shift from endogenous to exogenous energy sources, particularly carbohydrates, may cause depletions in serum concentrations of phosphate, magnesium, and potassium, which move intracellularly under the influence of insulin. This is described as the refeeding syndrome,[44] and may be seen with either parenteral or enteral nutritional support. Hypophosphatemia resulting in hemolytic anemia has been described in cats during the provision of enteral nutrition.[45] Eight of these nine cats were in poor body condition prior to feeding, and the ninth, which was an obese cat, had a history of anorexia. Initiating feeding at less-than-resting energy requirements may help prevent refeeding syndrome. In another case of feline refeeding syndrome, the phosphorus, potassium, and magnesium were all deficient, and the cat showed concurrent cardiac abnormalities,[46] which have also been reported in human refeeding syndrome.[44]

Hypophosphatemia and red blood cell abnormalities have also been reported in dogs during feeding after nutrient deprivation.[44] Phosphorus should be monitored daily for the first week of nutritional support in malnourished animals. Decreased serum potassium and magnesium and hyperglycemia all play a role in refeeding syndrome and should be closely monitored. As thiamine plays a role in carbohydrate metabolism, and it may be depleted during starvation, provision of thiamine supplementation prior to nutrient supplementation has been recommended.[44]

Appropriate nutritional support should be initiated early in patients, following rehydration and stabilization, and ideally within 24 hours of hospitalization. Initial feeding protocols may be formulated at less-than-resting energy requirements, as even small amounts of nutritional support reverse the catabolism of endogenous protein for energy.[47]

Monitoring of the patient's food intake is important, as often records only note that "the patient ate," and do not describe the quantity or the type of food eaten. Supplemental nutritional support may be provided orally, enterally via feeding tubes, or parenterally via either central or peripheral vein. Enteral feeding stimulates the gut-associated immune system and provides nutrients such as glutamine to the intestinal mucosa.[48] Enteral nutrition is also generally safer and more economical than parenteral nutrition. The reader is referred to Chapter 33 for further information about enteral and parenteral nutritional support.

OBESITY

Alexander J. German

Definition and Prevalence

Definition

Obesity is defined as a disease where excess body fat has accumulated such that health may be adversely affected.[1] BMI is most commonly used to quantify human adiposity and recent epidemiologic studies suggest that the optimal BMI for nonsmoking adult whites is 20 to 25.[1] Additionally, epidemiologic data confirm that disease and mortality risk progressively increases for people classified as "overweight" (BMI 25 to 30), "obese" (BMI 30 to 40), and morbidly obese (BMI >40).[2] Companion animals are currently classified as overweight when their body weight is more than 15% above their "optimal body weight," and classified as "obese" when their body weight exceeds 20% to 30% of optimal[3]; data suggest that, like in humans, adverse consequences develop when dogs and cats are not maintained in optimal body condition.[3-6]

Prevalence

Recent studies estimate the prevalence of overweight/obesity in the pet population to be between 34% and 41%.[4-9] Although most investigators would agree that, as in humans, the incidence in the pet population is increasing, there are limited data to support this.

Etiology and Pathogenesis

At its simplest, obesity arises from a positive mismatch between energy intake and energy expenditure for a significant period. Most animals are able to maintain a stable body weight despite dramatic fluctuations in caloric intake; however, in those that become overweight, a number of risk factors can be present that alter energy balance toward weight gain.

Risk Factors for the Development of Obesity

Coexisting Health Problems

Concurrent disease can affect energy balance either by increasing energy intake (e.g., by increasing appetite) or reducing energy expenditure (e.g., by decreasing physical activity or slowing the basal metabolic rate). Diseases that can predispose to obesity include endocrinopathies (e.g., hypothyroidism and hyperadrenocorticism), conditions leading to reduced activity levels (e.g., orthopedic and cardiorespiratory diseases), and conditions requiring a medical intervention that might predispose to weight gain (e.g., drug therapy with glucocorticoids or anticonvulsants, and neutering for animals with diabetes mellitus, idiopathic epilepsy, and pyometra).

Although hypothyroidism is commonly cited as an underlying cause of obesity in dogs, such cases are the exception rather than the rule. The prevalence of hypothyroidism is reported to be less than 1%, with less than half of such cases presenting with obesity[10]; this contrasts with the relatively higher prevalence (typically 30% to 50%) of excess body weight.[6-8] Spontaneous hypothyroidism is rare in cats and usually only seen following chemotherapeutic, radiation, or surgical thyroidectomy for hyperthyroidism.

Signalment

The prevalence of obesity, in both species, rises sharply after 2 years of age and is most prevalent in middle age.[5-6] Neutering is an important risk factor for obesity in both dogs and cats, most likely associated with increased food intake and decreased physical activity.[11,12] Sex itself is a predisposing factor in some canine studies, with females overrepresented.[6,8] In contrast, a recent feline study suggested that males might be overrepresented.[9]

Breed

Rare genetic defects are an occasional cause of obesity in humans, but no single-gene disorders have been described in the dog or cat. Polygenic effects predisposing to weight gain in people have been reported.[13] Given that a number of breed predispositions have been reported in both dogs (e.g., Cocker Spaniels, Beagles, Labrador Retrievers, Golden Retrievers, Shetland Sheepdogs, Rottweilers, and mixed-breed dogs) and cats (e.g., Domestic Shorthair),[5,6] genetic influences are also likely in companion animals.

Environment and Activity

Indoor living is a risk factor for canine obesity; indoor dwelling and apartment living have been shown to predispose to obesity in some, but not all, feline studies.[13,14] Furthermore, cats living with dogs or with houses with only one or two other cats may be at more risk.[13,14]

Dietary Factors

The type of diet (prepared pet food vs. homemade) does not predispose to obesity, but the cost of food may.[15] In this respect, obese dogs are more likely to have received inexpensive generic diets rather than more expensive foods, while some studies suggest premium pet foods may increase the risk of feline obesity.[5] This is most likely a result of the potential for a higher fat (and therefore energy) content in premium foods. However, this finding has been contradicted by other studies in which no association was found with a particular type of diet.[13] Although, there have been many anecdotal suggestions that feeding a high-carbohydrate diet to cats predisposes to obesity and diabetes mellitus, there is no evidence to support this assertion either. In fact, increased dietary fat rather than carbohydrate predisposes to weight gain in cats.[16]

Obesity in dogs is associated with the number of meals and snacks fed, the feeding of table scraps, and the animal being present when owners prepared or ate their own meal.[13,14,17,18] Finally, obese cats more commonly have free choice of food intake.[13,14]

Owner Factors and Behavior

Many owners of obese cats tend to anthropomorphize them, and to use them as a substitute for human companionship.[19] Overweight dogs also tend to be anthropomorphized, but a close human–dog relationship is not a factor.[15] Owners of overweight cats also spend less time playing with their pet, and reward with food rather than extra play. Owners of both overweight cats and dogs also observe their pet more closely during eating, are less interested in preventive health, and are more likely to be overweight themselves.[15,19]

However, unlike the owners of overweight dogs who tend to have a lower income,[15,20] there are no demographic differences amongst owners of overweight and normal weight cats.[19]

Behavioral factors also play a part in the development of obesity, especially in cats, and the factors implicated include anxiety, depression, failure to establish normal feeding behavior, and failure to develop control of satiety.[21]

Pathologic Consequences of Obesity

Human Obesity-Associated Disorders

It has long been known that obesity conveys increased risk of mortality in humans (Table 30-2). Most significant is the metabolic syndrome, which comprises a group of metabolic and vascular

Table 30-2 Diseases Associated with Overweight Body Condition and Obesity in Humans, Dogs, and Cats

Disease Category	SPECIES		
	Human	Dog	Cat
Endocrine and lipid	Type II diabetes Metabolic syndrome Dyslipidemias	Hypothyroidism, hyperadrenocorticism Diabetes mellitus; insulin resistance Metabolic syndrome (experimental)	Diabetes mellitus Hepatic lipidosis
Cardiorespiratory	Coronary heart disease, atherosclerosis, hypertension Obstructive sleep apnea, asthma	Tracheal collapse, expiratory airway dysfunction (experimental), hypertension (of doubtful clinical significance), portal vein thrombosis, myocardial hypoxia	
Orthopaedic and impaired mobility	Osteoarthritis Musculoskeletal pain Gout	Osteoarthritis, cruciate ligament disease Humeral condylar fractures Intervertebral disk disease; hip dysplasia	Increased lameness
Oncologic	Various cancers including breast (postmenopausal), renal, endometrial, prostatic, esophageal, colorectal hepatocellular carcinoma	Variable neoplasia risk, transitional cell carcinoma Mammary carcinoma (some but not all studies)	Increased neoplasia risk
Urogenital	(Diabetic) nephropathy	Urinary tract disease, USMI, calcium oxalate urolithiasis,[37] transitional cell carcinoma Glomerular disease (experimental), dystocia	Increased risk of urinary tract disease
Alimentary	Pancreatitis, hepatic steatosis, cirrhosis	Pancreatitis	Increased oral cavity disease and gastrointestinal disease
Other	Depression Postoperative complication Various dermatologic diseases	Reduced immune function	Increased risk of dermatoses

USMI, Urethral sphincter mechanism incompetence.
Reprinted with permission from German AJ, Ryan VH, German AC, et al: Obesity, its associated disorders and the role of inflammatory adipokines in companion animals. *Vet J* 185:4–9, 2010.

disorders that increase the risk of an individual developing type II diabetes mellitus and cardiovascular disease.[22] In humans, the prevalence of type II diabetes mellitus has increased dramatically in the last decade, primarily because of the link with obesity.[23] Tissues become "insulin resistant" with excessive caloric intake, and the risk of developing diabetes is known to increase with increasing BMI.[23] Thus, obesity, particularly abdominal obesity, is a major determinant of insulin resistance and hyperinsulinemia.

Obese humans have a higher prevalence of coronary heart disease, atherosclerosis, hypertension, and dyslipidemias.[24] Other comorbidities associated with obesity in humans include renal disease (mainly diabetic nephropathy), osteoarthritis, and respiratory impairment (including obstructive sleep apnea and asthma). There has been a recent recognition that obesity increases the risk of steatosis, cirrhosis, and hepatocellular carcinoma, and is now recognized to be the most prevalent form of liver disease in Western countries.[25] Obesity also predisposes to various types of neoplasia, including postmenopausal breast, prostatic, ovarian, colorectal, renal cell, and esophageal cancer.[26]

Obesity-Associated Disorders in Companion Animals

Table 30-2 summarizes obesity-associated disorders in companion animals.

Longevity

A long-term prospective study recently demonstrated that restricting caloric intake in dogs (to approximately 75% of ad libitum levels) improves longevity.[27] Such a strategy tends to maintain optimal body condition (body conditions scores of 4.5/9 vs. 6.8/9), and can extend lifespan by almost two years (13 years vs. 11.2 years in dogs fed ad libitum).

Endocrine and Metabolic Diseases

In dogs, obesity is reported to be associated with diabetes mellitus, hypothyroidism, and hyperadrenocorticism,[6] whereas obesity in cats is associated with diabetes mellitus only.[5] Cats most often suffer from an "insulin-resistant" form of diabetes mellitus, and there are similarities with "type II" diabetes in humans. Feline obesity is a known cause of insulin resistance in this species,[28] and weight loss in cats improves insulin sensitivity, thereby reducing the requirement for exogenous insulin therapy.

Diabetes in dogs is characterized by progressive β-cell loss and absolute insulin deficiency, such that affected dogs require exogenous insulin therapy and will develop ketoacidosis, if untreated. Although the pathogenesis of β-cell loss is poorly understood, pancreatitis and immune-mediated β-cell destruction are thought to play an important role. The association between obesity and diabetes mellitus in dogs has been shown in epidemiologic studies.[6] One possible explanation for the association is pancreatitis, as the prevalence is known to be higher in overweight dogs.[6] Insulin resistance also may be a contributing factor as it can be induced experimentally (along with other components of the metabolic syndrome) in dogs through weight gain caused by dietary manipulation.[29] Furthermore, dogs fed ad libitum throughout life have worse insulin sensitivity and glucose tolerance.[27] Moreover, a recent study of naturally occurring obesity in dogs demonstrated that the percentage of body fat

correlates with the degree of insulin resistance, and insulin sensitivity is improved significantly upon successful weight loss.[30]

Obese dogs have marginally higher serum total T_4 (thyroxine) and total T_3 (triiodothyronine) concentrations than nonobese dogs, but other parameters (free T_4, canine thyroid-stimulating hormone [cTSH], TSH stimulation) are not significantly different.[31] Thus, although obesity may have some effects on thyroid homeostasis, such changes are unlikely to affect the interpretation of thyroid function tests.

Hyperlipidemia and Dyslipidemia

The association between feline obesity and hepatic lipidosis is well established and was confirmed in an epidemiologic study (see Chapters 32 and 61).[5] Experimental studies in obese dogs have demonstrated mild, but likely clinically insignificant, elevations in serum cholesterol, triglycerides, and phospholipids, while laboratory dogs made obese have increased plasma nonesterified fatty acid and triglyceride concentrations (increased very-low-density lipoprotein [VLDL] and high-density lipoprotein [HDL]; decreased HDL cholesterol).[29] Such changes are associated with insulin resistance. Whether or not lipid alterations account for the increased incidence of pancreatitis in obese dogs requires further study.

Orthopedic Disorders

Obesity is a major risk factor for orthopedic diseases in dogs, with increased prevalence of a variety of orthopedic disorders, including humeral condylar fractures, cranial cruciate ligament rupture, and intervertebral disk disease.[32] There are also reported associations with hip dysplasia and osteoarthritis,[33,34] while weight reduction can lead to a substantial improvement in degree of lameness in dogs with hip osteoarthritis.[34]

As with dogs, obesity may be a risk factor for orthopedic disease in cats. One study suggested that obese cats were five times more likely to limp than cats of normal body condition.[4] However, not all reports have confirmed this association.[5] The lack of association in the latter study may relate to the fact that orthopedic disease is underrecognized, especially as clinical signs are subtle in this species.

Cardiorespiratory Disease and Hypertension

Obesity in dogs can have significant deleterious effects on the functioning of the respiratory system, as shown in a recent experimental study.[35] Although higher BCS did not influence airway function during normal breathing, airway resistance was markedly greater during hyperpnea. Furthermore, there was a tendency toward a lower functional residual capacity in markedly obese dogs compared with other dogs. Such effects are similar to those seen in humans, and may help to explain the link between obesity and certain respiratory conditions in the dog, most notably tracheal collapse, laryngeal paralysis, and brachycephalic airway obstruction syndrome.

Although obesity can affect cardiac rhythm and left ventricular volume, there is no evidence of an association with cardiac disease in dogs.[36,37] However, overweight dogs with heart failure have reduced survival times compared with cats in normal body condition.[37] The effect of obesity on blood pressure is relatively minor and unlikely to be of clinical significance as it is in humans. Finally, obesity may also be associated with portal vein thrombosis, and myocardial hypoxia.

Other Disorders

Some epidemiologic studies in both cats and dogs have reported an increased risk of neoplasia in obese animals.[5,6] However, this association is controversial as it has not been reported in all studies.[38] Overweight dogs are reportedly at increased risk for transitional cell carcinoma of the urinary bladder, but there is controversy over an association between obesity and mammary carcinoma.

Experimentally, the onset of obesity is associated with glomerular pathology in the dog, including increases in plasma renin and insulin concentrations, mean arterial pressure, and plasma renal flow.[39] However, no such association has been reported in naturally occurring obesity. For lower urinary tract diseases, associations between obesity and both urethral sphincter mechanism incompetence (USMI) and transitional cell carcinoma are reported, while obese animals have an increased risk of dystocia. Finally, although the reasons for an association are unclear, obese cats are at increased risk of oral cavity disease, dermatologic disorders, and diarrhea.[5]

Pathogenesis of Obesity-Associated Diseases

When present in excess, white adipose tissue can increase the risk of disease through both "mechanical" and "endocrine" mechanisms. Mechanical effects include excessive loading of weight-bearing structures (exacerbating orthopedic diseases), constriction of collapsible structures (increasing risk of upper respiratory tract and urinary system disorders), inability to groom, and reduced heat dissipation as a result of the insulating effect of fat. White adipose tissue is now understood to be a major endocrine organ, synthesizing a range of cytokines, chemokines, and other inflammation-related proteins, collectively termed *adipokines* (Fig. 30-2).[40] Thus, the endocrine effects of obesity arise through disturbance of its normal function, leading to a state of chronic mild inflammation. In humans, increases in the production of certain "inflammatory" adipokines (e.g., leptin, TNF-α, interleukin [IL]-6, plasminogen activator inhibitor [PAI]-1, and haptoglobin) have been directly linked to the development of the metabolic syndrome and other disorders linked to the obese state.[41] Although information is more limited, inflammatory adipokine gene expression was documented in both canine and feline white adipose tissue samples.[40] Plasma leptin concentrations have been shown to be independently associated with insulin sensitivity in lean and overweight cats, while mildly increased TNF-α, C-reactive protein, and haptoglobin are seen in obese dogs with insulin resistance, and which decrease after weight loss.[40] This suggests that similar pathogenetic mechanisms may exist in companion animal and human obesity.

Clinical Investigation

Upon initial presentation, the patient should be examined thoroughly, with the aim of quantifying the level of obesity, identifying predisposing risk factors, and determining overall health status. All concurrent diseases should be identified, whether they are obesity-associated or not. This enables the clinician to decide upon a plan for weight management, to determine an appropriate target weight, and to choose the safest and most effective approach for weight loss. The exact tests performed will depend upon the individual patient.

History and Physical Examination

The medical history should include details of environment, lifestyle, diet and exercise regimens, as well as a complete medical history including previous or current medical therapy. Physical examination should focus on associated diseases either causing or contributing to weight gain, or present as incidental findings.

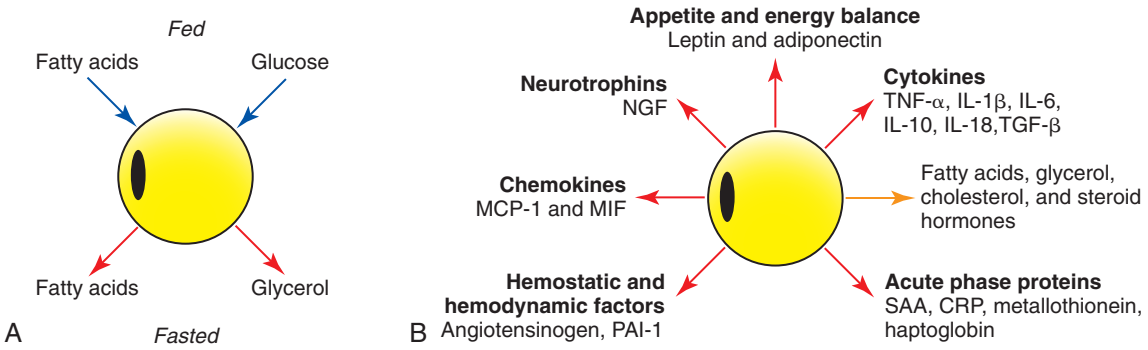

Figure 30-2 Evolving views of the biologic functions of adipose tissue. Adipocytes were previously considered to be inert storage depots releasing fuel as fatty acids and glycerol at times of fasting or starvation. However, it has become increasingly clear that adipocytes are endocrine cells, which secrete important hormones, cytokines, vasoactive substances, and other peptides. **A,** Inert storage depot. **B,** Secretory and endocrine gland. This figure outlines the range of such proteins secreted from white adipose tissue (WAT). CRP, C-reactive protein; IL, interleukin; MCP-1, monocyte chemoattractant protein-1; MIF, macrophage migration inhibiton factor; PAI-1, plasminogen activator inhibitor-1; SAA, serum amyloid A; TGF-β, transforming growth factor-β; TNF-α, tumor necrosis factor-α. Reprinted with permission from German AJ, Ryan VH, German AC, et al: Obesity, its associated disorders and the role of inflammatory adipokines in companion animals. *Vet J* 185:4–9, 2010.

Weight Measurement and Body Condition Score

It is advisable to use the same set of electronic weigh scales for weight measurement, and to calibrate these regularly. BCS is useful at the outset to establish the degree of obesity and predict the likely target weight of a particular animal.[42,43] BCS should be calculated periodically during the weight-reduction program to assess progress, and to adjust the target weight if required.

Further Investigations

Although not mandatory in all patients, routine complete blood count, serum chemistry, and urinalysis can provide general information on health. Additional investigations may be required in some circumstances depending upon history, physical examination findings, and clinical suspicions. For example, the further medical investigation might include blood pressure measurement, thyroid and adrenal gland functional assessments (dog), serum fructosamine measurements for diabetes mellitus, survey radiography for suspected orthopedic and respiratory disease, hepatic ultrasonography, and fine-needle aspiration cytology or liver biopsy for suspected hepatic lipidosis. Bacterial culture of the urine, bladder ultrasonography, and radiographic contrast studies for lower urinary tract diseases could also be included in the workup.

Diagnosis

Measurement of Obesity in Companion Animals

Body composition can be assessed in various ways, some more quantitative than others. First, DEXA is known to be precise and reliable, and can be used in a referral setting (Fig. 30-3),[44] but it is unsuitable for general practice, where noninvasive methods are preferred. BCS schemes assess adipose tissue mass through visual assessment and palpation.[42,43] They have shown good repeatability when used by trained individuals, and correlate well with body fat mass measured by DEXA.[42] BCS can determine the approximate degree of excess weight in obese dogs and cats, with each point (in a 9-point system) or half point (for a 5-point system) correlating with approximately 10% to 15% of excess body weight.[43] Finally, bioimpedance is another noninvasive method potentially applicable in general practice. It should be noted, however, that many handheld devices designed for dogs are unreliable, and inferior to the use of BCS.[45]

Treatment and Prognosis

Weight management in cats and dogs can be very challenging for the pet owner as well as for the veterinarian. Rather than simply reducing body weight, the main aims of weight management are to improve quality of life and reduce associated disease risk. In so doing, it is vital that a healthy relationship is established between the pet and its owner, or the weight-reduction program will likely fail over the long-term. The recommended rate of weight loss remains controversial: slow rates of loss can be met with frustration on the part of the owner, while overly rapid rates of loss could enhance fat mobilization and hepatic lipidosis in cats, and excessive lean tissue loss in both species. Weight-reduction rates should be tailored to the nutritional and metabolic needs of each individual cat or dog, but a rate of approximately 1% loss per week is thought to be safe and realistic.[46,47]

There are two phases to any weight-loss program: the weight-loss period itself, which can be of variable length (over many months), and maintenance, which involves stabilization of body weight and preventing rebound weight gain. In humans, the most successful approach for treatment of severe obesity is bariatric surgery, but it is not likely to be practical or ethically justifiable in companion animals. Dietary therapy remains the most common approach to obesity management, although microsomal membrane transfer protein (MTP) inhibitors are gaining increasing acceptability for the treatment of canine, but not feline, weight loss.[48] Whichever strategy is adopted, long-term substantive changes to lifestyle (e.g., increased physical exercise and alterations in feeding behavior) are fundamental to long-term success.

Dietary Management

Diet Formulation

Purpose-formulated weight-loss diets are recommended because they have restricted energy content while at the same time supplemented with protein and micronutrients. Rates of weight loss are principally determined by energy intake. Supplementing dietary protein relative to energy content does not speed up the rate of weight loss, but it ensures that lean tissue lost is minimized. L-Carnitine supplementation is thought to maintain lean tissue mass during weight loss, while supplementation of micronutrients, relative to energy content, ensures that deficiency states do not arise.

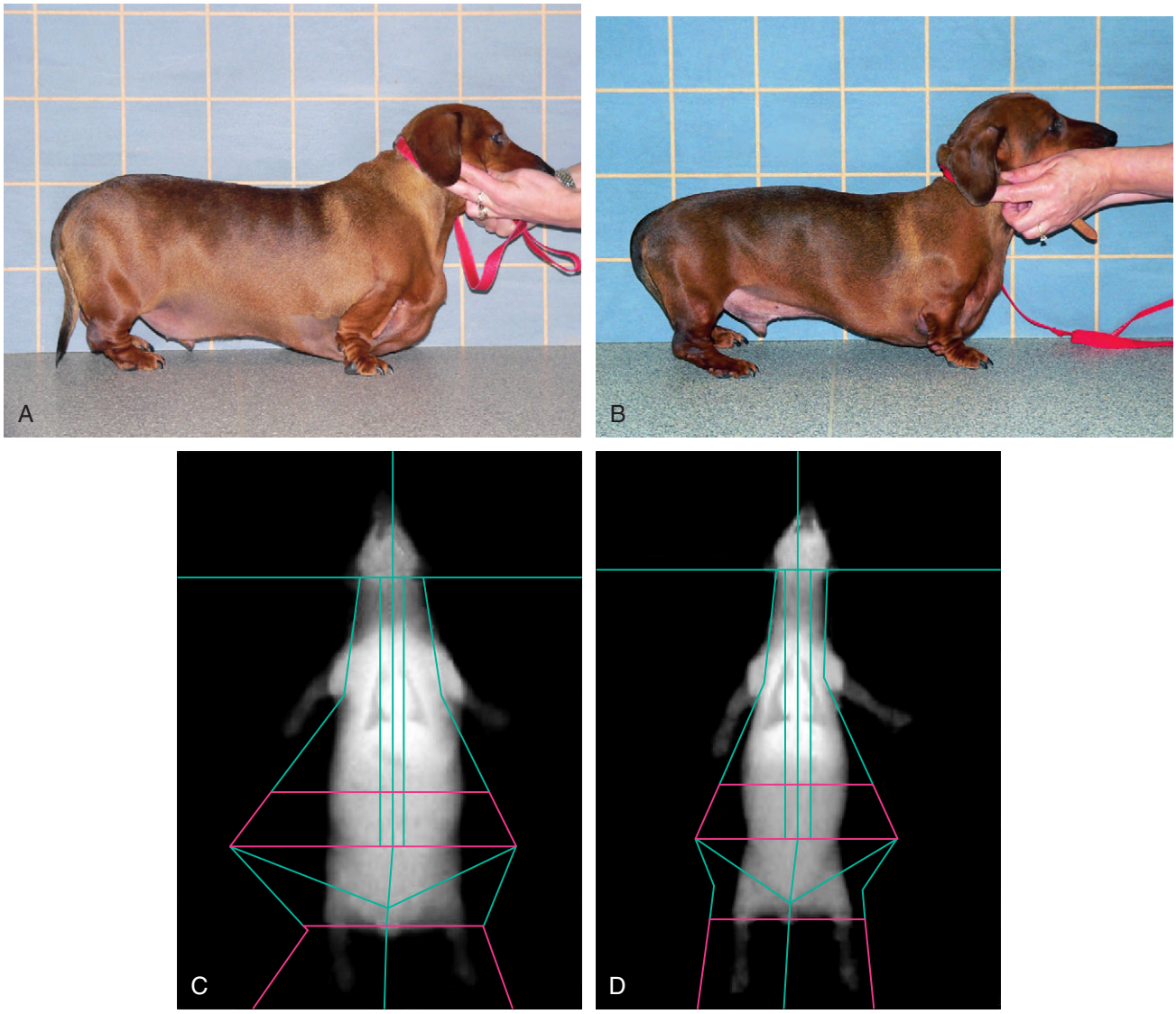

Figure 30-3 **A,** Photograph of an obese 3-year-old neutered male Dachshund, weighing 10.5 kg (23.1 lb), and condition score of 9/9. **B,** Photograph of the same dog, 363 days later, after successful weight loss on a high protein high-fiber diet. Body weight had decreased to 6.5 kg (14.3 lb), and condition score was 5/9. Total weight lost was 38% of starting body weight, at a rate of 0.7%/week. **C,** Dual energy X-ray absorptiometry (DEXA), performed prior to weight loss revealed a body fat mass of 49%. **D,** DEXA, repeated after weight loss, demonstrated that body fat mass had declined to 30%. Based upon the DEXA figures, the estimated composition of the body tissue lost was 81% fat and 19% lean.

Altering the macronutrient content of a weight-management diet can also improve satiety, especially when fiber is supplemented. Supplementing both protein and fiber relative to energy content provides the greatest benefit in dogs,[49] and such a formulation improves the outcome of the weight-reduction program.[50] Because protein content is a key determinant of voluntary food intake in cats, the best effect on satiety is with fiber supplementation, while only modestly increasing protein content.[51]

Energy Intake During Weight Loss

When calculating energy allocation for weight loss, it is essential to base the calculations on the target body weight and not the current weight. Exact recommendations on energy intake vary widely depending upon the diet, species, gender, reproductive status, and concurrent disease. In dogs, a study has suggested a typical starting allocation for weight loss of approximately 60 kcal/kg metabolic body weight (MBW [at target weight (TW)], $kg^{0.75}$),[46] with spayed female dogs requiring less energy than male dogs (either intact or neutered). It should be remembered, however, that the initial allocation is only a starting point, and may need to be modified depending upon response and clinical course. Indeed, in the study described previously, mean energy intake over the entire study period was 57 kcal/kg MBW TW.[46] An average starting allocation of 40 kcal/kg TW and mean energy intake of 32 kcal/kg TW has been recommended for pet cats with naturally occurring obesity.[47] With this degree of restriction, the mean rate of weight loss is 0.8% body weight per week for both species (see Fig. 30-3).[46,47]

Use of measuring cups should be avoided as measurements are imprecise. Electronic kitchen scales are less prone to human error. Close monitoring is required and energy intake must progressively be reduced to ensure continued weight loss.

If at all possible, no additional sources of food should be offered by pet owners to pets during their reduction programs. Healthy treats may be allowed, provided that they are accounted for in the

overall allocation, and provide less than 5% to 10% of total daily requirements. Liquids (e.g., milk) and food used to facilitate oral administration of medications can also be a source of significant caloric intake.

Pharmaceutical Therapy and Weight Loss

Mitratapide and dirlotapide are licensed for use in dogs in Europe, while only dirlotapide is licensed in North America. Neither are licensed nor safe for use in cats. Both drugs are MTP inhibitors, which have local effects at the level of the intestinal epithelial cells in inhibiting the assembly and release of lipoprotein particles into the bloodstream. Dietary caloric intake is decreased both by decreasing lipid absorption and by decreasing appetite. Both drugs are less potent when administered in conjunction with a low-fat (i.e., <10%) diet.

Mitratapide is designed only for short-term use, that is, in the first 8 weeks of a conventional weight-reduction program. Dirlotapide can be used continuously for up to 12 months. Weight loss occurs at a steady rate (0.75% per week on average), but periodic increases in dose are required to maintain weight loss.[48]

The most common side effects of MTP inhibitor treatment are vomiting and diarrhea, and can be seen in up to 20% of patients.[48] Anorexia is also reported in a number of animals and become concerning to many pet owners. If owners are forewarned that it may occur, it is usually better tolerated. Although these drugs can be successful in promoting weight loss, appetite returns rapidly when discontinued and other strategies (feeding and behavioral) may be needed to be successful. Without these additional strategies, rapid and predictable obesity rebound occurs.[48]

Lifestyle Management

Increased physical activity is recommended for most affected animals because, in addition to fat loss, physical activity may assist in lean tissue preservation and possibly help to prevent rapid regain in weight that can occur after a period of successful weight loss. The exercise program should be tailored to the individual, and take concurrent medical conditions into account. Suitable exercise strategies in dogs include lead walking, swimming, hydrotherapy, and treadmill running. Cats can be encouraged to increase their activity through regular play sessions with cat toys (e.g., fishing rod toys), motorized units, and puzzle feeders.

Monitoring of Weight Loss

Regular weight checks should be scheduled during the weight loss program. Initially, a 2-week interval between rechecks is recommended as adjustments are frequent at the start of the program. Thereafter, if weight loss is steady, the interval between rechecks can be increased, but ideally should not exceed 4-week intervals. It is usually best if a dedicated member of the staff takes charge of the weight-management program. In that way a rapport can be established with the client, and this may improve the likelihood of a successful outcome. Given that some clients require intensive support throughout the program, owner coaching may be needed. It is essential to continue to monitor body weight after ideal weight has been achieved to ensure that weight that was lost is not regained; as with humans, a rebound effect has been demonstrated after weight loss in dogs.[49,52]

Prognosis

When an animal is predisposed to obesity, both through individual and environmental factors, many of these predispositions will remain after weight loss. It should also be remembered that the maintenance energy requirements likely will be significantly lower following weight reduction.[53] For these reasons, the obesity can only be managed and never cured, and the prognosis for long-term success is guarded. In the author's experience, approximately two-thirds of dogs and cats successfully reach their TW, while partial success occurs in others. However, for unknown reasons, some dogs and cats fail to lose significant weight or are lost to followup. Also in the author's experience, approximately 50% of cases have weight rebound, although most regain less than half their initial loss. Therefore, as mentioned previously, continued monitoring of body weight during maintenance is recommended. Feeding a purpose-formulated diet (i.e., the one used for weight loss) can help to prevent rebound. Such diets are appropriate for the low-maintenance energy requirements of dogs postweight loss.[53]

Prevention

Given the variable outcome of weight management diets, prevention of obesity is likely to have a more significant beneficial effect on the health and welfare of all dogs and cats, rather than by treating once the problem has developed. Advice on correct nutrition and exercise should be included in all puppy consultations and continued for all dogs throughout their lives. Body weight and BCS should be assessed and discussed at every consultation and during the annual health check. By monitoring body weight and BCS throughout life, increasing adiposity can be more readily identified and rectified. Finally, veterinarians should be alert to the weight gain that can occur as a consequence of neutering. It is advisable to schedule two to three weight-checks in the first 6 to 12 months after neutering to identify those animals at risk of weight gain, and correct it before it becomes a problem.

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CHAPTER 31

Adverse Food Reactions

Nick Cave

Definition

An *adverse food reaction* is defined as any abnormal clinical response that occurs following ingestion of a food or food component. Adverse food reactions have been classified according to the underlying pathophysiologic mechanism. These classifications vary from highly specific mechanisms to broad categories. The classification presented in Box 31-1 is based on the mechanism of the reaction, but it should be recognized that in the vast majority of cases, the mechanism of the adverse reaction to food remains undetermined. Thus diagnostic and management principles apply to all clinical cases unless a specific mechanism is identified.

Adverse reactions can be initiated by single chemical elements within a food (e.g., individual protein antigens, histamine, lactose), may be caused by larger components of the food (e.g., the lipid or carbohydrate component), or may only be seen when a whole commercial diet is fed and not if the individual ingredients are fed. Adverse reactions may be seen with very small amounts of food (e.g., in immunoglobulin [Ig] E–mediated hypersensitivity) or may require overfeeding.

The prevalence of adverse food reactions in dogs and cats has not been precisely determined. In a study of 55 cats with chronic signs of gastrointestinal disease (vomiting and/or diarrhea), clinical signs resolved in 27 (49%) of the cats fed an elimination diet.[1] Of those 27 cats, 16 (29%) relapsed when challenged with the original diet. Similar studies have not yet been published in dogs. However dogs with acute vomiting and/or diarrhea are frequently seen in primary practice, and adverse reactions to food are commonly suspected (Box 31-1).

Mechanism and Pathophysiology

Nonimmunologic Adverse Reactions to Food (Food Intolerance)

Nonimmunologic adverse food reactions refer to those in which an innate or acquired immunologic response is not the underlying mechanism for clinical signs. The term *food intolerance* has often been used to describe all nonimmunologic adverse reactions to food. Food "additives" are frequently thought to be responsible for intolerance reactions in dogs and cats. A food "additive" is generally defined as anything that is not directly nutritive but imparts increased nutritional, gustatory, or cosmetic appeal. These include preservatives, humectants (hygroscopic substances), emulsifying agents, flavors, gelling agents, and colors.[2] Despite the wide range of compounds used in commercial pet foods under this term, and in contrast to popular opinion, there is little evidence that food additives are a cause of gastrointestinal disease in dogs and cats.

Food Toxicity

Food toxicity, or food poisoning, generally refers to reactions caused by microbial contamination, but could also include toxins such as benzoic acid or propylene glycol, which have been used in some pet foods. Food toxins include those incorporated into the manufacturing process, and those produced during storage as the result of microbial spoilage. Several mycotoxins have been identified in commercial foods, with corn, grain, and their by-products most commonly incriminated. Aflatoxins (produced predominantly by *Aspergillus* spp.) primarily cause acute hepatocellular necrosis, and dogs or cats may present with anorexia, vomiting, diarrhea that can progress to melena, and other signs of acute hepatopathy.[3,4] Deoxynivalenol (DON, also endearingly termed "vomitoxin") is the most prevalent mycotoxin produced by *Fusarium* spp. Dogs and cats are very sensitive to DON contamination, leading to anorexia, vomiting, bloody diarrhea, and leukopenia, signs that could be easily confused with those of parvoviral enteritis.[5] Enterotoxigenic strains of bacteria can contaminate food and produce acute enteritis, including *Escherichia coli*, *Staphylococcus pseudointermedius*, and potentially *Clostridium* spp. In the majority of these cases, there is usually a clear association between ingestion of a particular food substance and the onset of clinical signs, but pet owners may not present affected animals unless the clinical signs are serious or persistent.

Alterations in the Microflora

Ingested food has a profound effect on the number, species, and metabolic activity of the intestinal microflora. Abrupt dietary change is a common cause of diarrhea, and occasionally vomiting. Most cases are mild and self-limiting, although some will persist until the animal has returned to regular feedings. Persistence of clinical signs following dietary change is reason to suspect a food hypersensitivity or persistent intolerance, but many short-term cases are probably the result of induced disturbances in the enteric microflora. Nondigestible carbohydrate and protein serve as substrates for the microflora, but bacterial species vary greatly in their ability to ferment dietary compounds. In humans, changing from a conventional diet to a highly digestible, fiber-free liquid enteral diet reduces fecal bacterial numbers on a dry weight basis, as well as the fecal concentration of short-chain volatile fatty acids (acetate, propionate, butyrate).[6] The inclusion of fermentable fiber into liquid enteral diets

Box 31-1 Mechanistic Classification for Adverse Reactions to Food

Food intolerance (no primary immunologic basis)
Food toxicity (food poisoning)
Disturbed microflora
Dysmotility
Pharmacologic reactions
Maldigestion/malabsorption ("metabolic")
Physical
Nonspecific dietary sensitivity
Food hypersensitivity (food allergy)
Type I immunoglobulin E mediated
Type IV cell mediated (including gluten enteropathy)

provides substrate for distal ileal and colonic bacteria, and reduces the effect of shifting to highly digestible liquid enteral diets.

In addition to the effect of diet on total bacterial numbers, diet also has an important effect on microbial distribution. Dogs fed a high-protein canned diet have increased numbers of fecal *Clostridium* spp. and reduced numbers of fecal bifidobacteria when compared with dogs fed a lower-protein dry diet, although diet had no effect on fecal *Clostridium perfringens* enterotoxin detection.[7] Human patients placed on a fiber-free liquid enteral diet experienced varied and inconsistent alterations in their fecal microflora.[8] Patients who subsequently developed diarrhea during enteral feeding had higher total numbers of fecal *Clostridium spp*. and lower numbers of *Bifidobacterium* spp. Bifidobacteria have been shown to exert antimicrobial activity against many enteropathogens. Specific strains of bifidobacteria isolated from human feces inhibit the growth of *Salmonella* spp., *E. coli*, *Klebsiella pneumoniae*, and *Staphylococcus aureus* in vitro, and significantly reduce mortality when gnotobiotic mice are infected with *Salmonella typhinurium*.[9]

Similar mechanisms have been proposed to underlie most cases of antibiotic-associated diarrhea. Changes in the enteric microflora are associated with decreased fecal short-chain fatty acid concentrations and decreased concentrations of bifidobacteria species, both of which return to normal following antibiotic withdrawal.[10] Disruption of the commensal population following antibiotic therapy permits pathogen proliferation, which could cause diarrhea through toxin production.

Sources of fermentable carbohydrate have been shown to affect numbers of mucin-degrading bacterial species, which are associated with increased mucosal permeability and diarrhea.[11] A reduction in the specific strains of resident microflora, may reduce the overall pathogen inhibition effect, which then increases the risk of colonization with enteropathogens such as *Clostridium difficile or C. perfringens*. Substantial individual variability is seen in the susceptibility to dietary change. One of several explanations is the variability in an individual's microflora, and even within similar compositions there is variation. For instance, not all *Bifidobacterium* strains possess antibacterial activity, and this contributes to individual variability in response to dietary changes.

When introducing a new diet, a general pragmatic recommendation is to gradually wean the animal from one diet while introducing it to the next. A period of adaptation of intestinal function (e.g., brush-border enzyme expression), as well as microflora, minimizes the risk of diarrhea or vomiting. Clinical experience suggests that for most individuals, a 5-day transition period is adequate, and if clinical signs continue or develop after that time, a persistent adverse food reaction should be suspected.

Dysmotility

Foods that prolong gastric retention, especially high-fat diets and highly viscous diets (soluble fiber), or diets that contain poorly digestible starch may promote vomiting in susceptible patients.[12-14] Predictably, gastric retention times increase with increasing meal size, but also with increased dry matter content.[15] In humans with functional dyspepsia, dietary fat is frequently incriminated as an exacerbating and potentially causative factor leading to an exaggerated sense of fullness, nausea, and vomiting.[16] This is supported by studies that demonstrate symptoms after duodenal lipid infusions, but not after isoenergetic infusions of glucose.[17]

Feeding therefore can have an emetic effect, especially with preexisting gastric disease. Small, frequent feedings have been recommended to limit the duration of acid secretion at each meal and to minimize gastric distention, which can provoke nausea when the stomach is inflamed.

Studies of dietary influences on colonic motility have largely centered on dietary fiber, and their fermentation by-products, the short-chain fatty acids. Constipation is a relatively common presentation, and in the absence of a mechanical obstruction, can develop as a result of excessive dehydration and impaired motility. Dietary variables that lead to constipation have not been well defined in dogs or cats. There is a clear association with the consumption of indigestible material such as bone or wool.[18] In normal humans, colonic transit time is decreased as insoluble fiber is increased, whereas in patients with chronic constipation, increasing insoluble fiber does not speed fecal transit.[19] Whether that reflects a cause or effect is uncertain, as is the significance to canine and feline patients. It is likely that colonic transit time partly determines the response to dietary manipulation, as it does in people.[20] However, determination of colonic motility in dogs and cats is somewhat difficult (see Chapter 26), and there is no definitive evidence for recommending one intervention over another.

Insoluble, nonfermentable fiber increases fecal bulk and increases the frequency of defecation in healthy animals. Increasing fecal bulk may exacerbate constipation in an individual with impaired colonic motility. Perhaps the poorest choice of dietary fiber in constipation is a nonfermentable, insoluble fiber that increases fecal dry matter, but not fecal water content, such as cellulose.[21] Fiber that produces viscous gels (e.g., psyllium husk) will increase the fecal water content, in addition to increasing fecal dry matter. Short-chain fatty acids from colonic fermentation have been shown to stimulate longitudinal colonic smooth muscle contractions in vitro in kittens and adult cats.[22] However highly fermentable fiber may also result in the production of methane. Methane production varies greatly between individuals and depends on the presence of specific organisms.[23] Physiologic concentrations of methane slow small intestinal transit by augmenting circular muscle contractions in the ileum.[24] Constipation, small intestinal dysmotility, and discomfort are aggravated in human irritable bowel syndrome patients with methane production.[24,25] Similarly, the induction of nonpropulsive segmental contractions by methane may be a cause of motility dysfunction in dogs and cats. Consequently, the supplementation of diets with rapidly fermentable purified fiber sources, such as hydrolyzed guar gum, may exacerbate some cases of constipation, irritable bowel syndrome, and other motility disorders.

Pharmacologic Reactions

Methylxanthines. Theobromine and caffeine toxicity is well recognized in dogs. Most dogs will present with signs relating to central nervous system and cardiovascular effects. Anxiety, aggression, tremors, and tachycardia are commonly reported.[26] In other cases,

vomiting and diarrhea are more prominent clinical signs, but still usually accompanied by concurrent neurologic signs.[27]

Histamine. Histamine is found in various home-prepared and commercial foods. Higher concentrations have been detected in foods containing fish by-products, although ingredient lists are not always complete.[28-30] Histamine and other decomposition products are produced in raw fish by bacterial conversion of free histidine. Scombroid fish (e.g., tuna, mackerel, skipjack, bonito) have higher amounts of histamine because of the free histidine content in their muscles.[31] Adverse reactions to the ingestion of raw anchovies that was responsive to antihistamine administration has been reported in cats, and similar signs have been reported in dogs.[30] In those cases, salivation, vomiting, and diarrhea developed within 30 minutes of ingestion.

Some commercial foods contain concentrations of histidine equal to that of raw fish that, if spoiled, might result in high histamine concentrations. That said, the concentration of preformed histamine in unspoiled commercial foods is not that high.[29-31] Ingested histamine is rapidly metabolized by intestinal diamine oxidase (DAO). There is great variation in DAO activity within the human population, rendering some individuals very sensitive to dietary histamine content.[32] Variation in intestinal DAO activity in dogs and cats has not been reported, but large differences in plasma DAO activity do exist in cats.[33] Failure to degrade ingested histamine can result in vomiting and diarrhea that can be hemorrhagic, along with other systemic effects.[32,34]

It has been shown that several drug classifications are capable of profoundly inhibiting the activity of porcine and human intestinal DAO, including the β-lactamase inhibitor clavulanic acid.[34] The clinical significance of this is unknown, but it is conceivable that normally tolerated concentrations of dietary histamine may be sufficient to cause clinical signs when the capacity for intestinal metabolism is reduced during oral treatment with clavulanate.

Maldigestion and Malabsorption

Undigested dietary components can lead to osmotic diarrhea, and rapid fermentation in the distal intestine can lead to flatulence, abdominal pain, and vomiting. Lactose intolerance is the quintessential example of a maldigestive adverse food reaction. Intestinal lactase expression decreases rapidly around the time of weaning in most mammals. In kittens, lactase activity decreases almost tenfold between birth and 6 weeks of age.[35] However, expression in adult cats is highly variable, explaining large individual differences in the ability of the cat to tolerate dietary lactose. Fasting also significantly reduces the expression and specific activity of mucosal enzymes such as disaccharidases, which can lead to impaired digestion following the reintroduction of food.[36] Transient lactase deficiency is common, particularly after rotaviral gastroenteritis.[37] Occasionally it persists, and lactose intolerance may be a cause of postgastroenteritis diarrhea. Undigested lactose can lead to diarrhea by a direct osmotic effect. In addition, colonic and distal small intestinal bacteria rapidly ferment luminal lactose producing gas and volatile fatty acids that can worsen diarrhea, abdominal bloating, borborygmus, and painful intestinal dilation. Healthy adult dogs may tolerate up to 2 g/kg body weight (BW) of lactose, whereas adult cats will not tolerate more than 1 g lactose/kg BW without showing clinical signs.[38]

High-fiber diets may have an effect similar to lactose intolerance in sensitive individuals. High-fiber diets increase gas production by colonic flora and inhibit gas transit leading to gas retention, notable borborygmus, abdominal pain, and flatulence.[39] Ingestion of a "fiber-free" diet for 48 hours significantly reduces the total volume of flatus.[40] Highly purified, highly fermentable fibers such as xylan and pectin predictably cause a greater production of hydrogen, carbon dioxide, and methane than does cellulose or corn bran.[41] The amount of fermentable fiber that can be tolerated without adverse effects varies between individuals, and probably reflects differences in colonic transit time, as well as differences in intestinal microflora.[42]

Physical and Other Effects

Commercial pet foods and most home-prepared diets are unlikely to cause physical irritation, damage, or motility problems in the gastrointestinal tract. However, feeding of fresh carcass meat and "home-kill" often results in the ingestion of significant amounts of bone, wool, and hair, which can predispose to constipation, as well as acute colitis.[43] Dietary indiscretion can result in the ingestion of toxins, indigestible physical abrasives, excessive fat, and compounds that can cause significant gastric fermentation.

Nonspecific Dietary Sensitivity

The term *nonspecific dietary sensitivity* has been used to describe animals that have loose or poorly formed feces when fed particular types of commercial diets.[44,45] The most common cases are seen in large-breed dogs, although the phenomenon can also be seen in small dogs and cats. It has been suggested that reduced colonic capacity for fluid and electrolyte absorption in large-breed dogs makes at-risk individuals susceptible to high-moisture diets.[46] Alternatively, rapid intestinal transit may lead to a degree of malabsorption.[45] Only very mild lymphocytic infiltrates are seen in the small intestine of such animals, and it is not clear if these cases are truly a form of inflammatory bowel disease. To date, abnormal microflora populations have not been shown to be present, and although treatment of affected dogs with the probiotic *Lactobacillus acidophilus* strain DSM 13241 led to clinical improvement in one study, the fecal density of cultured bacteria such as *C. perfringens* and *E. coli* were not significantly altered.[47] In summary, the mechanism of the reaction to food is unclear in these cases, although they will rapidly and readily respond to appropriate dietary manipulation (see below).

Immunologic Adverse Reactions to Food

Complex foods contain a myriad of different proteins, the great majority of which are potentially antigenic, and in a lifetime, an animal will ingest many kilograms of these foreign antigens. Luminal antigens are presented to the largest single collection of T lymphocytes in the body, separated by an epithelial layer within which intraepithelial lymphocytes are directly juxtaposed to this antigen mass. Intact antigens are directly sampled from the intestinal lumen, and a small fraction can even be found in the systemic circulation following a meal.[48] For these reasons, it is perhaps more surprising that detrimental immune responses to dietary proteins do not more commonly occur.

Immune Responses to Dietary Antigens

Dietary antigens interact with the intestinal immune system in such a way as to prevent unnecessary and detrimental immune responses. In so doing, systemic immunity is rendered effectively unresponsive if the same antigen reaches the systemic circulation. This absence of reactivity to orally administered antigens is termed *oral tolerance*.

Peyer's patches are the primary inductive area of the intestinal immune system. Specialized M cells within the epithelium sample

particulate and insoluble antigens, and whole microorganisms.[49] Antigens and organisms are then transported to B cells, macrophages, and dendritic cells within basement membrane invaginations. In the normal intestine these antigen-presenting cells (APCs) lack costimulatory molecules such as CD80 and CD86. Antigens processed by these "unactivated" APCs are then presented to naive B and T cells within the follicle, resulting in the induction of hyporesponsive, T-helper (Th) type 3- or Th2-biased T cells.[50] Activated cells then leave via lymphatics and pass via the mesenteric lymph nodes into the systemic circulation. They then exit at mucosal sites via engagement of cellular adhesion molecules (CAMs) specifically expressed by the high-endothelial venules of mucosal tissues. Activated or memory B and T lymphocytes enter the lamina propria to await a secondary encounter with their specific antigen (Fig. 31-1).

Activated cells may secrete cytokines, but full differentiation into effector T cells or plasma cells may not occur without secondary exposure. For both cell types to be reexposed to antigen, intact antigens must reach the lamina propria. Intestinal epithelial cells are capable of antigen absorption, release to APCs, and limited antigen presentation to cells within the mucosa on major histocompatibility complex (MHC) class II. In the normal intestine, these secondary APCs lack costimulatory molecule expression and contribute to tolerance. Effector T-cell clones resident in the normal intestine secrete a bias toward Th2 and Th3 cytokines, in particular interleukin (IL)-10 and transforming growth factor (TGF)-β, thus directing B-cell isotype switching to produce IgA-secreting plasma cells, while inhibiting the development of Th1 lymphocytes and IgG production.

It is important that the immune system reserves the ability to rapidly respond to pathogens. This ability to recognize pathogenicity is based on the engagement of pathogen-associated molecular pattern (PAMP) receptors, such as Toll-like receptors (TLRs), producing "danger signals." Predictably, expression of TLRs is much greater in mesenteric lymph nodes than in the small intestine, which is generally higher than the large intestine where there is increased potential for deleterious activation by normal microflora.[51] The expression of TLRs is generally lower in the mucosal cells of the normal canine intestine than in the intestines of dogs with inflammatory bowel disease (IBD) or diet-responsive enteropathies, but expression can be rapidly turned on in response to inflammatory cytokines.[51] The absence of these "danger signals" results in relatively inefficient antigen processing by intestinal APCs, markedly reduced or absent tumor necrosis factor (TNF)-α/IL-1/IL-12 production, and the absence of CD80/86 costimulatory molecule expression. T cells activated by such an APC, divide less, with most clones undergoing early deletion by apoptosis, while the surviving memory cells tend to secrete IL-10, TGF-β, or no cytokines.[52] This combination of apoptosis, functional defects in surviving clones, and T cells secreting the antiinflammatory and IgA-supporting cytokines, is the general basis for immunologic tolerance to luminal antigens (Fig. 31-2).

Thus oral tolerance is composed of a delicate balance between induction of IgA, T-cell deletion, anergy, and immunosuppression; and the retention of antigen-specific lymphocytes capable of responding to invasive pathogens through antibody isotype switching to IgM, IgE, or IgG, and the production of inflammatory cytokines such as interferon (IFN)-γ, IL-12, and IL-6.

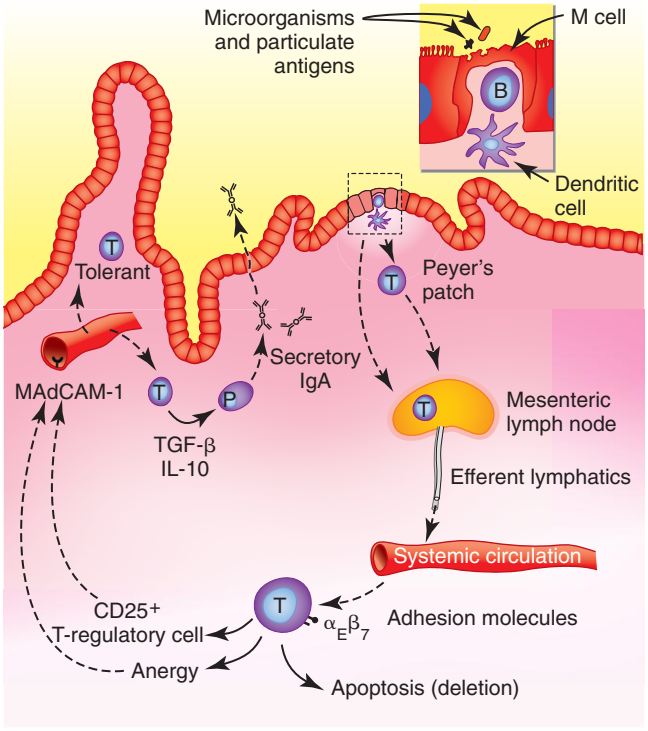

Figure 31-1 Activation and rehoming of intestinal lymphocytes. The primary inductive sites of immune responses to intestinal luminal antigens are the Peyer's patches. Dendritic cells in the Peyer's patch underlying M cells or residing in the mesenteric lymph nodes do not normally express costimulatory molecules (e.g., CD 86) and induce T-cell apoptosis, anergy, or a regulatory function. Lymphocytes activated within the mucosa are induced to express the adhesion molecule ($\alpha_E\beta_7$), which binds to mucosal addressin cell adhesion molecule (MadCAM)-1 expressed by venules within mucosal tissues. In that way lymphocytes activated within mucosal tissues leave to circulate systemically, then exit as effector cells within mucosal tissues.

Food Immunogenicity

In mammals, intact particulate and insoluble antigens are preferentially absorbed across the intestine through M cells overlying the Peyer patches.[53] Classically, such antigens tend to invoke active immunity appropriate for microorganisms. In contrast, soluble antigens are associated with oral tolerance.[54] It has also been shown oral tolerance can be abrogated when soluble proteins are fed in oil-in-water emulsions, resulting in robust systemic humoral responses.[55] This effect may also have relevance to the pet food industry where interactions between dietary proteins and lipids in canned or extruded diets during the cooking and the manufacturing process could feasibly result in novel interactions not present in their native states.

In chickens, particulate antigens induce tolerance, whereas soluble antigens provoke active immunity.[56] If the physical nature of the proteins within the natural diet of a species dictates how the intestinal immune system has evolved, this might have special relevance to species that are commonly fed diets different from their ancestors.

Commercial pet foods are subjected to significant heating during the manufacturing process. The effect of heat treatment on proteins is mostly to change the three-dimensional structure of the protein. Although this may disrupt some antigens, it may equally uncover previously hidden or create new antigenic determinants. Other reactions occurring at high temperatures include the Maillard reactions, which involve the reactions between certain amino acids and reducing sugars to produce less-digestible compounds called *melanoidins*, which give a characteristic brown color. Melanoidins tend to be less digestible and less soluble, and certain melanoidins are more "allergenic" than the original uncooked protein.[57,58]

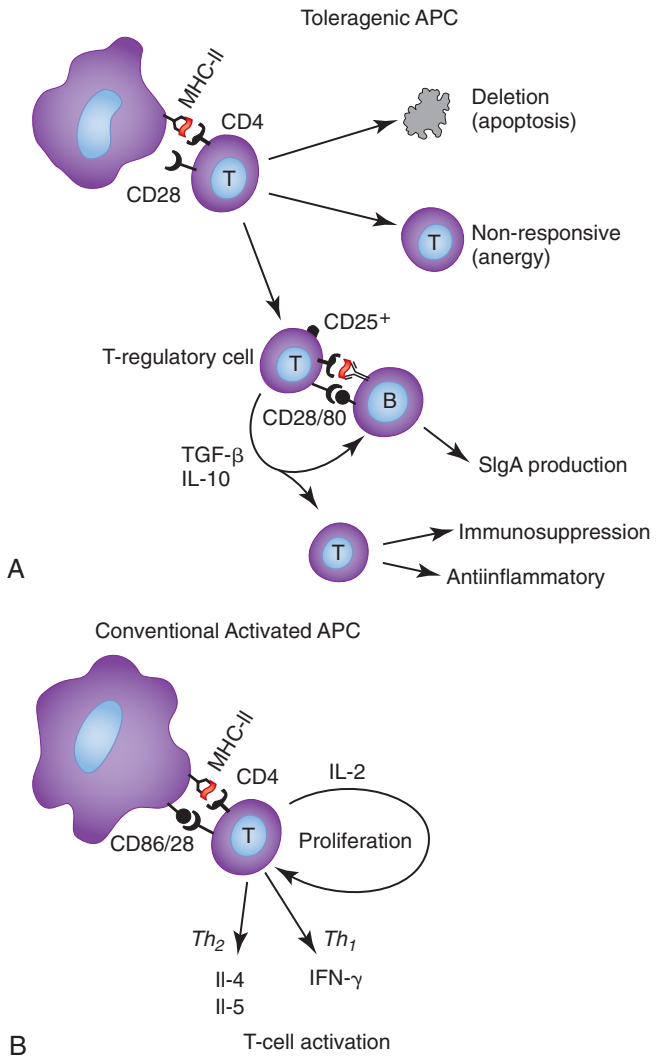

Figure 31-2 Antigen-presenting cells in the intestine are responsible for establishing immunologic tolerance to innocuous dietary antigens. **A,** Intestinal dendritic cells do not widely express costimulatory molecules such as CD86. Antigen presentation leads to tolerance to the antigen through deletion, anergy, or induction of regulatory or suppressor effects in the T lymphocyte. **B,** Elsewhere in the body, conventional antigen-presenting cells activate T cells by presenting antigen in association with costimulatory molecules, inducing either Th1 or Th2 effector functions.

The effect of heating during the canning process on the immunogenicity of dietary proteins has been evaluated in cats.[59] Using soy and casein proteins, the canning process resulted in the creation of new antigens not present in the uncooked product. In addition, a product of heated casein induced a salivary IgA response that was not induced by the raw product. Thus commercial food processing can qualitatively and quantitatively alter the immunogenicity of food proteins. As obligate carnivores, felids have evolved on a highly digestible diet.[60] In keeping with this is the relatively short intestinal tract of the cat, which suggests that they may be poorly suited to poorly digestible diets. It is well established that the commercial canning process decreases protein digestibility and that this has biologically significant effects in cats.[61] Although the significance of this finding is uncertain at present, it emphasizes the need for feeding highly digestible protein sources, or perhaps even more so, hydrolyzed proteins, when enteritis is present.

Loss of Tolerance to Dietary Antigens

The initiating events that lead to loss of oral tolerance, or prevent it from developing have not been described in dogs or cats, and remain poorly understood in any species. Suggested initiating events include the following:

- Increased mucosal permeability, for example, following mucosal injury (e.g., canine parvoviral enteritis) or the neonatal intestine.
- Coadministration of a mucosal adjuvant that activates and changes the phenotype of intestinal dendritic cells, for example, bacterial enterotoxins.[62] Potentially, the introduction of a novel protein at the time of acute bacterial or viral enteritis could lead to temporary or long term dietary sensitization.
- Parasitism. Intestinal parasitism in cats leads to an exaggerated systemic humoral response that includes increased production of food-specific IgE.[63]
- Altered intestinal microflora. The commensal flora are important for establishing normal mucosal immune responses. Lack of commensal flora or TLR-4 signaling augments allergic responses to food antigens in both animal models and humans, and feeding lipopolysaccharide restores oral tolerance in germ-free sensitized mice.[64]

Loss of tolerance to dietary antigens will produce a conventional but detrimental immune response against the dietary antigen. Such an inappropriate response may produce inflammation locally, or at another anatomical site. The response will be characterized by any of the following:

Local Cell-Mediated Inflammation. The resulting chronic stimulus may lead to lymphocytic intestinal infiltration characteristic of IBD. A complete clinical response to an elimination diet has been reported in a cat with duodenal and ileal lymphocytic infiltrates so marked that a histopathologic diagnosis of intestinal lymphoma was made.[65] Alternatively, local inflammatory cytokine release by food-specific T lymphocytes can lead to functional and structural changes leading to loss of absorptive surface area, maldigestion and malabsorption, and vomiting and/or diarrhea.

Local Antibody Production of Isotypes Other Than IgA. The production of IgE will lead to mast cell priming and immediate intestinal hypersensitivity. Following ingestion, mast cell degranulation results causing alterations in transport across the intestinal wall (increased secretory and/or decreased absorptive functions), increased permeability, and altered motility of the intestine.

Systemic Antibody Production. Circulating IgE will lead to priming of mast cells at sites distant to the intestine such as dermal hypersensitivity, that is, food allergy with pruritus as the clinical sign.

The precise nature of the immunologic responses in the vast majority of feline and canine cases is undefined. Although type 1 IgE-mediated hypersensitivities are thought to be present in some, it is likely that other mechanisms exist in a subset of cases. This is especially true for cases where only gastrointestinal signs are present.

Dietary Allergens

Foods contain an enormous variety of proteins, most of which are potentially antigenic (could stimulate an immune reaction if injected), and yet only a few have been shown to be allergenic (capable of stimulating an allergic response). The biochemical

properties that make a particular protein allergenic are not species specific, which is demonstrated by the allergenic potential of immunoglobulins.[66,67] Nonetheless, there are species differences in the relative importance of most allergens. For instance, while beef is the most common allergen in dogs and cats, it is not a common cause of allergy among people living in North America despite it being a significant source of protein in their diets.[68-71]

Mast cell degranulation requires crosslinking of two or more IgE molecules bound by high affinity (FcεR1) IgE receptors on the mast cell membrane. This requirement for divalency places a minimum size limit on molecules that can stimulate IgE-mediated reactions. Most publications refer to this lower limit as being 10 kDa, although smaller peptides could act as haptens, and in humans, peptides as small as 4.5 kDa retain allergenicity.[71-76] Proteins greater than 70 kDa are unlikely to be efficiently absorbed intact through the enteric mucosa and few food allergens are of that size.

Although the majority of the known food allergens are naturally occurring food proteins or glycoproteins, there is evidence that nonprotein molecules can function as allergens. Certain carbohydrates, free of proteins, such as pneumococcal polysaccharides and highly crosslinked dextran, induce allergic reactions in man.[71,77] Carbohydrate determinants have been implicated as protein-binding haptens (e.g., inulin), and as parts of antigenic glycoproteins (e.g., β-fructofuranoside).[78-80] They are also claimed to be responsible for crossreactivity between plant allergies, and are incriminated in false-positive IgE-binding assays, such as used in serum enzyme-linked immunosorbent assay (ELISA) allergy tests.[80] However, the role of true carbohydrate antigens in human allergy is still controversial and poorly defined, and nothing is yet known about their existence in canine and feline patients.

In cases where a dietary carbohydrate is implicated as a source of allergen, for example, maize, it is more likely that there is a protein allergen within the carbohydrate source than the existence of a true hypersensitivity to the carbohydrate molecules. Maize zeins, which are 20- to 23-kDa proteins, have been detected in hydrolyzed casein formulas when corn starch is used as the carbohydrate source.[81] Similarly, lipophilic protein allergens have been isolated in refined vegetable oils.[82] Thus the carbohydrate and lipid sources chosen for incorporation into hydrolyzed protein diets may be an important source of conventional protein allergens and should be considered when evaluating commercial diets.

The most commonly incriminated protein sources in cases of adverse food reactions where dietary hypersensitivity is suspected are the dietary staples. This is an important point that warrants emphasis. Dietary staples within commercial pet foods vary around the world, and to date there does not appear to be one dietary ingredient more likely to cause hypersensitivity than any other when quantity of exposure is considered.

Gluten Enteropathy

A unique dietary hypersensitivity to the storage proteins (gluten) of cereal grains has been described in genetically related Irish Setter dogs.[83,84] In affected dogs, there is reduced brush-border enzyme expression, villous atrophy, diffuse infiltration of the lamina propria and epithelium with increased numbers of lymphocytes, and goblet cell hyperplasia.[85,86] Increased mucosal permeability to macromolecules accompanies these changes, and may precede the development of enteritis in young dogs.[83] Clinical signs of small intestine diarrhea, variable vomiting, weight loss, and, eventually, panhypoproteinemia are characteristic, similar to those reported in other chronic inflammatory enteropathies, such as inflammatory bowel disease. Clinical signs and morphologic changes are reversible when dogs are maintained on a gluten-free diet.[84]

In humans, gluten enteropathy (also known as celiac disease) is a disease of the small intestine, characterized by inflammation in response to the gluten proteins of wheat, barley, and rye in genetically predisposed individuals.[87] Similar to affected dogs, human patients suffer from various degrees of enteritis, ranging from mere intraepithelial lymphocytosis to severe subepithelial (lamina propria) mononuclear cell infiltration resulting in total villus atrophy coupled with crypt hyperplasia.[88] Predictably, clinical signs in people vary from subclinical to severe malabsorption, and even intestinal T-cell lymphoma and other intestinal neoplasia.

In humans, nearly all patients have the MHC II (human leukocyte antigen [HLA]) alleles HLA-DQ2 or HLA-DQ8. Celiac disease in humans results from dysregulation of a usually suppressed T-cell response to gluten in a subset of carriers of HLA-DQ2 or HLA-DQ8. Gluten enteropathy appears to be inherited in Irish Setters as a single autosomal recessive locus.[89] However, genetic analysis of two large families of gluten-sensitive Irish Setter dogs revealed no genetic linkage between the MHC haplotypes and disease.[90] Thus the gluten enteropathy of the Irish Setter dog is not perfectly analogous to celiac disease in humans.

The prevalence of gluten sensitivity among the whole population of dogs has not been reported. A confirmed case of gluten enteropathy has not yet been published in any other breed or in cats. Nonetheless, gluten is suspected to be a common allergen, or as a cause of chronic enteritis, which may be more a reflection of the prevalence of the disease in humans.

Differential Diagnosis

Adverse reactions to food cause a diverse range of gastrointestinal signs, and can be cause for peracute clinical presentations, or a cause of chronic disease. Because of the wide range of clinical signs seen in adverse reactions to food (ARFs), they should be considered in the differential diagnosis of any patient presenting with diarrhea or vomiting. Importantly, ARF should be ruled out early as a differential diagnosis in both acute and chronic gastrointestinal disease unless serious clinical signs are present. This is because of the frequency of diet-responsive disease, the simplicity of diagnosis, and the importance of not pursuing invasive and expensive diagnostic tests (e.g., intestinal biopsy) in patients that would have improved with appropriate dietary manipulation alone.

Evaluation of the Patient

History

ARFs can manifest in any part of the gastrointestinal tract, from the oral cavity to the anus. For that reason, an ARF should be considered as a differential diagnosis for a wide range of gastrointestinal problems. However, the most common presenting problems are vomiting and diarrhea. ARF should be considered more likely if the animal presents with concurrent pruritic skin disease.[1,91] The index of suspicion is increased when there is a temporal association between the feeding of a specific food or ingredient, and the development of clinical signs. Certainly this is helpful in cases of acute ARF where signs develop soon after ingestion. However, even in acute ARF, the timing between ingestion and clinical signs can be misleading as reactions can occur immediately or hours after ingestion. This is particularly important when considering vomiting, which may occur hours after a meal. Moreover, several other gastrointestinal disorders may be associated with clinical signs shortly after

feeding, including acute gastritis, pancreatitis, hepatic failure, and diaphragmatic hernia with gastrointestinal incarceration. Other historical features, like presence or absence of food in the vomitus, large or small bowel-type diarrhea, and length of time the diet has been fed prior to the development of clinical signs, do not readily distinguish ARF from other gastrointestinal disorders. ARFs do not commonly lead to serious clinical signs such as marked weight loss, depression, protracted vomiting, melena, and hematemesis, but several types of ARF may be more severe. Food toxicity, chronic type IV hypersensitivity, gluten enteropathy, and histamine intolerance are examples.

Paramount to the successful diagnosis of ARF is a complete dietary history. Accurate documentation of protein, fat, and carbohydrate sources is essential for conducting appropriate elimination diet trials. For commercial foods, data should include the specific brand, formulation, and flavor variety. When considering the possibility of food toxicity, information should include food purchase date, location of purchase, and storage conditions. All other sources of nutrition should be determined, including treats, table scraps, supplements, food used for administering medications, and edible chew toys (e.g., rawhide). When a home-prepared diet is fed, the specific recipe should be obtained, and special consideration should be given to the potential for microbial contamination (e.g., uncooked meat). Finally, the owner should be questioned about the daily feeding regimen, including other animals in the household, as an indicator for other potential food sources.

Physical Exam

ARFs do not produce classical or pathognomonic physical examination findings. Therefore a physical examination in a patient with suspected ARF focuses on the detection of abnormalities that support other differential diagnoses for the gastrointestinal signs. The reader is referred to Section II of this text for relevant examination findings for each presenting problem. As previously mentioned, the combination of gastrointestinal and cutaneous signs may be present in up to 65% of cases of food hypersensitivity, and that particular combination should raise the index of suspicion of an ARF.[91,92] Thus a careful dermatologic examination should be conducted for signs of cutaneous food hypersensitivity such alopecia, broken hair shafts, papular dermatitis, saliva staining, erythema, pyoderma, and otitis externa.

Elimination and Challenge Diet Trials

A clinical diagnosis of ARF is often based upon the resolution of clinical signs when the offending food is removed from the diet, followed by relapse upon reintroduction of the same food or ingredient. The removal of all potential offending ingredients from a patient's diet is known as an elimination diet trial. The success of an elimination diet trial is dependent upon the correct identification of potential allergens, selection of an appropriate elimination diet, acceptance by the patient, and compliance by the owner. The ideal characteristics for an elimination diet for gastrointestinal disease are the following:

- Intact or hydrolyzed protein sources that are novel to the patient
- A single or limited number of protein sources
- High digestibility
- Restricted fat (dogs <30% of metabolizable energy)
- Avoidance of high protein
- Source of moderate content of fermentable fiber

For cases where gluten sensitivity is suspected, a gluten-free diet is obviously necessary. Animals, especially large-breed dogs, with mild diarrhea that are fed high-moisture canned diets, may benefit from the specific use of a dry diet formulation, in case of nonspecific dietary sensitivity.

The term *hypoallergenic diet* is, at best, an ambiguous one, and has been widely misused. It should be reserved for diets that have, at the very least, been demonstrated to possess a substantial reduction in antigenicity, and preferably been shown to be tolerated by the vast majority of patients known to be hypersensitive to the intact source protein.[93-95] However, defining at which point in the reduction in antigenicity or clinical reactivity a diet could be considered "hypoallergenic" is arbitrary, unless it is absolute, and thus use of the term is discouraged.

A general recommendation for elimination dietary trials is to gradually introduce the elimination diet to allow for intestinal and microbial adaptation to prevent exacerbation of the primary disease, and prevent the misinterpretation of continuing signs (e.g., diarrhea) as evidence of a negative response. In practice, however, when a diet is used with the attributes listed previously, adverse effects of the change are minimal, rarely detectable, and very unlikely to extend beyond the trial period.

Commercial Diets for Elimination Trial

Many commercial diets are suitable for elimination diet trials, and selection is based primarily on which diet is known to be novel to the individual patient, rather than a preconceived and unproven claim of superiority. Intact protein examples include Hill's Prescription Diet d/d (Potato and Duck, Rice and Egg), Royal Canin Veterinary Diet (Potato and Venison, Potato and Whitefish), and Nestle-Purina Veterinary Diets DRM.

Hydrolyzed Protein Diets

Dogs and cats are increasingly exposed to a wide variety of protein sources. The identification of a truly novel protein in patients presented for evaluation of dietary hypersensitivity can be difficult. Hydrolyzed protein diets allow greater confidence in the instigation of an elimination trial where a dietary history is either uncertain or reveals prior exposure to multiple proteins.

The primary aim of a hydrolyzed protein diet is to remove any existing allergens and prevent recognition by a patient sensitized to the intact protein. A secondary aim might be to disrupt the proteins to such an extent that there are no longer any antigens capable of eliciting an immune response and sensitization in a naive individual. Ideally, hydrolysis prevents the mast cell degranulation that would occur in response to the intact protein, and enables a patient hypersensitive to the protein to ingest the hydrolysate without clinical signs. It should be reemphasized that the precise nature of the immunologic response is never defined in the vast majority of cases. Thus, although type I IgE-mediated hypersensitivities are thought to be present in some, it is likely that other mechanisms exist in a subset of cases. The degree of hydrolysis needed to prevent an adverse reaction may be different, when adverse non–IgE-mediated immune responses are present.

Initial selection of a commercial hydrolyzed protein diet for a particular patient should probably be based on the protein source. No currently available diets are sufficiently hydrolyzed to guarantee the complete absence of any allergens. Therefore it is prudent to select a diet that does not contain a protein source known to have sensitized the patient. Secondary consideration should be given to the sources of carbohydrate and lipid, as sources of potential protein allergens, and as unproven as sources of carbohydrate or lipid antigenicity. Table 31-1 lists the hydrolyzed protein diets currently widely available.

Table 31-1 Complete and Balanced Hydrolyzed Protein Diets Available for Dogs and Cats*

Diet	Protein Source	Carbohydrate Source	Lipid Source
Hill's z/d Ultra Allergen Free	Chicken	Maize starch, cellulose	Soybean oil
Hill's z/d Low Allergen	Chicken, potato	Potato, potato starch, cellulose	Soybean oil
Hill's Feline z/d Ultra canned	Chicken	Corn starch	Soybean oil
Hill's Feline z/d Low Allergen dry	Chicken, Brewer's rice	Brewer's rice	Brewer's rice, Soybean oil
Nestle-Purina HA	Soy	Corn starch, cellulose, vegetable gums (gum arabic and guar gum)	Coconut oil, canola oil, corn oil
Royal Canin Hypoallergenic	Soy and poultry liver	Rice, beet pulp, fructooligosaccharides	Poultry fat, soybean oil, borage oil, fish oil

*Ingredients taken from product guides.

Osmolarity increases significantly with hydrolysis, and the high incidence of diarrhea in infants fed extensively hydrolyzed formulas has been attributed to this fact.[96] Although the osmolarity of jejunal contents following a normal meal is mildly hyperosmolar (300 to 350 mOsm/L), feeding high-osmolarity enteral solutions (up to 800 mOsm/L) is associated with diarrhea in humans.[97,98] Even higher osmolarities can cause sloughing of enterocytes.[99] In studies of acute diarrhea in children, an osmolarity of 250 mOsm/L or less is associated with improved rehydration, reduced stool volume, and less vomiting, compared with a solution of 311 mOsm/L.[100] However, the osmolarity of the jejunal contents following a meal of completely hydrolyzed diet is not easily predicted, as it is affected by other ingredients, and by the rate of gastric emptying. Thus a low-fat hyperosmolar solution will produce a different intestinal luminal osmolarity than that obtained with complex extruded dry diet. The osmolarity of the Hill's z/d Ultra diet has been determined to be 682 mOsm/L when mixed 1:1 wt:wt with water, compared with 293 mOsm/L for a standard intact protein maintenance diet.[101] Therefore it is conceivable that the high osmolarity could be detrimental in some dogs. However, in 46 dogs fed the diet for 6 to 8 weeks as part of an evaluation for suspected food hypersensitivity, only four dogs developed soft feces during the trial.[102] Also, of the 46 dogs, 21 dogs had gastrointestinal signs as part of their original presentation, and the feces of all 21 improved on the hydrolysate diet. In the aggregate, these findings would suggest that hyperosmolar diarrhea is not a significant problem with that diet.

Home-Prepared Diets

Home-prepared elimination diets are sometimes suitable alternatives to commercial diets. There are several published sources for suitable recipes, and individual recipe formulation can be made by a veterinary nutritionist.[103] Home-prepared diets offer the flexibility of selecting the desired protein and carbohydrate sources, and the macronutrient proportions, followed by the addition of further ingredients to balance the diet. This gives much greater flexibility than diets available commercially. The high digestibility of home ingredients adds to their efficacy, and they may be less immunogenic than commercial diets. It is often stated that these diets are more palatable than commercial diets. Although such a broad statement cannot be strictly tested, one study that compared home-prepared diets with a commercial hydrolyzed protein diet found that there was no general difference in acceptance.[91] The neophilic effect of offering a home-prepared diet to an animal normally fed a commercial diet may be significant. Likewise, high-moisture foods tend to be more palatable than dry food.

Home-prepared diets can, and should, be formulated to the same standard of commercial diets. However, a combination of inadequate recipes, owner (and veterinarian) ignorance, and the natural tendency for "recipe drift" may conspire to yield a large proportion of inadequate diets. In Europe, a survey of recipes found that energy, fat, and protein were above Association of American Feed Control Officials (AAFCO) recommendations, whereas ratio of calcium to phosphorus, vitamins A and E, and potassium, copper, and zinc concentrations were below recommendations.[104] Relative fatty acid contents of serum phospholipid fractions of home-fed dogs were significantly lower in 18:2(n-6) and 20:4(n-6) than in those from a population of 37 normal dogs consuming commercial dry diets. In the United States, previous studies found that the great majority (>90%) of recipes are nutritionally inadequate.[105] The most common nutritional inadequacy is a deficiency of calcium and a low ratio of calcium to phosphorus, which is an inevitable consequence of an unsupplemented meat-based diet. Other common deficiencies include vitamins B_{12}, E, D, and A, and copper, manganese, and iodine. Common excesses include total fat, 18:2(n-6), and B vitamins.

That dogs and cats do not apparently become ill with short-term feeding of such diets is believed to be a result of:

- The current inability to measure the effects of short-term nutritional inadequacy.
- The uncertainty of absolute physiologic requirements.
- The difference between long-term requirements averaged out as a daily requirement versus true short-term requirements.
- Noncompliance and the pragmatic tendency for a varied diet to be more likely to be completed than a restricted one.

Elimination diets should be fed for as long as it is reasonable to expect improvement in clinical signs. For patients with gastrointestinal disease that appears to be no longer than 3 weeks in duration, and for most patients it may be much shorter. Indeed, cats with proven ARF as the cause of the gastrointestinal signs (vomiting and/or diarrhea) all responded within 7 days of the new diet.[1]

Ideally, a convincing improvement would be followed with challenge of the original diet or individual dietary components to both confirm the diagnosis of an ARF, and identify the specific offending ingredient. In cases where clinical signs are severe, identification may be important to minimize the risk of repeated exposure. However, when a complete and balanced commercial diet is selected as the elimination diet, owners will frequently, and reasonably, decide to continue feeding the novel protein selections.

Food-Specific Serum Immunoglobulin

Several commercial companies offer testing for food-specific antibodies using ELISA and RAST (radioallergosorbent test) techniques, ostensibly to aid in the diagnosis of food hypersensitivity, and in the identification of relevant allergens. Systemic immunoglobulin is commonly produced in response to dietary proteins.[59,106]

This is perhaps surprising in light of the concept of oral tolerance. However the immunoglobulin classes are dominated by IgA and IgG in healthy animals. If the dietary protein is introduced to animals infected with intestinal ascarids, greater quantities of food-specific antibody are produced, and there is a shift toward food-specific IgE.[63] In addition, gastrointestinal disease from a variety of causes, including IBD, is associated with increased food-specific serum IgG.[106] There is, however, no evidence that the food-specific antibody production contributes to disease in these cases. Nor is there any evidence of the diagnostic utility of measuring serum food-specific immunoglobulins either as an aid to diagnosing food hypersensitivity or in identifying offending allergens.[107]

Endoscopic Food-Sensitivity Testing

Even if a single protein source is identified as the cause of an ARF by using elimination and challenge diet trials, differentiation between food intolerance and food hypersensitivity cannot be made as the mechanism for clinical reactivity remains unknown. Direct visualization of a gastric mucosal reaction in response to topically applied antigen solutions can be achieved endoscopically and is used as compelling evidence for an IgE-mediated hypersensitivity. Gastroscopic food-sensitivity testing involves the dripping of a soluble antigen solution onto the gastric mucosa, and the area is observed for up to 5 minutes.[108] Positive changes include focal mucosal swelling and erythema at the site of application, more generalized mucosal erythema, and gastric hyperperistalsis. To assist solution placement, solutions (100 to 500 μL) are applied adjacent to a biopsy site taken at the time of the procedure. A positive control solution of histamine is used to validate an immediate-type response. Biopsies are taken from any reactive sites to support the immunologic mechanism. Difficulty with localization of the solution once applied, and the inability to reliably test more than two or three antigen solutions during one endoscopic procedure, limit the diagnostic utility of this approach. An alternative approach is to inject the solutions (300 μL) directly into the mucosa, allowing better localization, and potentially increasing the number of antigen solutions that can be tested. Injection of solutions around the ileocolic valve during colonoscopy (colonoscopic allergen provocation) has been shown to have a higher sensitivity than gastroscopic food-sensitivity testing, using oral challenge tests as a gold standard in a small number of dogs.[109] However, the practical clinical value of endoscopic food-sensitivity testing has not yet been established. The gold standard of oral challenge testing is cheaper, noninvasive, and in the absence of life-threatening clinical signs, without significant risk. For the time being, endoscopic food-sensitivity testing cannot be recommended in routine clinical practice.

Treatment and Management

Long-term management of ARF, regardless of whether it is an intolerance or specific hypersensitivity, involves avoidance of the incriminated food. To be successful, thorough challenge trials to identify the offending food are required. In practice, once a clinical resolution is apparent, clients are usually understandably reluctant to subject their pet to further investigations. In those cases, empirical recommendations should be made regarding the potential for hypersensitivity to any of the previous diet's ingredients, and avoidance of those in the future is a pragmatic recommendation.

Individualization is required for successful dietary modification in patients with chronic constipation. When colonic motility is known or suspected to be impaired (e.g., megacolon), low-residue diets with moderate (<10% dry matter basis) contents of total dietary fiber are recommended. When colonic motility is still suspected to be reasonable, increasing nonfermentable, gel-forming fiber is likely to be beneficial. A total dietary fiber content of 10% to 20% dry matter basis is reasonable.

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CHAPTER 32

Nutritional Strategies in Gastrointestinal Disease

GASTROINTESTINAL TRACT

Sherry Lynn Sanderson

Definition

The gastrointestinal tract (GIT) in dogs and cats is a dynamic organ that performs numerous functions (see Chapter 1) essential for the health and well-being of the animal. A critical function of the GIT is digestion and absorption of nutrients, as well as elimination of potentially harmful substances and waste products. In addition, the GIT is the largest immunologic organ in the body and it also functions as an endocrine organ. Nutrition is important for maintaining a healthy GIT, and it plays a key role in the management of many GIT problems.

Protein

Protein and amino acids are important for synthesis and repair of tissue, and also play a role in energy metabolism. Although all proteins are functional, protein is the second largest potential store of energy in the body after adipose tissue.[1] Energy and protein needs are tied together, and amino acids from protein can be converted to glucose by gluconeogenesis. They serve as a continuing supply of glucose after glycogen is consumed during fasting. The GIT is the primary route by which protein enters the body, and protein balance in the body is dependent on both the availability of dietary protein and the ability of the GIT to digest and absorb protein. Disorders affecting the absorption of protein can rapidly deplete protein stores in the body and lead to protein malnutrition. Protein malnutrition has adverse effects on numerous functions in the body, including muscle strength, organ function, and immune function. Protein malnutrition can also result in mucosal atrophy in the GIT, further impairing protein absorption.

Dietary protein also serves as a source of food allergens. The GIT uses a variety of immunologic and nonimmunologic mechanisms to prevent foreign proteins from entering the body. Under normal circumstances, food antigen exposure via the GIT results in a local immunoglobulin (Ig) A response, activation of regulatory lymphocytes that reside in the gut-associated lymphoid tissue (oral tolerance), and systemic immune response.[2,3] However, in some incidences there is an abnormal interaction between food allergens, the GIT, and the immune system that can result in some GIT disorders such as inflammatory bowel disease (IBD) and acute enteritis. (The reader is referred to Chapter 31 for additional information on adverse reactions to food.)

Glutamine

Specific amino acids play a key role in maintaining a healthy GIT.[4] For example, the amino acid glutamine has traditionally been considered a nonessential amino acid; however, it is now recognized as a conditionally essential nutrient under stress conditions, such as starvation, infection, injury, and recovery from surgery. Glutamine is a fuel for enterocytes lining the small intestinal epithelium, providing as much as 40% of the energy needs for these cells. It is also used by white blood cells and contributes to normal immune system function, as well as being involved in critical processes such as nucleotide synthesis, protein synthesis, and gluconeogenesis. Studies show that dietary glutamine supplementation decreases susceptibility of enterocytes and lymphocytes to apoptosis while enhancing antioxidative function and cell proliferation in the small intestine. It was once believed that only luminal glutamine supported gut function and mucosal integrity. More recent studies show that supplementing total parenteral nutrition (TPN) with glutamine is also an effective route of administration for the gut.[4a]

Arginine

Arginine is important for promoting immune system function. It also serves as a precursor for nitric oxide (NO), polyamines, and creatine, and that it may also activate the mammalian target of rapamycin (mTOR) signaling pathway in the small intestines, which plays a major role in cell growth and proliferation.

Arginine stimulates intestinal fluid secretion through a NO-mediated mechanism, and inhibition of NO synthase (NOS) leads to decreased intestinal secretion and intestinal ischemia. Arginine supplementation is also effective in improving intestinal barrier function and vascular development. Oral arginine decreases the mucosal injury caused by lipopolysaccharide endotoxemia in mice, and pretreatment with arginine enhances survival and intestinal mucosal barrier function after intestinal mesenteric ischemia. Arginine-enriched diets fed to rats also have been shown to protect the gut mucosa from injury caused by radiation-induced enteritis, accelerate healing ability, and prevent translocation of bacteria. However, it is important to keep in mind that the beneficial effects of arginine may be dose dependent. Lower levels of arginine supplementation (0.7%) have beneficial effects on microvascular development, but higher doses of dietary arginine (1.2%) can cause adverse effects, such as gut dysfunction.[4b]

Glycine and Lysine

Both glycine and lysine are directly utilized by the intestine for protein synthesis and other metabolic processes and may have protective effects on the gut.[4] The small intestinal mucosa utilizes glycine to synthesize glutathione (GSH), and it may have powerful cytoprotective effects, such as osmoprotection, scavenging of oxygen free radicals, extracellular signaling, and modification of biologically active molecules. Although research using glycine and lysine supplementation in GIT disorders are just underway, one or both of these amino acids may be useful in the management of some GIT disorders.

Protein Digestibility

Modulation of dietary protein is often very effective in managing many types of GIT disorders. It is very important that protein used in intestinal diets be highly digestible (>87%).[5] This is particularly important in conditions where protein maldigestion or malabsorption is present. Most dietary protein is absorbed in the small intestines, and unabsorbed protein that pass into the large intestines are metabolized by bacteria and produce undesirable metabolites such as gas.

Carbohydrates

Although dogs and cats do not have an absolute dietary requirement for carbohydrates, carbohydrates are a major component of most diets for dogs and cats. The predominant carbohydrate found in pet food is starch. Starch is the storage form of carbohydrates in plants, whereas glycogen is the storage form in animals. The digestibility of dietary starch is dependent upon the source and the degree and type of processing. If properly processed, corn, wheat, rice, and barley can be highly digestible (>90%).[5] Other starches, such as potato and tapioca, are less digestible, especially if undercooked.

Lactose

Lactose is the primary carbohydrate found in milk, and it is broken down by the brush-border enzyme lactase. Puppies and kittens normally have adequate levels of intestinal lactase to permit digestion of lactose in the mother's milk. However, lactase activity often decreases after weaning, and some adult dogs and cats are lactose intolerant. If these animals consume dairy products, such as milk, osmotic diarrhea often results. In humans with lactose intolerance, some studies have shown that the use of probiotics decreases or suppresses symptoms of lactose intolerance.[6-8] Some lactic acid bacteria produce enzymes that hydrolyze lactose, thereby alleviating clinical signs. The majority of the research in this area has been done in humans, and it is unknown at this time whether similar beneficial effects occur in dogs and cats. Carbohydrate intolerance also develops secondary to enteritis, and inadequate disaccharidase activity may be one of the factors responsible for diarrhea associated with rapid changes in the diet.

Fiber

Although the effect of various nutrients on the GIT in dogs and cats has been studied for decades, it is only in the past 10 to 15 years that significant knowledge and understanding of the role that dietary fiber has in maintaining health and preventing diseases has been recognized. Historically, fiber has not been considered essential in the diets of dogs and cats, but the critical role that fiber has in promoting a healthy GIT is increasingly being recognized.

Introduction of Dietary Fiber

Dietary fiber was originally defined as "the remnants of plant cell walls not hydrolyzed by the alimentary enzymes of man," but the definition was subsequently modified to include all plant polysaccharides and lignin, which are resistant to hydrolysis by digestive enzymes.[9] More recently, the definition of fiber has been modified further and is now defined as the composite of all dietary constituents that are not digested by endogenous enzyme secretions in mammals. Although not digestible, dietary fiber is considered to have nutritional value because of its importance in maintenance of the functional integrity of the GIT.[9a]

Dietary fiber consists of material of diverse chemical and morphologic structure. Large differences exist in the physical form and the physiologic effect of various classes of dietary fiber in dogs and cats, and it is now recognized that specific fiber types can be utilized for specific effects on the GIT. Major components of dietary fiber include nonstarch polysaccharides, cellulose, hemicellulose, mixed-linkage β-glucans, pectins, gums, and mucilages. Lignins are also included in the estimates of total dietary fiber because they are plant cell wall constituents that can greatly affect the digestibility of plant-derived foods.[10] Quantitatively, lignins do not make a significant contribution to total dietary fiber intake unless intact seeds are consumed.

The diverse nature of fiber has led to numerous ways of classifying fiber, including by solubility in water, rate of fermentation, digestible and indigestible fractions, water-holding capacity, viscosity, fecal-bulking ability, cation exchange capacity, bile acid–binding ability, and microbial fuel value.[11-14]

In the past, dietary fiber has been classified by its solubility (soluble vs. insoluble). This classification is based on how fiber reacts with water.[11] All fibers hold water to some degree; however, the soluble fibers have a greater water-holding capacity than insoluble fibers, and they may form gels and viscous solutions in the GIT (Table 32-1). In more recent years, this classification of fiber has fallen into disfavor. Categorization of fiber types based on fermentability (Table 32-1) is a more meaningful way to describe certain fiber sources for dogs and cats because the fermentability or the capacity for fiber breakdown by intestinal bacteria more accurately assesses fiber's potential beneficial effects in the GIT than does solubility.

Beneficial Effects of Fermentation of Fiber by Intestinal Bacteria

Fiber usually passes through the stomach and small intestines intact in dogs and cats because they do not endogenously produce the

Table 32-1 Dietary Fiber Fermentation in Dogs[15]

Fiber Type	Solubility	Fermentability
Beet pulp	Low	Moderate
Cellulose	Low	Low
Rice bran	Low	Moderate
Gum arabic	High	Moderate
Pectin	Low	High
CM-cellulose	High	Low
Methylcellulose	High	Low
Cabbage fiber	Low	High
Guar gum	High	High
Locust bean gum	High	Low
Xanthan gum	High	Moderate
Inulin	High	Moderate
Psyllium	Both	Moderate

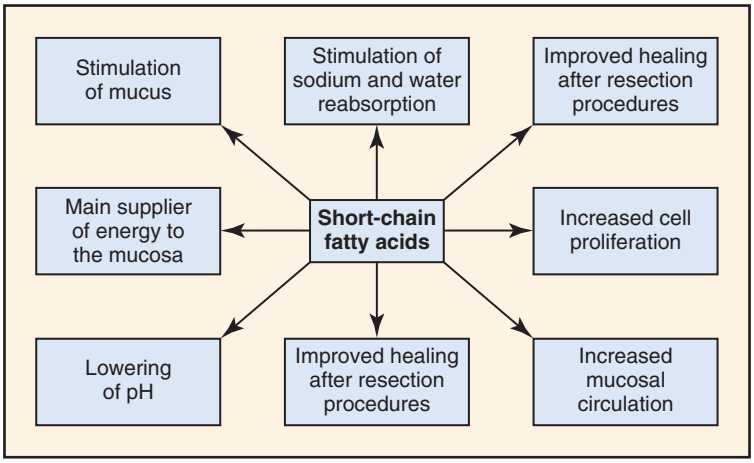

Figure 32-1 Beneficial effects of short chain fatty acids. Adapted from www.nutrition-partner.com

enzymes needed to digest fiber. Until recently, fiber fermentation was thought to be irrelevant in dogs and cats. However, once fiber reaches the large intestines, intestinal bacteria are able to ferment certain types of fiber, resulting in the production of short-chain fatty acids (SCFAs). As a result, fermentation of fiber is very important in dogs and cats. The major SCFAs produced from fermentation are acetate, propionate, and butyrate. In ruminants and herbivorous animals, SCFAs provide a significant source of energy (i.e., up to 75% of daily energy requirement [DER]) in these species. However, dogs and cats have a relatively short and simple structure of the large intestines, and as a result, SCFAs provide less than 5% of energy needs and have little effect on energy balance.[16,17]

Although production of SCFAs in the large intestines of dogs and cats provides very little energy, it does have a number of beneficial effects (Fig. 32-1). Some of the beneficial effects of SCFAs include the following:

1. **An energy source for colonocytes.**[18] Colonocytes derive more than 70% of their energy needs from luminally derived SCFAs. As a result, fermentation of fiber provides a readily available source of energy for colonocytes that aids in maintaining the health and function of these cells. SCFAs are also important for cell renewal and repair. Epithelial cells of the GIT turnover rapidly and must be replaced on average once every 3 days. By providing energy for intestinal cells, SCFAs facilitate the replacement of cells that have been sloughed during the normal process of cell turnover.
2. **Maintenance of normal intestinal electrolyte and fluid balance.**[19] SCFAs facilitate the absorption of sodium, chloride, and water in the colon. For example, a study in dogs showed that sodium and SCFA absorption could account for the entire osmotic absorption of water from the colon. As a result, providing fermentable fiber in the diet is essential in maintaining the normal homeostatic absorptive function of the intestine of dogs.
3. **Maintenance of ileal and colonic motility.**[20] Normal ileal motility appears to be influenced by the presence of SCFA. Kamath et al. infused bolus doses of physiologic concentrations of SCFA into the ileum of dogs. As the dose of SCFA increased, ileal motility increased. Therefore providing fermentable fiber in the diet may be important in maintaining normal ileal and colonic motility.
4. **Amelioration and prevention of pathogenic bacterial overgrowth.**[21] Harmful bacteria (e.g., *Clostridium*, *Salmonella*, enterobacteria) can produce (a) toxins, (b) carcinogens, and (c) putrefactive substances.[22] Beneficial bacteria (e.g., bifidobacteria, lactobacilli) (a) inhibit the presence of harmful bacteria, (b) stimulate immune function, (c) aid in digestion and/or absorption of food, and (d) synthesize vitamins. Maintenance of beneficial indigenous bacterial populations is important in prevention of pathogenic bacterial overgrowth in the intestine. Indigenous bacterial populations in the dog or cat GIT ferment certain fiber sources that result in the production of SCFA.[17,23] The presence of SCFA inhibits the growth of pathogenic bacteria.[24,25] As a result, not only are indigenous bacterial populations necessary for the production of SCFA, but they can also directly inhibit pathogenic bacterial overgrowth in the gut. A growing body of evidence supports the theory that certain dietary fiber sources can modify the composition of the intestinal microflora.
5. **Maintenance of optimal colonic morphology.**[26,27] Dogs fed a fermentable source of fiber had increased colon weight, increased mucosal surface area, and mucosal hypertrophy compared with dogs fed a nonfermentable fiber source (cellulose). These effects on the colon also aid recovery after intestinal surgery.[28]
6. **Amelioration of intestinal inflammation.**[29] Diets containing nonfermentable fiber (cellulose) as the sole source of dietary fiber fed to dogs resulted in a higher incidence of mucus distention and cryptitis when compared with similar diets that contained a fermentable fiber source.

All Fermentable Fibers Are Not Created Equal

Fiber sources can vary in their level of fermentability (see Table 32-1). As fermentation rate of fiber increases, gastrointestinal transit time decreases, fecal bulk decreases, and fecal bile acid excretion increases. Fibers with low fermentability (e.g., cellulose, methylcellulose, oat fiber, peanut hulls, xanthan gum, locust bean gum) are not metabolized well by intestinal bacteria to produce SCFAs. Rather they retain their structure while passing through the GIT intact and act as bulking agents. Highly fermentable fibers (e.g., pectin, guar gum) are rapidly metabolized by intestinal bacteria. One of the products from bacterial

fermentation of fiber is SCFAs. However, less-desirable substances are also produced from bacterial fermentation, including carbon dioxide, hydrogen, and methane. If a fiber source is rapidly fermentable, large amounts of gases will be rapidly produced in the colon, resulting in diarrhea, flatulence, and cramping. Moderately fermentable fiber sources (e.g., beet pulp, rice bran, gum arabic, xanthan gum) produce SCFAs without resulting in rapid production of gases and associated diarrhea. Therefore, moderately fermentable fiber produces the beneficial effects associated with production of SCFAs without the undesirable effects seen with rapidly fermentable fiber. An ideal fiber source for dogs and cats should contain a moderately fermentable portion to facilitate SCFA generation, as well as a nonfermentable portion to provide bulk and enhance peristalsis.[29a]

Fat

Dietary fat can play a very important role in the management of GIT disorders. Some disorders respond best to low-fat diets, whereas others respond best to medium- or high-fat diets. Not only is the quantity of fat in the diet important, but the type of fat is very important in determining its effect in the GIT. To fully understand the properties of various types of fat, it is important to first understand the nomenclature of fat.

Nomenclature of Fat

Fatty acids are classified as short-, medium-, or long-chain fatty acids. SCFAs contain fewer than six carbons, medium-chain fatty acids (MCFAs) contain six to 12 carbons, and long-chain fatty acids (LCFAs) contain more than 12 carbons. LCFAs are the predominant type of fat consumed in the diet by dogs and cats. When LCFAs are absorbed from the GIT, they first enter the lymphatics before eventually making their way to the blood via the thoracic duct. Generally, once SCFAs and MCFAs are absorbed in the GIT, they bypass the lymphatics and instead directly enter the portal vein.[30] However, it has been shown that when dogs are fed low-fat diets (5.35%, as fed) containing 3.2% (as fed) eight-carbon and 1.5% (as fed) 10-carbon length medium-chain triglycerides (MCTs), that some MCT is absorbed into the intestinal lymphatics.[31] Nonetheless, the ability of MCFAs to bypass the lymphatics in most situations make them useful in managing some types of GIT disorders, especially those involving the lymphatics (lymphangiectasia). However, the diet must always contain LCFAs because these provide the essential fatty acids required in the diet of dogs and cats. Diets containing MCTs usually restrict the amount of MCTs to 25% to 30% of the fat in the diet because MCTs are not very palatable, and animals will often refuse to eat diets containing higher quantities of MCTs. Because MCTs are ketogenic, they should be avoided in patients with acidosis or ketosis.

Triglycerides are composed of three fatty acids esterified to a glycerol molecule. Fatty acids can vary in their chain length as well as the number and arrangement of double bonds. Saturated fatty acids contain no double bonds on the carbon chain, and therefore they are fully saturated with hydrogen molecules. Animal fats, such as beef tallow, are dietary sources of saturated fatty acids in dogs and cats. Fats also can be unsaturated, which means they contain one or more double bonds in the carbon chain. The location of the double bond(s) is determined by counting from the terminal methyl carbon (designated as n or ω [omega]). If the first double bond in omega fatty acids occurs either at the three-, six-, or nine-carbon, they are referred to as omega-3 (n-3), omega-6 (n-6), or omega-9 (n-9) fatty acids, respectively. Fats that contain one double bond on the carbon chain are called *monounsaturated fatty acids*, and fats that contain two or more double bonds on the carbon chain are called *polyunsaturated fatty acids* (PUFAs). All of the essential fatty acids for dogs and cats are PUFAs.

Both dogs and cats have a dietary requirement for linoleic acid (LA), which is an n-6 fatty acid.[32] Cats also require arachidonic acid (AA), which is also an n-6 fatty acid. Dogs, however, are able to synthesize adequate amounts of AA from LA and therefore do not have a dietary requirement for AA. Although definitive studies have not been done in dogs and cats, most nutritionists believe that the n-3 fatty acid, α-linolenic acid (ALA), is also necessary in the diet of dogs and cats. Although both dogs and cats have the ability to synthesize eicosapentaenoic acid (EPA) from ALA, their ability to synthesize docosahexaenoic acid (DHA) from ALA is very limited or not present at all. Because DHA is very important for retinal and brain development, DHA is considered a conditionally essential fatty acid. Including DHA in the diet of puppies and pregnant bitches improves learning abilities of the puppy (data on file, P & G Pet Care). Dietary sources of EPA and DHA include fish oils, such as menhaden oil.

Eicosanoid Production from Fatty Acids

PUFAs are important for maintaining membrane fluidity and related cell functions such as transport, metabolic regulation, and the epidermal water barrier in the skin. Cell membrane stability, structure, and function are dependent on having unsaturated fatty acids incorporated into them. The cell membranes from tissues such as adipose tissue, liver, muscle, and kidney tend to be composed predominantly of n-6 fatty acids. Reproductive and neurologic tissues, as well as cell membranes of the rod cells in the eye, tend to be composed predominantly of n-3 fatty acids, in particular, DHA. However, the composition of the cell membranes in many tissues, such as the skin, changes in response to the types of PUFAs provided in the diet.

When PUFAs are metabolized in the body, n-6 fatty acids produce eicosanoids that are different from those produced by metabolism of n-3 fatty acids. These differences can be useful when managing certain types of GIT disorders, especially those associated with inflammation. Eicosanoid synthesis begins with metabolism of AA or EPA by one of two enzyme systems. The first enzyme system is cyclooxygenase, which yield prostaglandins (PGs) and thromboxanes (TXs). The lipoxygenase system yields leukotrienes (LTs), as well lipoxins (LXs), hydroperoxyeicosatetraenoic acids (HEPEs), and hydroxyeicosatetraenoic acids (HETEs). The amount and types of eicosanoids synthesized is dependent upon the availability of the fatty acid precursors, and the activity of the cyclooxygenase and lipoxygenase pathways. The eicosanoids produced from the n-6 fatty acid, AA, are proinflammatory, whereas those produced from n-3 fatty acid, EPA, promote minimal to no inflammatory activity. Because many of the GIT disorders are associated with inflammation, feeding a diet supplemented with n-3 fatty acids may prove useful in reducing the level of inflammation in the GIT. For example, diets supplemented with n-3 fatty acids have been shown to reduce the degree of inflammation in experimental models of colitis.[33]

Fat Malassimilation

Dietary fat is one of the most complex nutrients to process in the GIT. Many steps are involved in the digestion and absorption of lipids (see Chapter 1). In the small intestine, large dietary fat droplets must first be emulsified by bile salts from the liver. This dramatically increases the surface area available for enzyme action. The

resulting smaller fat droplets (triglycerides) are broken down into free fatty acids and monoglycerides by the actions of pancreatic lipase and then incorporated into micelles before absorption through the epithelial membrane. Once both the free fatty acids and monoglycerides are inside the enterocytes, they are repackaged into triglycerides, coated with a lipoprotein to form chylomicrons before entering the lymphatic vessels. Because this process involves multiple organs and multiple steps, disruption of fat digestion and absorption may take place in several gastroenterologic disorders. The resulting fat malassimilation not only interferes with fat absorption, but also interferes with fat-soluble vitamin, mineral, and bile salt absorption. Malabsorbed fat and bile acids are hydroxylated and deconjugated by colonic bacteria to produce potent secretagogues. The deconjugated bile acids and hydroxylated fatty acids are toxic to the colonic mucosa, causing increased mucosal permeability, altered motility, and secretory diarrhea. Dogs and cats with this type of diarrhea can become rapidly dehydrated, develop electrolyte abnormalities, and experience rapid weight loss. The best way to manage these patients is to address the underlying cause of the problem if possible, such as exocrine pancreatic insufficiency, biliary obstruction, and IBD. These animals may also benefit from a lower-fat diet until the underlying cause is addressed. However, it is very important to keep in mind that fat has 2.25 times more energy density per gram than protein or carbohydrate, and if dietary fat intake is reduced, it may be more difficult to meet the energy needs of the patient.

Vitamins and Minerals

Numerous electrolyte and vitamin abnormalities can be associated with GIT disorders, including perturbations in folate and cobalamin (vitamin B_{12}) metabolism. A decrease in serum folate concentrations can be associated with proximal small intestinal disorders, while a decrease in serum cobalamin concentrations can be associated with distal small intestinal disorders and exocrine pancreatic disease. Both serum folate and cobalamin may be decreased with diffuse small intestinal disease. It is particularly important to keep these two vitamin abnormalities in mind for patients with chronic diarrhea and an unthrifty, unkempt appearance, especially cats. Dietary therapy alone is unlikely to resolve these problems. The reader is referred to Chapter 53 for further discussion of folate and cobalamin metabolism.

Folate

Most folate found in pet foods is in the form of folylpolyglutamate and very little is found in the free folate (folylmonoglutamate) form. Liver, animal by-products, and oil-seed meal, such as soybean meal, are the most common sources of folate in pet foods.[34] Dogs reportedly are able to absorb folylpolyglutamates across the small intestines and therefore are much less likely to develop folate deficiency than are cats. However, only the folylmonoglutamate form of folate is actively transported across the small intestines in cats. Folylpolyglutamate in food needs to be deconjugated by the brush-border enzyme, folate deconjugase, to produce folylmonoglutamate. Deficiencies of folate result in impaired biosynthesis of DNA and RNA, and, thus, reduced cell division. The GIT is lined by a rapidly dividing population of cells, and folate deficiency can interfere with this process. Decreased DNA synthesis caused by folate deficiency can also result in megaloblastosis. Treatment of folate deficiency involves identifying and treating the underlying intestinal problem, as well as supplementing the diet with folic acid (200 µg of folic acid per day for 1 month).[35]

Cobalamin (Vitamin B_{12})

Synthesis of vitamin B_{12} is limited almost exclusively to bacteria. As a result, it is found only in foods that have been fermented and those derived from the tissues of animals that have obtained it from their intestinal microflora. Vitamin B_{12} is absorbed in bound form (to intrinsic factor), and it is absorbed only in the ileum. A recent study showed that 61% of 80 cats with clinical signs of chronic gastrointestinal disease had decreased serum cobalamin concentration,[36] and almost all cats diagnosed with exocrine pancreatic insufficiency (EPI) had cobalamin deficiency.[37] Some cats with EPI will respond poorly to pancreatic enzyme therapy unless cobalamin deficiency is concurrently treated. Unfortunately, supplementation to correct cobalamin deficiency requires that it be given parentally and not enterally because cobalamin deficiency causes cobalamin malabsorption. The dose of cobalamin in cats is 150 to 250 µg of cobalamin (cyanocobalamin injection, Elkins-Sinn, Goldline, or others) given subcutaneously once a week.[35] The serum concentration of cobalamin should be rechecked before the fifth and sixth injection. If serum cobalamin concentration has normalized, the dosing schedule can be modified to one injection every 2 to 4 weeks. These animals generally will require lifelong therapy with cobalamin injections.

Prebiotics, Probiotics, and Synbiotics

Companion animals have extensive gastrointestinal bacterial ecosystems. For example, the mammalian digestive system contains more than 500 different species of bacteria.[38] The balance between beneficial and pathogenic bacteria has an effect on the overall health of the animal. As a result, the microbial population in the GIT is recognized to play a substantial role in the health of animals, and its role appears to extend beyond the GIT. Many of the extra-gastrointestinal effects appear to be related to changes in the immune system. Enteric bacteria also contribute significantly to the host's resistance to infectious disease. It is well recognized that a healthy gut bacterial flora is essential for overall health, and this flora is often disrupted during illnesses and may, in some cases, be a precipitating factor.

Establishment of Intestinal Bacterial Flora

Intestinal microflora are established at birth as the neonate passes through the birth canal and after birth through suckling and environmental exposure. Optimal maturation of the gut-associated immune system during the first months of life depends on the development and composition of this native microflora. The most common bacteria with potential to enhance health in pets are the bifidobacteria and lactobacilli. With advancing age, the level and diversity of these beneficial bacteria begin to decline, while less-favorable *Clostridium* spp. bacteria increase.[41] In addition, the bacterial flora composition in the GIT is influenced by many factors including host species, breed, age, dietary history, environmental conditions, geographic locale, intestinal motility patterns, disease, and medication history.

Definitions of Pre-, Pro-, and Synbiotics

Prebiotics are defined as nondigestible food ingredients that beneficially affect the host by selectively stimulating the growth and/or activity of one or a limited number of beneficial bacteria in the colon that improve host health. The most common prebiotic found in diets of dogs and cats is dietary fiber.[22,42]

Probiotics are defined as living beneficial bacteria, which upon ingestion in sufficient numbers exert health benefits to the host.[43] It

is very important that both parts of the definition are met in order to call a product a probiotic.

Synbiotics are defined as a mixture of prebiotics and probiotics that beneficially affect the host. In addition to the beneficial effects of prebiotics alone, in synbiotics, the prebiotic is used to improve the survival of the probiotic organisms.

Prebiotics

Fiber as a Source of Prebiotics

Not all fiber types serve as a source of prebiotics. Three criteria are required for a fiber to serve as an effective prebiotic. First, a prebiotic fiber must be resistant to degradation by stomach acid, mammalian enzymes, and hydrolysis. Second, beneficial bacteria in the intestines must be able to ferment the prebiotic fiber. Third, the prebiotic must selectively stimulate the growth and/or activity of the beneficial bacteria in the intestines. As a result, some fiber sources are ineffective prebiotics.

Prebiotics have received a lot of attention recently as a way to modulate bacterial populations in the colon. Appropriate types of prebiotics can also optimize stool characteristics and reduce fecal odor because fermentation of fiber reduces fecal ammonia, indole, and phenol concentrations, compounds that are implicated as the major malodorous components of feces and as toxins in the colon.

Two fermentable fiber sources that function as prebiotics in the colon are fructooligosaccharides (FOS) and mannanoligosaccharides (MOS). Although both of these fiber sources can have a dramatic effect on the microbial population in the colon, the mechanism by which they accomplish this is different between the two sources.

Fructooligosaccharides

Certain fermentable fiber sources, such as FOS, are good sources of prebiotics for dogs and cats, and the proportion of different bacterial species is related to the type of fermentable substrate available. Fructooligosaccharides are found naturally in many different foods, including plants like beet root (after pulp processing), soy (in the hulls), psyllium, chicory (after hydrolysis), and numerous other fruits, vegetables, and grains.[44] They can also be synthesized commercially. Beneficial intestinal bacteria (e.g., lactobacilli and bifidobacteria) use fermentable fiber as a metabolic fuel, whereas pathogenic bacteria (e.g., *Salmonella*, *Escherichia coli*, *Clostridium perfringens*) cannot metabolize FOS for energy. Production of SCFAs from fiber by beneficial bacteria also lowers colonic pH, further impeding the growth of bacterial pathogens.[45] As a result, in the presence of FOS, beneficial bacteria thrive, multiply, and crowd out pathogenic bacteria. In addition, a study by Willard et al. showed that supplementing the diet of dogs with FOS resulted in a significant decrease in the number of aerobic and anaerobic bacteria in the small intestine of dogs with small intestinal bacterial overgrowth (SIBO).[46] Similarly, FOS supplementation increased numbers of beneficial bacterial and decreased numbers of potential pathogens in the large intestine of healthy cats.[47]

In a recent study, beneficial and pathogenic bacteria in canine feces were cultured and compared while consuming identical diets with various levels of FOS supplementation (data on file, P&G Pet Care). The beneficial bacteria measured was *Lactobacillus*. FOS supplementation resulted in a statistically significant increase in *Lactobacillus* when compared with a diet not supplemented with FOS. In this same study, the pathogenic bacteria *Bacteroides*, *E. coli*, and *Eubacterium* were evaluated. When the diet was supplemented with FOS, there was a statistically significant reduction in the pathogenic bacteria compared with the diet not supplemented with FOS.

Dried beet pulp is another fermentable fiber source in the diet of dogs that beneficially enhance the growth and survival of good bacteria in the gut. Beet pulp is the fiber material that remains after sugar is extracted from sugar beets.[47a] It has been widely used in the livestock industry for many years, and in the last 10 years, the use of beet pulp has expanded into the pet food industry as a source of fiber. It is a safe fiber source and contains no known toxins.

Mannanoligosaccharides

MOS are unique fiber sources similar to FOS. The difference between FOS and MOS is that fructose is the predominant sugar molecule in FOS, whereas mannose is the predominant sugar molecule in MOS. MOS are natural fibers found in yeast cells, and they prevent the growth of harmful bacteria in the GIT through a different mechanism. Pathogenic bacteria establish themselves in the GIT by attaching to the intestinal wall and colonizing the GIT. Pathogenic bacteria are able to attach to the intestinal wall because they have finger-like projections, called *fimbriae*, that allow them to bind to specific residues (e.g., mannose) on intestinal cells. Because MOS contains mannose, fimbriated mannose-specific pathogens can bind to MOS instead of the intestinal wall.[48] By preventing these bacteria from adhering to the intestinal wall, MOS can inhibit the growth of pathogenic organisms, reduce their effects in the GIT and aid in the excretion of these harmful bacteria. They are very effective in preventing diarrhea and contribute to the prevention of digestion-related infectious diseases.

Fructooligosaccharides and Mannanoligosaccharides Enhance the Effectiveness of the Gastrointestinal Immune System

The GIT contains a large population of bacteria, and it is critical to the health of dogs and cats that these bacteria remain in the gut and are prevented from translocating systemically. The GIT is constantly under antigenic stimulation from both bacteria and food, and the integrity of the GIT is essential for maintenance of intestinal health.

The gut contains both nonimmunologic barrier defenses and immunologic barrier defenses. Nonimmunologic barriers include (a) the anatomy of the gut (intact microvilli and tight junctions between cells); (b) peristalsis and mucus, which makes it difficult for pathogens to attach and enter cells; (c) low pH of gastric secretions; and (d) digestive and bactericidal enzymes secreted by the stomach, pancreas, and epithelial cells to inhibit the attachment and growth of bacteria.[49]

The gut is also the largest immunologic organ in the body (see Chapter 3). As a result, immunologic barriers play a critical role in maintaining normal health and function both locally and systemically. Gut-associated lymphoid tissue (GALT) is composed of cells residing in the lamina propria, intraepithelial lymphocytes interspersed between epithelial cells, and immune cells located in organized lymphatic tissue (Peyer's patches and mesenteric lymph nodes).

Fermentable prebiotic fibers, such as FOS, can have a major impact on the gut immune function. In a study by Field et al., dogs were fed isonitrogenous, isoenergetic meat-based diets supplemented with either a combination of fermentable fibers (beet pulp, gum arabic, and FOS) or with nonfermentable fiber (cellulose).[50] Each diet contained similar amounts of fiber but differed in fermentability. The diet supplemented with fermentable fiber significantly ($P < 0.05$) decreased the proportion of Ig^+ cells and increased the CD4/CD8 (i.e., T-helper cell-to-cytotoxic T cell ratio) in peripheral blood. Therefore, adding fermentable fiber to the diet of dogs changes the composition and function of immune cells in GALT.

Probiotics

The most common type of probiotic bacteria are the lactic acid bacteria, such as *Bifidobacterium* and *Lactobacillus*. Probiotics have been used for many years in human medicine. Studies evaluating their potential use in dogs and cats are only in their infancy, but so far they have demonstrated their effectiveness at improving gastrointestinal health in both humans and animals.[50a] The appealing properties of probiotics include their ability to reduce antibiotic use, the apparent high indicator of safety, and the public's continuing positive perception about "natural" therapies.

The mechanisms by which probiotics benefit the host are not completely understood, but may involve immune-enhancing and antiinflammatory activities, modifications to intestinal pH, suppression of pathogenic bacteria through production of inhibitory substances, and competition with pathogens for nutrients and mucosal attachment sites. Bacteria in the gut may also influence the number and distribution of cell types in the GALT and modulate immune response. It is through a combination of these activities that the full range of probiotic benefits is achieved.

When choosing a probiotic, it is important that the product meets both parts of the definition of a probiotic: (a) the supplements containing live (viable) bacteria in sufficient numbers, i.e., billions of organisms; and (b) they have been shown to exert health benefits in the intended species. Unfortunately the veterinary market is flooded with products claiming to be probiotics for dogs and cats. Oftentimes these products contain probiotic bacteria from human preparations. Even if these products are effective probiotics for humans, most have not been demonstrated to exert health benefits in dogs and cats, and therefore these products do not meet the criteria to be called a probiotic. There are only a small handful of probiotic products in the veterinary market that do meet this definition and have research to document clinical efficacy. The following is a list of additional important characteristics that successful probiotics possess.

Stability

A probiotic preparation must be able to withstand commercial processing and storage. Those probiotics that may be stored on a shelf and do not require refrigeration have an advantage in ease of handling from the manufacturing site to the client's possession. A low-moisture environment and avoidance of air are important in the preservation of viable microbes.

Survivability

Survival is the key to a good probiotic supplement. For probiotics to provide a health benefit, adequate numbers of viable organisms must reach the appropriate area of the intestinal tract. For this to happen, probiotic organisms should be selected for their ability to survive transit through the acid environment of the stomach and resist digestion by bile and pancreatic enzymes.

Colonization

An effective probiotic must reside at the desired target sites in the GIT long enough and at sufficient concentrations to elicit probiotic effects. Adherence on the intestinal surface lengthens the retention time of a probiotic, which is important in the small intestine because of the short transient time of intestinal material. Adherence and temporary multiplication of probiotic bacteria at the target site would result in an enhanced concentration of probiotics at the optimal site potentially at a lower dosage. Preferential adherence to the epithelial of the gut helps to maintain gut barrier function and possibly exclude enteric pathogens.

Fermentation of Fructooligosaccharides and Beet Pulp

Among the numerous groups of beneficial bacteria, there are those that can effectively utilize fermentable dietary fibers such as FOS and beet pulp. Bacterial fermentation of these fibers produces SCFAs, which are the preferential fuel for intestinal cells. Health benefits associated with higher densities of bacteria capable of producing SCFAs in the GIT include enhanced intestinal structure and function, stimulation of enteric and systemic immune systems, treatment of gastrointestinal disease, increased absorption of minerals and improved stool characteristics.

Species Specificity

There are inherent differences in the bacterial microflora among species. Probiotics originating from the target species may be better adapted to adhere and possibly colonize the intestinal tract. Adherence and colonization allows greater concentration of the beneficial microbe to help maintain gut barrier function as well as competing with pathogens for sites.

Antipathogen Effects

Probiotic species have protective antipathogen effects by limiting colonization of undesirable bacteria through occupation of certain environmental or nutritional niches; through the production of specific antibacterial products, such as bacteriocins and bactericidal substances; through immune regulation of the host; and/or by inhibition of the production or action of bacterial toxins.

Safety

Probiotics have been widely used for many years in human medicine and overall have an excellent safety record. Potential probiotic bacteria are generally regarded as safe as opposed to antibiotics, which have a number of recognized adverse effects. Concern exists, although insufficiently documented, regarding the possible transfer of antimicrobial resistance from probiotic strains to more pathogenic bacteria in the intestinal microbiota. Newly developed probiotic strains should be evaluated for safety before marketing. There are a limited number of conditions where the use of probiotics is contraindicated until studies document safety.

Contraindications

Patients undergoing long-term immunosuppressive therapy (i.e., patients receiving chemotherapy or those receiving long-term corticosteroids), patients with bloody diarrhea (e.g., parvoviral enteritis patients) and bacterial translocation, and patients with pancreatitis, are a few examples of situations where the use of probiotics would not be advised.

Clinical Benefits of Probiotics in Patients with Gastrointestinal Tract Disorders

Numerous clinical trials have validated the use of probiotics for specific clinical conditions in humans. Although research on probiotic use in dogs and cats lags behind that in humans, it is becoming increasingly clear that probiotics confer many of the same health benefits to dogs and cats. New research has now demonstrated that probiotics can positively affect gastrointestinal conditions in dogs. It is known that the microbial flora of the gut play a role in the normal function and maintenance of health of the GIT. Recent studies have shown that feeding of probiotics to dogs improves stool quality (P&G Pet Care, unpublished research). In one study, young dogs (14 to 16 months old) were fed a probiotic (canine-derived *Bifidobacterium animalis* AHC7; Iams, Prostora Max) or placebo prior to traveling to a training

kennel. Fewer of the dogs that received the probiotic experienced loose stools during the transition to the kennel compared with dogs that received placebo. Another study examined the effects of feeding this same probiotic product to dogs with acute severe watery diarrhea.[51] The time to resolution of diarrhea was approximately 40% less (2.5 days faster) in dogs that received the probiotic than in dogs that received the placebo. Another study examined the effects of this same probiotic in service dogs. Service dogs typically spend the first 14 to 16 months of their lives in a foster home before returning to the service organization for training. It is not uncommon for dogs to develop diarrhea during this transition, which interferes with their training. When compared with dogs that received the placebo, there was a statistically significant reduction in the number of dogs with less-than-ideal fecal scores when probiotics were started 5 weeks prior to this transition. In addition, serum C-reactive protein (CRP) concentrations, which reflect inflammation, were evaluated in both groups. The dogs that received the placebo had elevated levels of CRP above the reference range for at least the first 10 days at the training facility, whereas levels of CRP remained within the reference range the entire time in dogs that received the probiotic. This study illustrates how probiotics not only have beneficial effects in the GIT but systemically as well. These studies indicate that feeding this organism may promote GIT health in dogs, even in the setting of acute diarrhea.

Beneficial Effects of Probiotics on Healthy Dogs

The balance between beneficial bacteria and pathogenic bacteria in the GIT is vital to overall health, and even clinically healthy dogs may have low numbers of pathogenic bacteria, such as *Clostridium* spp., in their GIT. Finding ways to inhibit the growth and reproduction of pathogenic bacteria in the GIT supports overall well-being. In a study conducted by P&G Pet Care, 12 healthy adult dogs were fed either a probiotic product containing canine-derived *B. animalis* (Prostora Max) or a placebo for 6 weeks, and fresh fecal samples were cultured for bacteria prior to any treatment and 5 weeks into either probiotic or placebo treatment. Compared with the control group, the dogs that received the canine-derived *B. animalis* (Prostora Max) had a significant reduction in the total number of fecal *Clostridium* spp. organisms, as well as a significant reduction in a specific clostridial organism (*Clostridium difficile*). Therefore, the probiotic was shown to be effective in reducing the number of pathogenic bacteria, which may reduce the likelihood of disrupting the balance between beneficial bacteria and pathogenic bacteria.

Yogurt as an Alternative to Commercial Probiotics in Dogs

Not all yogurts contain live probiotic organisms because some yogurts are pasteurized, which kills the bacteria. In addition, the two most common probiotic organisms found in yogurt are *Streptococcus thermophilus* and *Lactobacillus delbrueckii* subspecies *bulgaricus*. Neither of these organisms is derived from dogs. As a result, although yogurt that contains probiotic organisms may be beneficial in humans, similar benefits have not been documented in clinical studies when administered to dogs.

An additional hindrance to using yogurt as an alternative to commercial probiotics in dogs is the number of organisms present in yogurt. The generally accepted effective dose of probiotics is a daily dose of 10^9 to 10^{10} organisms. It is estimated that 3.5 cups of yogurt per day would be needed to reach effective levels of organisms, which is not very practical in dogs.[52] When most clinicians have recommended to owners to add yogurt to their dog's food, in most incidences only 2 to 3 tablespoons of yogurt are added to the food, which is too small of a quantity to provide any clinical benefit.

Synbiotics

A two-point approach to maintaining gastrointestinal health can be achieved through the use of synbiotics. When prebiotics and probiotics are administered simultaneously, the prebiotic can be used to increase intestinal survival of the probiotic organism. Beneficial bacteria, such as *Lactobacillus* and *Bifidobacterium*, are able to utilize prebiotics as a source of nutrition, whereas pathogenic bacteria, such as *Salmonella* and *E. coli*, are not.

It is important to demonstrate that the prebiotic fiber selectively stimulates the growth and/or activity of the beneficial bacteria in the intestines because not all fiber sources are effective prebiotics. For example, the effects of various fiber sources were studied to determine their effects on the number of probiotic organisms *B. animalis* AHC7 in healthy dogs (data on file, P&G Pet Care). The fiber sources studied included cellulose, beet pulp, and FOS. At baseline, there was no statistically significant difference in the number of *B. animalis* AHC7 organisms among fiber groups. However, 24 hours after administering the various fibers, there was a statistically significant difference in the number of *B. animalis* AHC7 organisms among fiber groups. Cellulose resulted in the lowest number of *B. animalis* AHC7 organisms, and beet pulp resulted in statistically significant increase in the number of *B. animalis* AHC7 organisms when compared with the cellulose group. FOS resulted in the highest number of *B. animalis* AHC7 organisms and was statistically higher than that seen with both the cellulose and beet pulp groups. As a result, this study demonstrated that there is a symbiotic relationship between the probiotic *B. animalis* AHC7 organism and the prebiotic FOS, and there may be additional benefits of administering synbiotics over administering a prebiotic or probiotic alone.

LIVER AND BILIARY TRACT

Craig G. Ruaux

The liver holds a position of central importance in metabolism (see Chapters 1, 29, and 61). Among the myriad roles of the liver, metabolism of ingested nutrients and toxic compounds is particularly critical. As the source of both the assimilated nutrients and many potentially toxic compounds is either directly from the diet, or from alteration of dietary components by the intestinal microbiota, dietary modification has many potential benefits in animals with hepatic disease.

The traditional approach to management of animals with liver disease has been heavily influenced by a perceived need to protect the patient from hepatic encephalopathy. This emphasis has resulted in the formulation and use of "liver diets" that may be inadequate to meet the caloric and protein requirements of many animals with liver disease. With few exceptions, nutritional interventions should be aimed at optimizing the ability of the liver to heal and regenerate, including provision of sufficient metabolic energy to meet the needs of the patient. In most cases, protection of animals from hepatic encephalopathy is not as important as the provision of dietary energy and preservation of body mass through adequate calorie and protein intake.

Metabolic Energy and Protein Requirements in Chronic Hepatic Disease

Animals with chronic hepatic disease are typically in an advanced catabolic state; consequently, dietary protein restriction may actually slow recovery (as has been shown in studies of human patients).[1,2] To maintain a positive nitrogen balance, protein requirements in animals with acute and chronic hepatitis may be higher than in normal animals.[3] A sizable proportion of this increased metabolic energy and protein requirement is a result of increased protein turnover. In the absence of adequate dietary intake, which is common in animals with liver disease, protein-calorie malnutrition can develop. Protein-calorie malnutrition is associated with loss of lean body mass, blunted immune responsiveness, decreased hepatic albumin synthesis, loss of plasma oncotic pressure, and increased risk of dehiscence of surgical wounds.[4]

Hepatic disease is often accompanied by concurrent malassimilation. Cholestatic liver diseases, for example, are associated with decreased biliary secretion, reduced bile salt availability, incomplete emulsification and micellarization of dietary fat, and steatorrhea. Cats with cholangitis/cholangiohepatitis may have concurrent exocrine pancreatic disease and inflammatory bowel disease (IBD) that may further compromise nutrient absorption through decreased digestive enzyme activity and mucosal dysfunction, respectively.

Patients with liver disease often experience significant nausea and anorexia. As hepatic functional mass declines, less glycogen storage capacity is available within the liver, necessitating the mobilization of lean muscle glycogen stores and protein as substrates for gluconeogenesis. Reduced voluntary intake and increased muscle protein mobilization can lead to rapid weight loss in animals with hepatic disease. Further complicating the management of these cases, skeletal muscle is a storage site for much of the total body pool of ammonia, which is a major toxin of hepatoencephalopathy (see Chapter 17). Failure to meet the animal's metabolic energy requirements and maintain a positive nitrogen balance through provision of adequate dietary protein and fat can thus promote the development of hepatic encephalopathy through release of muscle ammonia stores.

Many clinicians will prescribe protein-restricted diets early in the course of liver disease. This may actually worsen the clinical state of the patient if low dietary palatability leads to insufficient caloric intake. The first aim of nutritional support for most animals with hepatic disease should be to ensure sufficient caloric intake to meet the metabolic energy requirements of the patient.[5] Normal canine maintenance diets utilizing high-quality, readily digestible protein sources are indicated in most dogs with liver disease, unless overt hepatic encephalopathy is present. Provision of adequate calories via dietary fat and carbohydrate spares lean muscle protein, and redirects ingested amino acids for synthesis and repair of muscle mass. Although the actual metabolic energy requirements of animals with hepatic disease are not well defined, clinical experience suggests that most of these patients require at least the same dietary metabolic energy input as healthy, active animals. Unfortunately, many diets utilized for protection of animals from hepatic encephalopathy have reduced palatability, particularly in animals with nausea as a consequence of liver disease, making the provision of adequate caloric intake from these diets difficult.

In obligate carnivores like the domestic cat, the provision of adequate protein intake is even more important to the maintenance of lean body mass. Cats have a minimal dietary protein requirement two to three times greater than that of dogs and other omnivores.[6] The amino acids taurine, arginine, methionine, and cysteine are either essential in cats or become conditionally essential in disease states characterized by decreased voluntary intake. Bile salt conjugation in the cat is dependent exclusively upon taurine,[7] a circumstance which may be further exacerbated if there are disruptions in the enterohepatic recirculation of bile salts.[8] Indeed, total body taurine deficiency readily develops in cats with hepatic disease.

Many diets recommended for use in liver disease cases have a reduced protein content. Although reduced protein content may be protective against hepatic encephalopathy, the use of these diets in animals with nonencephalopathic disease carries the risk of protein-calorie malnutrition. Given that the majority of liver diseases encountered in companion animals do not carry a risk of encephalopathy except in their end stage, the use of unsupplemented "liver diets" with markedly reduced protein content is not recommended in most veterinary patients with liver disease.[3] Diets with mildly reduced protein content, utilizing a high digestibility protein are a preferred choice in most companion animals with liver disease.

Nutraceuticals in Hepatic Disease

A nutraceutical can be defined as a food, food-derived compound, or dietary supplement that is given with the intent to modulate disease or provide health benefits. Many nutraceutical compounds have been suggested as supplements in human beings and animals with hepatic parenchymal disease[9]; however within the veterinary literature only two compounds, *S*-adenosylmethionine and silymarin, have received meaningful attention (see also Chapters 40 and 47).

S-Adenosylmethionine (SAMe) is a compound derived from the essential amino acid methionine and adenosine triphosphate. SAMe is involved in many essential metabolic processes, including hepatic detoxification of drugs and xenobiotics via sulfuration and methylation reactions.[10] Adequate availability of SAMe is critical to the synthesis and reduction of GSH, which is one of the most important early protection mechanisms within the cell against oxidant stress.[10-12] Oxidative stress, with subsequent mitochondrial dysfunction and activation of cell death pathways, is a major cause of hepatocyte death in many disease processes.[13]

SAMe has been assessed prospectively in healthy, untreated cats and in healthy dogs receiving chronic prednisolone therapy.[10,14] In both dogs and cats supplemented with SAMe, hepatic GSH concentrations were increased, with an increase in the ratio of reduced GSH to the oxidized glutathione (GSSG) form. No significant effect was seen on clinicopathologic or histologic manifestations of glucocorticoid-induced vacuolar hepatopathy in the dogs.[14] Apparently successful therapeutic use of SAMe has been reported in a dog with acetaminophen toxicity, severe Heinz-body anemia, and markedly increased aspartate aminotransferase activity; it should be noted, however, that SAMe was only one component of the critical care therapy provided for this patient.[15]

Cats are particularly susceptible to acetaminophen-induced hepatotoxicity, and SAMe appears to be a rational therapeutic application for this condition. Unfortunately, controlled studies of the effect of SAMe therapy on a model of acetaminophen hepatotoxicity in the cat showed little to no effect, with most changes failing to reach statistical significance.[11] At this time, there are no well-controlled evidence-based clinical studies assessing the efficacy of SAMe as a therapeutic agent for chronic liver disease in either dogs or cats.

Silymarin has a potent antioxidant effect in several models of oxidant-mediated liver disease.[16] The use of silymarin has been

investigated in oxidant-mediated pathology in humans, including alcoholic liver disease and viral hepatitis.[17,18] Similar studies in companion animals are lacking, although the oral bioavailability of a silybin-phosphatidylcholine complex has been described.[19] Meta-analysis of clinical trials using silymarin in human beings reveal little evidence for clinical benefit except in *Amanita phalloides* mushroom poisoning.[20]

Although there is a strong theoretical underpinning for the use of many of the available nutraceutical preparations,[21,22] evidence-based medicine studies in support of these compounds is unconvincing. At this time, accurate diagnosis of the primary liver disease and implementation of therapy directed toward this diagnosis are recommended in preference to empirical therapy with nutraceutical compounds.

Copper-Restricted Diets

Hepatic copper accumulation is a feature of several canine liver diseases. Copper retention and hepatopathy is a well-characterized autosomal recessive disorder in the Bedlington Terrier, resulting from a defect in the COMMD1 gene.[23] In several other dog breeds, including the Doberman Pinscher, Cocker Spaniel, West Highland White and Skye Terriers, and the Labrador Retriever,[24,25] there is evidence of excessive hepatic copper accumulation. As copper can accumulate with cholestasis as well as primary hepatocellular disease, the significance of copper retention as a primary pathophysiologic event is less clear in these breeds. Experimental studies of Labrador Retrievers with hepatic copper accumulation, however, show that reduced copper diets are associated with improvement in chronic inflammatory liver disease and slowing of disease progression.[26]

Animals with hepatic copper accumulation sufficient to cause overt hepatopathy are best treated with specific medical therapy using chelating drugs such as D-penicillamine, at least until hepatic copper content is reduced below toxic levels. Dietary copper restriction can then be useful in the maintenance phase of management for dogs with these diseases. Typical maintenance canine diets contain at least 7 parts per million (ppm) copper, while copper-restricted diets may contain as little as 3 ppm on an as fed basis.

Additional dietary manipulations to decrease hepatic copper accumulation include supplementation with ascorbic acid (vitamin C) and elemental zinc. Zinc supplementation increases the intestinal expression of metallothionein, an avid metal-binding protein within the enterocytes.[27] Metallothionein has a higher affinity for copper than zinc. With zinc supplementation and increased metallothionein expression, copper in the diet is bound with high affinity within the mature enterocyte and lost in the feces as the enterocyte is shed.[27] Zinc is given at a loading dose of 100 mg elemental zinc per os twice weekly for 3 weeks, followed by a maintenance dose of 50 mg elemental zinc per os twice weekly. Administration of the zinc with a small amount of food may reduce the side effects of nausea and vomiting. Interestingly, in the previously cited study of dietary copper restriction in Labrador Retrievers with copper-associated hepatic disease,[26] no additional benefit was found with zinc gluconate supplementation.

Vitamin and Mineral Supplementation in Patients with Liver Disease

Liver disease patients often present with vitamin and/or mineral deficiencies. Several factors, including reduced voluntary intake, fat malabsorption, reduced gastrointestinal mucosal function, and loss of reserve stores in hepatic tissue can all contribute to the development of vitamin and mineral deficiencies.

Water-soluble vitamins such as folic acid, thiamine, cobalamin, niacin, and riboflavin are often critical cofactors in enzymatic reactions. It has been suggested that in cats with hepatic lipidosis, deficiencies of these vitamins are common.[28] Most water-soluble vitamins do not have substantial body stores and daily replacement from dietary sources is necessary. Administration of multivitamin supplements is cost-effective and simple, and should be included in any nutritional support plan for patients with liver disease.

Malabsorption of cobalamin has been documented in association with feline liver disease.[29] Cobalamin malabsorption is not easily resolved with dietary supplementation, and parenteral therapy is necessary.[30] A dose range previously described for use in cats with cobalamin deficiency caused by intestinal disease is 250 μg/cat injected subcutaneously, once a week for 6 weeks, once every 2 weeks for 6 weeks, then once a month thereafter.[30] Because the concentration of cobalamin in parenteral multivitamin preparations is typically insufficient to supply this amount of cobalamin in a reasonable injection volume, the use of pure preparations of cobalamin is recommended in dogs and cats with documented cobalamin deficiency.

In animals with long-standing liver disease, particularly those characterized by cholestasis, fat and fat-soluble vitamin (A, D, E, K) malabsorption is a significant problem. Significant elevations in the plasma concentration of proteins induced by vitamin K antagonism (PIVKA) have been documented in both cats with hepatic lipidosis and in cats with cholangitis associated with IBD.[31] Vitamin E deficiency in liver disease patients reduces cellular defenses against oxidant-mediated damage, potentially playing a role in copper-associated hepatoxicity.[32,33] Vitamins E, A, and D supplementation by intramuscular injection at 3- to 4-month intervals has been recommended in companion animals with long-standing liver disease, particularly those complicated by obvious steatorrhea. Cats with hepatic lipidosis should be screened for vitamin K deficiency, particularly if there is any evidence of bleeding tendencies. If detected (ideally via PIVKA assay), subcutaneous vitamin K administration at 1 to 5 mg/kg/day for 2 to 3 days is indicated.

Carnitine and choline are essential cofactors for hepatic cellular fatty acid transport. Carnitine is essential for transport of fatty acids from the cytosol to the mitochondria for β-oxidation of LCFAs, while choline is essential for export of very-low-density lipoproteins (VLDLs) from hepatocytes. Carnitine and choline supplementation are both potentially beneficial in the management of feline hepatic lipidosis.

Nutritional Intervention in Hepatic Encephalopathy

Hepatic encephalopathy (HE) results from loss of hepatic detoxification function and subsequent accumulation of toxic metabolites within the systemic circulation and central nervous system. These metabolites may be directly toxic to neurons and glia (e.g., ammonia), or may act as "false neurotransmitters," interfering with central nervous system function.[34] HE in humans is graded in physiologic and neurologic scoring systems, using the West Haven Criteria.[34] In this scoring system, HE is scored from 0 (no clinical signs) to 4 (hepatic coma). Because subtle neurologic impairments, equivalent to inattention or mild tremor, are more difficult to detect in companion animals, most animals in whom a diagnosis of HE is made will fall within the West Haven Criteria scores of 2 to 4. Most animals with liver disease, however, will not meet these criteria. According to a recent consensus statement of the European

Society of Parenteral and Enteral Nutrition, protein restriction is not indicated in human patients with an HE score of 0 to 2, as negative protein balance and resultant malnutrition are negative prognostic factors.[1] Protein restriction is indicated in human patients with West Haven Criteria scores of 3 to 4 (i.e., severe cognitive impairment, hepatic coma), but this finding is also a strong negative prognostic factor with patient death typically within 1 year.[1] Assuming a similar relationship in animals with a diagnosis of liver disease, most of whom do not present with HE signs consistent with scores of 3 to 4 in the West Haven Criteria, aggressive protein restriction may be counterproductive, even in mild encephalopathy patients.

Although very severe cases of hepatic lipidosis in cats can result in HE and necessitate the use of low-protein diets for a short period of time, encephalopathy is not a consistent feature of most cases of feline hepatic lipidosis, and use of low-protein diets may be associated with an adverse outcome.[35]

Recommendations for dietary protein content in diets fed to animals with severe HE vary within the veterinary literature. Overall, most dogs can be managed with diets containing 3 to 4 g of protein per 100 kcal of diet, whereas cats require at least 6 to 7 g/100 kcal. Note that the recommendation is for protein proportion within the diet, not for protein intake per kilogram of animal.

The amino acid makeup of the diet used in patients with HE is an unsettled controversy. It has been suggested that aromatic amino acid (AAA—tryptophan, phenylalanine, tyrosine)-rich diets are likely to potentiate HE, the AAAs potentially acting as substrates for the production of encephalotoxins.[3] The molar ratio of AAA to branched chain amino acids (BCAAs – isoleucine, leucine, valine) in plasma is increased in veterinary patients with HE.[3] BCAAs are important substrates for gluconeogenesis, thus the presence of protein-calorie malnutrition will lead to depletion of these amino acids in the plasma. Although these changes in the AAA-to-BCAA ratio are well documented in veterinary and human patients, their significance as a direct cause of HE rather than as a epiphenomenon is unclear. Experimental studies using dogs with surgically created portosystemic vascular anomalies found more pronounced HE and higher blood ammonia concentrations in the dogs receiving a low AAA-to-BCAA ratio diet, however the dogs receiving this diet ate more than those receiving a high AAA-to-BCAA ratio diet, resulting in greater total protein intake.[36] Based on metaanalyses of studies in human beings with HE, BCAA supplementation is recommended in patients who develop HE with Westhaven Criteria scores 3 to 4 during enteral nutrition.[1] The situation is much less clear with lower-grade HE human patients and in most veterinary patients. In most cases BCAA supplementation is unlikely to lead to a net negative benefit, unless voluntary intake is reduced. Most veterinary prescription diets specifically labeled for hepatic disease are formulated to achieve a higher BCAA content and derive a significant proportion of metabolizable energy from fats and carbohydrates.

Feeding of several small meals throughout the day is often beneficial for animals with overt HE, reducing the total ammonia load following each meal. Other strategies used to control HE in small animals include antibacterial therapy with neomycin or metronidazole, and the use of enteric lactulose therapy (oral or via enema) to reduce ammonia production and absorption, respectively, from the GIT.

Hepatic Lipidosis in Cats

Appropriate nutritional management is absolutely central to successful resolution of hepatic lipidosis (HL) in cats.[37] Although the underlying pathology of hepatic lipid accumulation in cats has not yet been completely elucidated, several biochemical and nutritional risk factors have been identified (Box 32-1).[38] There is a general consensus that reduced caloric intake and protein-calorie malnutrition are important predisposing factors. Obese cats are commonly thought to be at increased risk,[28,39,40] but this is not exclusively a disease of the overweight cat. Underlying disease is believed to initiate the anorexia and starvation that typify this syndrome. Successful management in the medium- to long-term will require addressing the underlying disease process to permit a return to more normal appetite. In the short-term, diligent attention to restoration of positive caloric balance is necessary. Short-term stabilization may be a necessary precedent to initiating a rational diagnostic workup.

Box 32-1 Factors Predisposing the Domestic Cat, an Obligate Carnivore, to Fat Mobilization and Hepatic Lipidosis

- Essentiality of dietary arginine
- Low levels of hepatic ornithine
- High dietary protein requirements
- Lack of hepatic enzyme adaptation to low protein
- Insufficiency of hepatic glutamate reductase
- Insufficiency of intestinal ornithine transcarbamylase
- Diversion to orotic acid metabolism
- Differences in lipoprotein metabolism (HDLs)

Summarized from MacDonald ML, Rogers QR, Morris JG: Nutrition of the domestic cat, a domestic carnivore. *Ann Rev Nutr* 4:521–562, 1984.

The feline liver has relatively small glycogen stores, thus cats become all too quickly dependent upon systemic lipolysis and hepatic metabolism of triglycerides with the onset of starvation or anorexia. Carnitine, choline, and arginine deficiency are believed to contribute to the development of this syndrome. Healthy cats fed arginine-deficient diets, even if fed in quantities necessary to supply adequate caloric intake, rapidly develop severe HE, as the urea cycle is compromised.[38] Choline and carnitine are important in mitochondrial fatty acid transport and packaging of fatty acids into VLDLs for export from the hepatocyte, thus deficiency of these trace elements may contribute to fat accumulation. Arginine, choline, and carnitine supplementation are commonly recommended in the nutritional management of cats with HL. If the diet used for initial feeding is deficient in arginine, as is the case with most human liquid enteral formulations, this amino acid should be supplemented at dose of 250 mg/100 kcal of diet delivered. The author empirically supplements HL cats with arginine, carnitine, and taurine regardless of the enteral nutrition formula used. Oral administration of L-carnitine, 250 to 500 mg/day, and taurine, 250 to 500 mg/day, are also recommended by several sources.[37,40]

Advances stages of HL are characterized by severe anorexia. Assisted feeding should be implemented as soon as feasible in these patients. Oral forced alimentation is not recommended as many cats will rapidly develop food aversion, while the stress of handling and syringe feeding can precipitate rhabdomyolysis in hypokalemic and hypophosphatemic cats. Medical agents for appetite stimulation in cats are often ineffective in HL cats, may take days to weeks to show benefit, and may require hepatic detoxification. Early placement of a feeding tube, at the minimum an esophagostomy tube, should be considered standard of care. Critically ill cats at risk for anesthetic procedures can be fed initially with a nasoesophageal tube (5 to 8 French). These tubes are more prone to clogging and failure because

of vomiting, regurgitation, or removal by the patient. Nasoesophageal tubes also require placement and maintenance of an Elizabethan collar, and the small lumen of the tube limits diet choice to liquid formulations. Placement of an esophagostomy tube allows use of larger bore tubes (10 to 14 French) that make feeding easier and open up the possibility of blenderized diets. Percutaneous endoscopically placed gastrostomy (PEG) tubes are larger still (up to 20 French), and allow greater movement of the head and neck of the cat (as these areas are not bandaged), which appears to reduce morbidity in some cats by allowing self-grooming. Clinicians experienced in this technique can place a PEG tube in a 10- to 15-minute procedure. If a large-bore PEG tube can be placed, assisted feeding by owners becomes more feasible in the home environment. As some cats require assisted feeding for weeks to months, this can be an important aspect of successful home care. Cats presenting with vitamin K deficiency and elevated PIVKA should receive subcutaneous vitamin K for 1 to 2 days before either esophagostomy or PEG tube placement is recommended. It has been suggested that surgical placement of gastrostomy tubes via celiotomy in cats with hepatic lipidosis is associated with high risk for postoperative morbidity and an unacceptable risk of stomach displacement.[28]

Dramatic, potentially life-threatening electrolyte derangements can occur during initial reinstitution of feeding, particularly in serum potassium (K^+) and phosphate (PO_4^{3-}). These are both predominantly intracellular ions, but during periods of extended malnutrition both K^+ and PO_4^{3-} move into the extracellular space to maintain cellular membrane potentials. With the reintroduction of oral intake and renewed insulin activity, there can be a rapid shift of both ions intracellularly; this shift can be rapid enough to result in rhabdomyolysis and hemolysis in severely affected cats. These changes should be anticipated, and in severely affected cats parenteral administration of PO_4^{3-} and K^+ should begin preemptively. Potassium replacement can be dosed using routine sliding dose scales, whereas PO_4^{3-} is commonly administered intravenously at a rate of 0.01 to 0.03 mmol/kg/h. Phosphate is commonly available with K^+ as a cation, and care should be taken to ensure that the total K^+ input does not exceed 0.5 mEq/kg/h. Oral administration of K^+ as the gluconate salt is also recommended. Twice-daily measurement of serum electrolytes, including magnesium, is recommended during the initial management of critically ill cats with hepatic lipidosis. Electrolyte abnormalities should be anticipated during the first few days of therapy, and should be addressed as early as possible though judicious intravenous fluid supplementation.

Many cats with HL will have water-soluble vitamin deficiencies because of extended periods of anorexia; these are commonly supplemented by adding multivitamin preparations into the IV fluids at a dose of 1 to 2 mL/1 L bag. Fluid bags and lines should be protected from light. Cobalamin deficiency is also common, and can be addressed with subcutaneous cobalamin injections as previously described. Thiamine deficiency is particularly insidious in HL cats. Both thiamine and K^+ deficiencies can result in obtundation, weakness, and ventriflexion of the neck. These signs may be misinterpreted as HE, and these abnormalities should be screened for and corrected before instituting low-protein diets for presumed encephalopathy in hepatic lipidosis patients.

Nutritional Considerations in Diseases of the Biliary Tract

Nutritional management of biliary tract disease has not been discussed in great detail in the veterinary literature. In most cases, management has been limited to medical and surgical approaches.

There is a well-recognized risk of biliary disease in dogs with hypertriglyceridemia.[41] Hypertriglyceridemia has been associated with vacuolar hepatopathy and gallbladder mucocele in dogs, and successful resolution of gallbladder mucocele has been reported in a limited number of dogs using therapies that included low-fat diets and ursodeoxycholic acid therapy.[42,43] Breed-associated predispositions for hypertriglyceridemia have been reported, and many of these breeds are also considered at higher risk for development of gallbladder mucocele.[41] In this context, nutritional interventions directed toward management of hypertriglyceridemia, such as feeding of fat-restricted diets, can be considered a risk-reduction strategy to prevent possible biliary disease.

In clinically healthy dogs, omega-3 fatty acid supplementation has been shown to reduce serum triglycerides significantly and with no perceived adverse effects.[44] Experimental studies in rodents have shown that administration of omega-3 fatty acids reduces the histologic severity of lesions induced by bile duct ligation, suggesting that these compounds may have a role in management of long-term cholestatic disorders such as biliary fibrosis, cirrhosis, and atresia.[45] Controlled studies demonstrating benefit of omega-3 fatty acid supplementation in dogs with preexisting hypertriglyceridemia, however, are lacking.

Chronic cholestasis is associated with fat malassimilation and deficiency of fat-soluble vitamins, as previously discussed. Although successful management of cholestatic diseases will usually require specific medical and surgical therapy, attention to the possibility of fat-soluble vitamin deficiencies and the need for supplementation is indicated.

PANCREAS

Jennifer Larsen

Diseases affecting the exocrine pancreas generally fall into two categories: pancreatic inflammation and/or necrosis and EPI. The pancreas produces a fluid rich in electrolytes, bicarbonate, and enzymes, in addition to antibacterial proteins and cobalamin-binding intrinsic factor (see Chapters 1 and 60). Digestive enzymes include proteases, amylase, and lipase, which carry out the digestion of dietary proteins, carbohydrates, and lipids, respectively. Colipase, nonspecific esterase, and phospholipase are cosecreted and have an important role in triglyceride, cholesterol, lecithin, and fat-soluble vitamin digestion. Digestive enzymes are essential for life; when they are lacking, as in patients with EPI, the outcome is severe maldigestion and malnutrition. To protect the pancreas itself from autodigestion, these same enzymes are incorporated as inactive zymogens into secretory granules following intracellular synthesis. In response to neural and hormonal stimuli, zymogens are secreted into the pancreatic ductal system and small intestine. Inactive trypsinogen, a major component of pancreatic secretion, is catalytically activated by brush-border enterokinase to form active trypsin. Trypsin, in turn, activates other zymogens, thereby initiating the normal process of protein, carbohydrate, and lipid digestion. If activated prematurely, digestive enzymes digest the structural elements of the pancreatic acinar cells resulting in necrosis and inflammation (pancreatitis). The proximate cause of premature activation is believed to be inhibition of secretion and colocalization of digestive zymogens with lysosomal hydrolases (see Chapter 60). The resulting disease process is typically classified as acute or chronic, with recurrences not uncommon. As with EPI, risk factors and clinical signs are well

established; however, individual variation in the clinical picture should be expected. Dietary therapy remains an important component of the management of patients with either pancreatitis or EPI, and recommended strategies have evolved with clinical experience and research data.

Pathogenesis of Pancreatitis

Risk factors for dogs include, but are not limited to, diet history (especially high-fat foods and obesity), breed (including Miniature Schnauzers and Yorkshire Terriers), concurrent disease (including hyperlipidemia and diabetes mellitus), and drugs (phenobarbital, azathioprine, and many others).[1] For cats, risk factors include trauma, infection (including toxoplasmosis), and IBD; however, most cases remain classified as idiopathic.[2,3] Although dogs often show clinical signs of vomiting and/or diarrhea, signs in cats remain elusive, with lethargy and anorexia as the most commonly reported clinical signs.[4,5] In some cases, adverse sequelae and concurrent disease can complicate management; however, supportive medical care and both short- and long-term dietary therapy can help alleviate symptoms and prevent or reduce recurrence.

Approach to Therapy of Pancreatitis

Nutritional Management

The traditional approach to acute pancreatitis is "nil per os" during the immediate period of treatment and hospitalization. Research evidence and clinical experience have suggested that the nil per os approach is not necessary and may not be beneficial. Many patients are hyporexic or anorexic during this time, and intervention is necessary to provide appropriate nutritional support. In particular, animals in poor body condition, those with a history of weight loss, and all cats should have a nutritional management plan in place as early as possible and no later than after 3 to 5 days of anorexia. Longer-term dietary management of patients with either acute or chronic pancreatitis is highly dependent on diet history, concurrent disease, and the fat tolerance of the specific animal.

Role of Nutrition in Pancreatic Secretion

Neural (acetylcholine, substance P, vasoactive intestinal peptide) and endocrine (cholecystokinin [CKK], secretin) mechanisms are responsible for the regulation of exocrine pancreatic secretion (see Chapters 1 and 60 for more details). Secretin stimulates the secretion of a bicarbonate-rich fluid from pancreatic ductal cells as well as from biliary epithelial cells. Not surprisingly, its secretion is stimulated by protons and fatty acids in the duodenal lumen. CCK stimulates pancreatic enzyme secretion as well as gallbladder contraction. The secretion of CCK is stimulated by amino acids, long-chain fatty acids (LCFAs), and gastric protons, but there are some species differences with regard to the relative potency of different nutrients. In humans, amino acids, proteins, and long-chain triglycerides are more potent than carbohydrates in promoting CCK secretion.[6,7] In dogs, fatty acids, amino acids, and peptides stimulate CCK release, but intact proteins do not.[8,9] Cats secrete CCK in response to long-chain triglycerides and proteins,[10] with intact protein being more potent than amino acids.[11]

Management of Acute Pancreatitis

Early Feeding Versus Nil Per Os

The long-standing nutritional strategy of withholding food from patients with acute pancreatitis was based on the erroneous assumption that excessive stimulation of secretion was the underlying pathogenesis of pancreatic acinar cell necrosis, and that fasting (i.e., placing the pancreas at "physiologic rest") should reduce pancreatic secretions. Cell biology experiments of the past decade have shown that pancreatic necrosis and inflammation are instead associated with inhibition of secretion (reviewed in Chapters 1 and 60). These studies further suggest that feeding may help to mobilize prematurely activated enzyme from the inflamed pancreas. Fasting therefore should be restricted to those patients with intractable vomiting and who are at risk for aspiration pneumonia. Recommendations to use the GIT whenever possible are increasingly accepted, with evidence that patients that have been traditionally managed with nil per os orders may actually benefit from early enteral feeding.[12,13] It has been shown that parenteral nutrition, as compared with enteral nutrition, has a negative impact on gut barrier function within 7 days of induction of experimental pancreatitis and is associated with decreased intestinal villi height, mucosal thickness, and total protein and DNA content.[12] Although caution should always be exercised when feeding a patient with suspected gastrointestinal dysfunction (such as protracted vomiting, severe ileus, or malabsorption), early enteral feeding may facilitate more rapid return to function in many gastrointestinal syndromes.[14] The concurrent use of effective antiemetic agents may facilitate earlier return to function. There is no documented benefit to maintaining nil per os orders longer than 1 to 2 days, especially if vomiting is reasonably controlled. Water tolerance should be tested first, and if there is no vomiting, food can then be offered.

Some patients may not be able to tolerate oral or intragastric feeding; however, delivery of enteral nutrients is still possible. Nasojejunal, gastrojejunostomy, and jejunostomy tubes enable postgastric feeding (all detailed in Chapter 33), which may decrease the incidence and severity of vomiting. Historically, nutritional management of acute pancreatitis has been focused on reducing stimulation of pancreatic enzyme secretion,[15,16] but enteral feeding in a dog model of severe acute pancreatitis is associated with decreased endotoxin and bacterial translocation and does not cause worsening of pancreatic pathology.[12]

While parenteral nutrition (PN) is an effective way to deliver nutrients to critically ill veterinary patients, it is advisable to strive for enteral nutritional support as soon as practical. In people with pancreatitis, early enteral feeding via the jejunal route is safe and is recommended in this context because of cost-effectiveness compared to PN.[17] At the author's institution, it is not uncommon to provide at least a small amount of food enterally (approximately 10% of the daily calories including by the gastric route) in patients receiving parenteral nutrition, with the goal of maintaining enterocyte function and gastrointestinal motility.

Dietary Selection: The Role of Dietary Fat

Modification of dietary fat content is a consideration in the management of both acute and chronic pancreatitis. In healthy dogs fed diets with fat concentrations varying from 15% to 38%, there were no differences in pancreatic physiologic responses as measured by serum pancreatic lipase immunoreactivity (PLI), trypsin-like immunoreactivity (TLI), and gastrin concentration,[18] although effects on pancreatic pathology were not reported in these studies. Dogs maintained on 60% fat diets develop more severe pancreatic pathology in induced models of pancreatitis compared with those fed a 20% fat diet.[19] Together with other research data, as well as clinical evidence of efficacy, the practice of dietary fat restriction continues to be the cornerstone of nutritional management of acute pancreatitis.

When PN is not possible, assisted enteral feeding is indicated for patients with acute pancreatitis that will not voluntarily eat adequate calories of an appropriately fat-restricted diet (<20% fat calories). Various diets may be utilized depending on the type of feeding device. If a smaller-diameter nasoenteral, gastrojejunostomy, or jejunostomy tube is placed, liquid diets are necessary. Although liquid veterinary diets are generally high in fat (up to 57% of calories), some human enteral formulations provide comparable energy density while restricting fat (as low as 6% of the calories); these are acceptable alternatives for fat-intolerant patients. For cats, it should be noted that many human enteral liquid diets are not supplemented with taurine, and some contain fructose, high concentrations of which should be avoided in cats because of fructosuria.[20] To reduce the occurrence of maldigestive diarrhea, any diet fed into the jejunum should be "elemental" to resemble the normal characteristics of chyme. Elemental diets provide the basic components of macronutrients such as simple sugars or hydrolyzed starch rather than high-fiber complex carbohydrates, and amino acids or hydrolyzed peptides rather than intact proteins.

For animals with preserved appetite or those fed through an esophageal or gastric tube, several low-fat, highly digestible options exist. Commercially available diets providing 20% or less fat calories can be attempted; however, in many patients, the need for more severe fat restriction necessitates a home-cooked diet. For example, cottage cheese and rice slurries are useful for tube feeding and are generally palatable to dogs and some cats; a volume ratio of 1:1 of 2% fat cottage cheese and white rice provides approximately 10% fat calories. For cats, canned tuna and baby rice cereal is another reasonable option. Both mixtures can be supplemented with a source of essential fatty acids and micronutrients if necessary for longer-term feeding, but many patients can be maintained on a higher-fat diet after recovery.

Diet selection for longer-term management is highly dependent on diet history and disease progression. Some dogs with acute pancreatitis associated with intake of high-fat foods or dietary indiscretion can tolerate the previous diet as long as snacks and treats are more judiciously selected. Other dogs will not tolerate the previous diet and require further fat restriction. In the author's opinion, in those cases, as well as in all dogs with chronic pancreatitis, the initial diet chosen for long-term feeding should provide no more than half of the fat (on a percent-calories basis) as the diet fed previously. A detailed diet history is crucial; in many cases, however, especially if a large amount and variety of treats and snacks are fed, it will not be possible to determine the fat level of the overall diet (or the range of the highest to lowest fat meals). In that case, given the nature of the disease, it is prudent to be conservative and choose a fat-restricted diet (<20% fat calories). In any patient, if the lowest fat commercial diets fail to resolve pancreatitis (or in the case of concurrent disease such as food allergy), or when those diets are not palatable, a customized home-cooked diet can be formulated by a veterinary nutritionist.

Adjunctive Treatments and an Individualized Approach to Pancreatitis

Supportive care and aggressive management of complications is necessary in most cases of acute pancreatitis (see Chapter 60 for details). Generally chronic pancreatitis can be managed on an outpatient basis, with monitoring and intervention as needed. Many patients will have concurrent diseases that may benefit from nutritional management, such as diabetes mellitus, obesity, or hyperlipidemia. In these cases, the patient's diet history as well as all relevant problems should be taken into consideration in a prioritized way when choosing a diet for both short- and long-term feeding.

Pathogenesis of Exocrine Pancreatic Insufficiency

Progressive pancreatic acinar and ductal atrophy is the most common pathogenesis of EPI in dogs. It likely has several underlying etiologies, one of which is presumed to be immune- mediated destruction of exocrine tissue. An important secondary cause is chronic pancreatitis with necrosis of acinar, duct, and occasionally islet cells. This is also the presumed cause of most cases of EPI in cats, but the rarity of the syndrome and the lack of epidemiologic studies prevent establishing a direct cause-and-effect relationship. In both species, and regardless of etiology, clinical signs of EPI are related to severe nutrient maldigestion with resultant steatorrhea, diarrhea, and abnormal intestinal motility. Weight loss with ravenous appetite completes the classic clinical picture. Bacterial overgrowth is an important complication, and antibiotics are often necessary, along with enzyme replacement therapy, dietary management, and other adjunctive treatments.

Approach to Therapy of EPI

Enzyme Replacement Therapy

Enzyme replacement therapy (ERT) has been well established as the principal therapy for long-term management of EPI. Very few patients can be managed without ERT.[21] The concentration and overall potency of enzymes provided by fresh raw pancreas and by commercially available ERT products varies widely. The cost of ongoing management of a pet with EPI is reported to be a common reason for euthanasia,[22] and rapid identification of cost-effective treatment is important in most cases.

As pancreatic enzymes are proteins, they are subject to degradation by exposure to gastric acid, pepsins, and bile acids. To overcome these problems, a variety of approaches has been tried, including pretreatment or coadministration with acid secretory inhibitors (H_2 blockers and proton pump inhibitors) and enteric-coated preparations of ERT. In general, acid secretory inhibitor therapy has not been widely adopted except in refractory cases because of the increased cost, reduction in compliance when additional medications are prescribed, and incomplete evidence of efficacy. Enteric-coated preparations have not typically been recommended; indeed one study showed that these products were less effective than standard ERT therapy.[22] In a more recent study, their use had no impact of survival in dogs with EPI.[21]

Acid-resistant fungal lipase has been investigated with mixed results. In pancreatectomized dogs fed complex meals containing both fat and protein, this product showed promising results, with a similar reduction of steatorrhea, but at a lower lipase dose, compared to treatment with lyophilized porcine pancreatin (a mixture of lipase, trypsin, and amylase).[23] However, in people with pancreatic steatorrhea caused by cystic fibrosis who were fed meals of emulsified long-chain triglycerides, acid-resistant fungal lipase did not result in reductions in steatorrhea.[24] Whether this difference is a result of ERT product preparation, study design, species physiology, or other factors is unclear. Bacterial lipase shows similar dose-dependent effects on fat absorption in dogs with experimental EPI but at a 75-fold lower dose compared with porcine lipase.[25] Most commercially available products are porcine or bovine in origin; for patients with confirmed adverse food response to these antigens,

fungal or bacterial lipase products may be an option assuming availability and financial feasibility.

Nutritional Management

Because of variation in biologic response in the patient population, differences in diet characteristics, composition, and amounts fed, and the dissimilarity among available ERT products, interpreting the impact of dietary strategies is difficult. Dietary strategies have been investigated, and research findings are often conflicting, which may reflect study design and the use of diets varying in multiple parameters but also suggests a need for an individualized approach to management of EPI patients. Unfortunately, there are very little data available for assessing the role of dietary therapy in the management of EPI in cats.

Macronutrients

Role of Dietary Fat

The role of dietary fat (amount and type) is a major focus of interest in the management of canine EPI. Fat is a highly digestible macronutrient, yet digestion depends on a complex interaction of dietary triglycerides, pancreatic enzymes, coenzymes, and bile salts. The presence of fat in the intestinal lumen slows transit by activating the ileal brake and delaying gastric emptying (see Chapters 1 and 60 for more details). This braking mechanism helps to ensure that fat is adequately emulsified and micellarized for successful digestion and absorption, respectively. Traditionally, low-fat diets have been recommended for a number of reasons. Steatorrhea is a major clinical sign in patients with uncontrolled disease, and higher dietary fat concentration is associated with intolerance (diarrhea, visceral pain, and other gastrointestinal signs).[26] Further, maldigested and malabsorbed fat in the intestinal lumen is a substrate for bacterial hydroxylation, leading to osmotic effects. Fat malabsorption can also result from deconjugation of bile salts by intestinal microflora, which produce additional osmotic effects. Antibiotic therapy is important to control bacterial overgrowth, and in some cases it is logical to reduce dietary fat while addressing ongoing diarrhea or during the initial stages of adjusting therapy after diagnosis. Indeed, fat restriction is not uncommonly recommended, and a diet providing 12% to 13% of calories from fat is a successful strategy in the immediate postdiagnosis period, after which most dogs continue to do well on a wider variety of diets.[27]

Despite continued recommendations of low-fat diets for canine EPI patients, their impact on disease progression and outcome remains unclear. Research in this area has been complicated and has not consistently shown benefits of either a low- or high-fat diet. In a recent retrospective study, more than one-third of canine EPI cases were fed "a fat-restricted diet" (dietary fat concentration not reported), which had no negative nor positive effect on survival.[21] Improvement or regression of clinical signs in response to diet change are often difficult to attribute to any one food characteristic. Diets are complex and differ not only in fat content and digestibility, but also in fiber content and type, protein source, and digestibility, and many other factors. A prospective study in untreated pancreatectomized dogs demonstrated lower digestibility of dry matter and fat when dogs were fed a maintenance diet compared with a veterinary-exclusive, lower fiber, highly digestible diet with 18% lower fat. Clinical and laboratory parameters improved but remained statistically insignificant after treatment.[28] Which dietary factor, or combination thereof, had the biggest influence on these findings is unclear. Indeed, a more recent prospective study showed that patient responses to diet changes were highly variable and did not correlate with dietary fat concentration.[29]

Many EPI patients have poor body condition, and could benefit from a palatable, energy-dense diet that is higher in fat content. Research has not shown a clear disadvantage to moderate or high dietary fat concentrations in dogs with EPI. In lipase-treated dogs with experimental EPI, there was no change in fecal scores or in total amount of fecal fat produced each day when fed diets providing 33%, 43%, or 47% of the calories as fat.[30] Additional work by the same group showed that dogs with lipase-treated EPI had increased fat absorption when fed a diet with 43% fat calories compared to one with 18% fat calories.[25] A case series of three dogs with naturally occurring EPI and adverse food reaction showed good clinical response with weight gain and improved fecal scores when fed a hydrolyzed diet with 41% fat calories.[31] It seems prudent to recommend low-fat (<20% of calories) diets for patients with suspected or confirmed bacterial overgrowth or with concurrent fat intolerance (such as lymphangiectasia or hyperlipidemia), whereas other patients may benefit from moderate- (20% to 35% of calories) or high- (>35% of calories) fat diets, especially those in poor body condition.

Digestibility and Fiber

Digestibility is assumed to be an important strategy in the management of dogs with EPI, but this has not been strictly differentiated from the role of other dietary factors. Although veterinary therapeutic diets with high digestibility have been used with success in both experimental[28] and naturally occurring EPI,[32] there may be an influence of fiber type and content on digestibility of a diet. Rigorous research is lacking and generalized recommendations are not warranted at this time. Very-high-fiber diets are less energy dense, which could be a disadvantage for underweight or volume-intolerant dogs and cats. Other patients may have concurrent fiber-responsive diseases, which should be considered in the nutritional management.

Micronutrients

Cobalamin (Vitamin B_{12})

The absorption of cobalamin (vitamin B_{12}) is unique among nutrients, in that both a binding protein and a receptor-mediated process are necessary for transport across the intestinal mucosa. Dietary sources of cobalamin include primarily animal proteins, but enriched cereals are also now widely available, as is free cobalamin in the form of dietary supplements. Cobalamin is bound to dietary proteins and released by the action of gastric acid and pancreatic proteases. Intrinsic factor (IF) is a binding protein necessary for absorption of free cobalamin. In the dog, IF is produced in the pancreas and to a lesser extent by the gastric parietal cells,[33] whereas in the cat the pancreas is solely responsible for synthesis of IF.[34] The IF–cobalamin complex is recognized and absorbed by a receptor-mediated process in the ileum of both species.

As in many malabsorptive diseases, dogs diagnosed with EPI also often present with low serum concentrations of cobalamin. Retrospective studies have shown that 75% to 82% of dogs diagnosed with EPI have low serum cobalamin concentration,[21,22] and this is associated with shorter survival.[21] This appears to be a very common comorbidity in cats with EPI as well, with two studies reporting low cobalamin in all feline EPI patients.[35,36] A prospective study with experimentally induced EPI showed that dogs with ligated pancreatic ducts had decreased cobalamin absorption as evidenced by increased fecal excretion, but the decrease in serum cobalamin concentrations did not reach significance.[37] The B_{12} binding ability of the intestinal microflora is also probably a factor in the absorption of cobalamin in dogs with EPI. Serum cobalamin concentration should be monitored and corrected if necessary in dogs diagnosed

Table 32-2 Nutritional and Medical Management of EPI and Its Complications

Feature	Pathogenesis	Management
Steatorrhea	Fat maldigestion; fat malabsorption	Enzyme replacement therapy; dietary fat modification
Diarrhea	Acid injury	Histamine H_2-receptor antagonists, H^+K^+-ATPase antagonists
	Bacterial proliferation	Oral antibiotics
Mucosal atrophy	Intrinsic factor deficiency	Vitamin B_{12}
Ravenous appetite	Protein-calorie malnutrition	Highly digestible diet
Weight loss	Protein-calorie malnutrition	Highly digestible diet
Refractory clinical signs	Acid inactivation of ERT	Histamine H_2 receptor antagonists

ATPase, adenosine triphosphatase; ERT, enzyme replacement therapy.

with EPI; lifelong parenteral supplementation is generally recommended.

Fat-Soluble Vitamins (Vitamins D, E, A, and K)

Fat-soluble vitamin status is largely dependent on adequate digestion and absorption of dietary fat. Many veterinary patients with steatorrhea caused by EPI may require supplementation.[38]

The degree of control of EPI appears to play an important role in fat-soluble vitamin status in veterinary EPI patients. In one study of dogs with naturally occurring and well-controlled EPI, only 8% (two of 24) had serum 25-OH vitamin D concentrations below the reference range, while 17% (four of 24) had serum hypovitaminosis E.[39] Vitamin A malabsorption was not apparent in this population as serum vitamin A did not differ among dogs with or without EPI when eating the same diet.[39] In dogs with untreated experimental EPI, serum vitamin A concentrations were lower than those of control dogs at baseline and after a single oral dose of vitamin A; however, coadministration of enzyme preparation increased the absorption of vitamin A in the EPI group only, but normal serum concentrations were not achieved.[40]

In addition to the degree of control of EPI, diet composition also appears to play a role in fat-soluble vitamin status. Absorption of vitamin E was higher for both normal dogs and those with controlled EPI when fed diets with 35% of the fat (by weight) provided by MCTs compared to diets fed with 0% MCTs.[39] The authors speculated that the effect may have been a result of enhanced absorption of vitamin E into portal circulation (vs. via lymphatics) as seen in other species when fed MCTs.[41] Higher serum concentrations of fat-soluble vitamins do not necessarily correlate with improved clinical signs or changes in other parameters[39]; consequently, the importance and benefit of maintaining potentially arbitrary serum concentrations with either parenteral or enteral supplementation is unclear.

Although any patient with EPI and clinical signs of coagulopathy should be evaluated for vitamin K deficiency, empirical supplementation does not appear to be warranted. There is one report of vitamin K–dependent coagulopathy secondary to uncontrolled EPI in a cat consuming a balanced commercial diet. Serum fat-soluble vitamins were not assessed and the cat improved with ERT alone.[42] Vitamin E supplementation is often recommended for patients with EPI. Given the wide margin of safety of vitamin E compared with vitamins A and D, empirical supplementation of moderate amounts is unlikely to be harmful but may or may not be helpful. It appears that most canine patients with controlled EPI are unlikely to show clinically significant deficiencies of fat-soluble vitamins. Similar data are not available for cats. Dogs and cats with well-controlled EPI that are consuming complete, balanced diets, appear to be at low risk of fat-soluble vitamin deficiency. In refractory cases with ongoing steatorrhea or for those with concurrent disease that is difficult to manage, supplementation may be warranted.

Adjunctive Treatments and an Individualized Approach to Exocrine Pancreatic Insufficiency

Other treatments may be needed in many patients with EPI (Table 32-2). Many patients need intermittent and recurrent antimicrobial therapy to control "overgrowth" of the intestinal microflora that follows loss of antibacterial secretion in the pancreatic fluid of EPI patients (see Chapters 1 and 60). Diarrhea may persist for several reasons, including bacterial hydroxylation of dietary fat, bacterial deconjugation of bile salts, and gastric acid injury to intestinal villi as a result of loss of pancreatic bicarbonate (HCO_3^-) secretion. Persistent clinical signs of gastrointestinal disease are not uncommon in dogs treated for EPI,[21] but it is unclear whether this represents concurrent disease problems or inadequate control of EPI. Histopathologic changes of the small intestine, including villus blunting and increased cellularity of the lamina propria, have been demonstrated in experimental EPI, which suggests these are direct adverse effects of EPI not attributable to distinct disease processes.[43] Regardless, it is clear that some patients will require adjustments in therapy, as well as investigation and treatment of concurrent disease.

Patients with diabetes mellitus or other concurrent disease will need these problems managed in a prioritized way to maintain a balance of good clinical response, appropriate therapy, and cost. Nutritional, medical, and surgical plans should be coordinated to ensure that control of any one problem is not to the detriment to the others. Although the pancreas plays a critical role in the assimilation of food, processes initiated in the stomach are also important. Hydrochloric acid and pepsinogen for digesting dietary protein, gastric lipase for digesting fat, and intrinsic factor for absorption of cobalamin are all secreted by the stomach. It is possible that variations in absolute or adaptive production of these substances may account for some of the variation among individuals treated for EPI.

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CHAPTER 33

Enteral and Parenteral Nutrition

Stanley L. Marks

Nutritional support is aimed at minimizing development of malnutrition in animals at risk, while maintaining or enhancing immunologic and intestinal barrier function. The specific indications for enteral nutrition in people have changed over the years, and it is no longer contraindicated in patients with pancreatitis, ileus, and intestinal dysmotility.[1] Many techniques for obtaining enteral access are available, and the approach depends on several variables, including anticipated duration of enteral support, risk of aspiration, integrity of the gastrointestinal tract, the animal's temperament, the clinician's expertise, and the animal's tolerance of anesthesia.

Rationale for Enteral Nutritional Support

Enteral feeding is indicated for animals unable to ingest adequate amounts of calories, but that have sufficient gastrointestinal function to allow digestion and absorption of feeding solutions delivered into the gastrointestinal tract via an enteral feeding device. The rationale for prescribing enteral nutrition rather than parenteral nutrition (PN) is based on the superior maintenance of intestinal structure and function,[2] reduced infection rates,[3] and reduced cost of enteral alimentation. The average daily cost of total parenteral nutrition (TPN), hereafter referred to as central parenteral nutrition (CPN), for maintaining the caloric requirements of a 20-kg dog at the University of California, Davis, Veterinary Medical Teaching Hospital, is approximately five to 30 times greater (excluding catheter costs) than the cost of a commercial liquid enteral formula, and 60 times greater than the cost of a commercial canned diet for intestinal disorders. The most important stimulus for mucosal cell proliferation is the direct presence of nutrients in the intestinal lumen.[4] Bowel rest as a consequence of starvation or administration of CPN leads to villous atrophy,[5] increased intestinal permeability, and a reduction in intestinal disaccharidase activities.[6] Prolonged fasting in the stressed, critically ill animal can lead to intestinal barrier failure and increased permeability to bacteria and endotoxins. However, enteral nutrition may have shortcomings including underfeeding, perceived intolerance, aspiration, access-related complications, and diarrhea.[7]

Patient Selection for Nutritional Support

Efforts to assess nutritional status and attempts to decide whether nutritional support is required on the basis of a single biochemical measurement or body weight determination are simplistic and of limited value. Objective methods of assessing nutritional status, such as body composition measurement (anthropometry, bioelectrical impedance measurements, dual-energy X-ray absorptiometry) are still in their infancy in clinical veterinary medicine, with the result that a subjective global assessment of an animal's nutritional status needs to be performed. This technique is based on easily collected historical information (changes in oral intake, degree of weight loss, presence of vomiting or diarrhea) and changes found on physical examination (muscle wasting, body condition, and presence of edema or ascites). A technique referred to as subjective global assessment was developed for the nutritional assessment of human patients approximately 30 years ago.[8] The technique relies upon readily available historical and physical parameters to identify malnourished patients who are at increased risk for complications and who would benefit from nutritional intervention. The assessment involves determining (a) whether nutrient assimilation has been restricted because of reduced food intake, maldigestion, or malabsorption; (b) whether any effects of malnutrition on organ function and body composition are evident; and (c) whether the patient's disease process influences its nutrient requirements. The subjective global assessment can be adopted to dogs and cats by determining the following five aspects of the animal's medical history: (a) weight loss, (b) voluntary food intake, (c) the presence of persistent gastrointestinal signs, (d) the animal's functional capacity (e.g., presence of severe weakness or exercise intolerance), and (e) the metabolic demands of the patient's underlying disease state.

The body weight of the animal cannot be equated with its state of nourishment because it does not differentiate between fat, lean tissue, and extracellular water. The animal's serum albumin concentration and total lymphocyte count are insensitive determinants of nutritional status because of the large number of disease processes that influence these parameters unrelated to the effects of malnutrition (see Chapter 30). Nutritional support should be considered for animals that demonstrate recent unintentional weight loss that exceeds 10% of optimal body weight or for those whose oral intake has been or will be interrupted for more than 5 days. Animals with increased nutrient losses from chronic diarrhea or vomiting, wounds, renal disease, or burns should also be considered for nutritional support. Numerous methods exist for quantifying body composition and body fat mass in companion animals. In a clinical setting, the most widely accepted and practical method of body condition evaluation is condition scoring using visual assessment and palpation. This method affords a reproducible and clinically useful assessment of nutritional status. The body condition score is not affected by fluid shifts that can readily impact body weight, facilitating the improved assessment of nutritional status in the hospital or

intensive care environment. The most widely accepted system is the nine-integer scale system, which correlates well with body fat mass determined by dual-energy X-ray absorptiometry.[9] Body condition scoring schemes do not incorporate the loss of lean body tissue, although the recent implementation of a muscle condition score could further enhance the assessment of nutritional status[10] (see Chapter 30).

Calculation of Nutritional Requirements

Nutritional support provides substrates for gluconeogenesis and protein synthesis[11] and provides the energy needed to meet the additional demands of host defense, wound repair, and cell division and growth. The anticipated duration of nutritional support should be determined and factored into the nutritional support plan. In addition, the most optimal route of nutritional support should be determined (enteral versus parenteral) based on the underlying disease process, the integrity of the gastrointestinal tract, and the patient's clinical signs (intractable vomiting or diarrhea, dysphagia, etc.).

The provision of nutritional support should provide sufficient substrates for gluconeogenesis, protein synthesis, and energy to sustain vital physiologic processes such as immune function, wound repair, and cell division.[12] Although energy expenditure has been determined using indirect calorimetry in research populations of dogs, utilization of mathematical formulas remains the most efficient, cost-effective, and practical means of estimating a patient's energy requirement. An estimate of an animal's resting energy requirement (RER) is needed to determine the minimum amount of food necessary to sustain critical physiologic processes. The RER is the animal's energy requirement at rest in a thermoneutral environment and in a postabsorptive state. A linear formula can be applied to determine the RER of dogs and cats weighing between 2 and 45 kg, or, alternatively, an allometric formula (preferred by the author) can be applied to dogs and cats of all weights.

$$\text{Allometric formula: RER (kcal/day)} = 70\ (\text{body weight in kg})^{0.75}$$
$$\text{Linear formula: RER (kcal/day)} = 30\ (\text{body weight in kg}) + 70$$

Until recently, many clinicians multiplied the RER by an "illness factor" between 1.1 and 2 to account for the increased metabolism associated with different disease states and injuries. Veterinary nutritionists discourage the implementation of this extrapolated and subjective practice, and advocate a more cautious approach to minimize overfeeding and potential metabolic complications such as refeeding syndrome.[13] Nutritional support should initially deliver sufficient calories and protein to meet the patient's RER at its current weight, adjusted for body condition. Close observation of changes in body weight, physical examination findings (decreased subcutaneous fat stores, muscle wasting, and presence of edema or ascites), and ongoing losses (diarrhea, vomiting, exudative wounds) will help determine whether to increase or decrease the patient's caloric intake.

Diet Selection

The type of formula to feed the patient depends on the selected route of feeding, the functional status of the gastrointestinal tract, and the animal's nutrient requirements. Other factors, such as cost, availability, and ease of use also may be important. Animals fed via nasoesophageal or jejunostomy feeding tubes are limited to receiving liquid enteral formulas that have a caloric density of approximately 1.0 to 1.3 kcal per mL. Caution should be heeded when using human enteral formulas for longer than 2 weeks, particularly in cats, because most of these formulas contain less than 20% protein calories and they lack the essential amino acids, taurine, and arginine.

Polymeric solutions contain macronutrients in the form of isolates of intact protein (casein, lactalbumin, whey, egg white), triglycerides, and carbohydrate polymers. The carbohydrates are usually glucose polymers in the form of starch and its hydrolysates and the fats are of vegetable origin. The osmolality varies between 300 and 450 mOsm/kg in solutions with a caloric density of 1 kcal/mL; however, the osmolality may reach 650 mOsm/kg in solutions with a greater caloric density. Monomeric solutions contain protein as peptides or amino acids, fat as long-chain triglycerides, or a mixture of long-chain triglycerides and medium-chain triglycerides, and carbohydrates as partially hydrolyzed starch maltodextrins and glucose oligosaccharides. These solutions require less digestion and their absorption is more efficient than regular foods or polymeric solutions; however, the partially digested macronutrients contribute to the higher osmolality, which is between 400 and 700 mOsm/kg.

A variety of disease-specific enteral formulas are available for the management of critically ill human patients with renal disease, liver disease, diabetes mellitus, chronic obstructive pulmonary disease, and food allergies. The hepatic formulas offer increased amounts of branched chain amino acids: valine, leucine, and isoleucine; and reduced amounts of aromatic amino acids: phenylalanine, tyrosine, and tryptophan, compared with standard products. These alterations purportedly promote a reduced uptake of aromatic amino acids at the blood–brain barrier, reducing the synthesis of false neurotransmitters, and thereby ameliorating the neurologic symptoms that occur with hepatic encephalopathy (refer to Chapters 17 and 61).[14,15] Evidence supporting the use of hepatic formulas is very limited and controversial, and there is currently no clear consensus supporting the use of branched chain amino acids supplementation in people with hepatic cirrhosis and encephalopathy.[14,15] Enteral formulas enriched with arginine, omega-3 fatty acids, glutamine, and nucleotides are considered to enhance the immune response, although a systematic review of the evidence by Heyland et al. showed that immunonutrition reduced septic complications in critically ill adults, but this reduction did not result in reduced mortality.[16]

Commercial blended pet food diets are recommended for feeding via esophagostomy or gastrostomy tubes. In select cases, the feeding of a liquid enteral formulation may be indicated for feeding via nasoesophageal or jejunostomy tube. Feeding should be delayed for 12 to 24 hours after placement of a gastrostomy tube, to allow return of gastric motility and allow formation of a fibrin seal. In contrast, feeding can be instituted immediately after esophagostomy tube placement, once the animal has fully recovered from anesthesia. Diet can be administered as bolus feedings or continuous infusion when a gastrostomy tube is used for feeding. Improved weight gain and decreased gastroesophageal reflux have been reported in human patients given continuous feedings,[17] although similar studies are lacking in the veterinary literature. If continuous feeding is employed, it should be interrupted every 8 hours to determine the residual volume by application of suction to the feeding tube. If the residual volume is more than twice the volume infused in 1 hour, feeding should be discontinued for 2 hours, and the rate of infusion decreased by 25% to prevent vomiting. Treatment with metoclopramide (1 to 2 mg/kg/24 h as a constant-rate infusion) may be used to enhance gastric emptying and decrease vomiting.[18]

With bolus feeding, the required daily volume of food should be divided into four to six feedings. Dogs and cats are usually fed

approximately 25% of their caloric requirement on the first day of feeding, with a gradual increase of 25% of the caloric requirement per day. Most animals are able to reach their energy requirement by the fifth or sixth day of feeding. The food should be warmed to room temperature and fed slowly through the tube to prevent vomiting. Flushing the tube with 15 to 20 mL of lukewarm water helps prevent clogging. Before each feeding, the tube should be aspirated with an empty syringe to check for residual food left in the stomach from the previous feeding. If more than half of the last feeding is removed from the stomach, the feeding should be skipped and residual volume rechecked at the next feeding. Jejunal feeding can be started within 6 hours of tube placement if peristalsis is present. Continuous feeding should be used with jejunostomy feeding to avoid abdominal cramping and diarrhea associated with bolus feeding via this route. Continuous infusion is recommended at an initial flow rate of 1 mL/kg/h and increased gradually over 48 hours until the total daily volume can be given over a 12- to 18-hour period.[19]

Enteral Feeding Access Devices

Most feeding tubes today are made of polyurethane or silicone. The main shortcoming of silicone is related to its stiffness and flexibility. Silicone feeding tubes require thick sidewalls to obtain tube-wall integrity or stiffness. Because of this, the internal diameter of a silicon feeding tube is smaller than the internal diameter of a similar-sized polyurethane tube that does not require the degree of sidewall thickness for tube integrity.[20] The flexibility and decreased internal diameter of silicone tubes may lead to clogging or kinking of the tube. In addition, silicone is known for notch sensitivity that is associated with propagation of a defect in the material when the silicone gets a nick or a tear in it.[20] New feeding tube materials are being developed that are copolymers of silicone and polyurethane and other polymer end groups in an effort to mimic the softness of silicone and the durability and wall thickness of polyurethane. The French unit measures the outer lumen diameter of a tube (each French unit is equal to 0.33 mm).

Nasoesophageal Tubes

Nasoesophageal tubes are a simple and efficient choice for the short-term (less than 10 days) nutritional support of most anorectic hospitalized animals that have a normal nasal cavity, pharynx, esophagus, and stomach.[21] Nasoesophageal tube feeding is contraindicated in animals that are vomiting, comatose, or lack a gag reflex. Polyvinylchloride (Infant Feeding Tube, Argyle Division of Sherwood Medical, St. Louis, MO) or red rubber tubes (Robinson catheter, Sherwood Medical, St. Louis, MO) are the least-expensive tubes for dogs and cats, although the polyvinylchloride tubes may harden within 2 weeks of insertion and cause irritation or ulceration of the pharynx or esophagus. Although tubes made of polyurethane (MILA International, Inc., Erlanger, KY) or silicone (Global Veterinary Products, Inc., New Buffalo, MI) are more expensive, they are less irritating and more resistant to gastric acid, allowing prolonged usage. An 8-French, 91-cm tube with or without a tungsten-weighted tip is suitable for dogs weighing more than 15 kg. A 5-French tube is more comfortable for cats and smaller dogs.

The tube should terminate in the distal esophagus to decrease the likelihood of reflux esophagitis,[22] and this is facilitated by ensuring that the length of the tube approximates the distance from the tip of the nose to the seventh or eighth intercostal space. A tape marker is placed on the tube once the appropriate measurement has been made. Desensitization of the nasal cavity with 0.5 to 1 mL of 0.5% proparacaine hydrochloride is recommended. The head is tilted upward to encourage the local anesthetic to coat the nasal mucosa. The tip of the tube is lubricated with 5% lidocaine viscous prior to passage. The tube is passed by maintaining the animal's head in the normal angle of articulation (avoid hyperflexion or overextension of the head and neck) and gently directing the tip of the tube in a caudoventral medial direction. The tube should move with minimal resistance through the ventral meatus and nasopharynx and into the esophagus. Nasoesophageal intubation is more difficult to perform in dogs because of their long, narrow nasal passages and extensive turbinate structures. In addition, the presence of a small ventral ridge at the proximal end of the nasal passage in dogs necessitates directing the tip of the tube dorsally initially to allow passage over the ventral ridge and into the nasal vestibule (Fig. 33-1).[21] The tube is then directed in a caudoventral and medial direction while pushing the external nares dorsally.[23] This maneuver opens the ventral meatus and guides the tube into the oropharynx.

If the tube is unable to be passed with minimal resistance into the oropharynx, it should be withdrawn and redirected because it could be positioned in the middle meatus with the tip encountering the ethmoid turbinate. Once the tube has been passed to the level of the tube marker, it should be secured as close to the nostril as possible, with either suture material (Fig. 33-2A) or glue (Superglue, Loctite Corp., Cleveland, OH), although glue can cause a dermatitis in some animals. A second tape tab should be secured to the skin on the dorsal midline between the eyes (Fig. 33-2B and C). In the cat, the tube must not exit laterally nor come in contact with the whiskers. An Elizabethan collar is usually required for dogs to prevent inadvertent tube removal; most cats, however, do not require such a device. Removal of the tube is facilitated by clipping the hair that is attached to the glue.

After placement, the tube position is checked by injecting 5 to 10 mL of air while ausculting the cranial abdomen for borborygmus, by infusing 3 to 5 mL of sterile saline or water through the tube and observing for a cough response[21] (although a lack of a cough response is not always a reliable indicator of tube placement), or by obtaining a lateral survey thoracic radiograph. Verification of placement can also be done with an end-tidal CO_2 monitor. Tubes placed within the esophagus or stomach should yield no CO_2 when checked with an end-tidal CO_2 monitor. The most common complications associated with the use of nasoesophageal tubes include epistaxis, dacryocystitis, rhinitis, tracheal intubation and secondary pneumonia, and vomiting.[21]

A major disadvantage of nasoesophageal feeding tubes is their small diameter, necessitating the use of liquid enteral formulas. Commercially available canned pet foods that are diluted with water will invariably clog the feeding tube. The caloric density of most human and veterinary liquid enteral formulas varies from 1 to 2 kcal/mL. Diets are fed full strength on continuous (pump infusion) or bolus feeding schedules.

Esophagostomy Tubes

Esophagostomy feeding tubes are easily inserted, require only light general anesthesia with isoflurane or heavy sedation, and intubation with a cuffed endotracheal tube. The technique is minimally invasive and no specialized endoscopic equipment is needed.

The patient should be placed in right lateral recumbency, and the left lateral cervical region clipped and aseptically prepared for tube placement.[24-26] Placement of the feeding tube in the left side of the neck is preferred because the esophagus lies slightly left of midline making left-sided placement more desirable. A 14- to 20-French red rubber catheter (Robinson catheter, Sherwood Medical, St. Louis, MO), silicone catheter (Global Veterinary

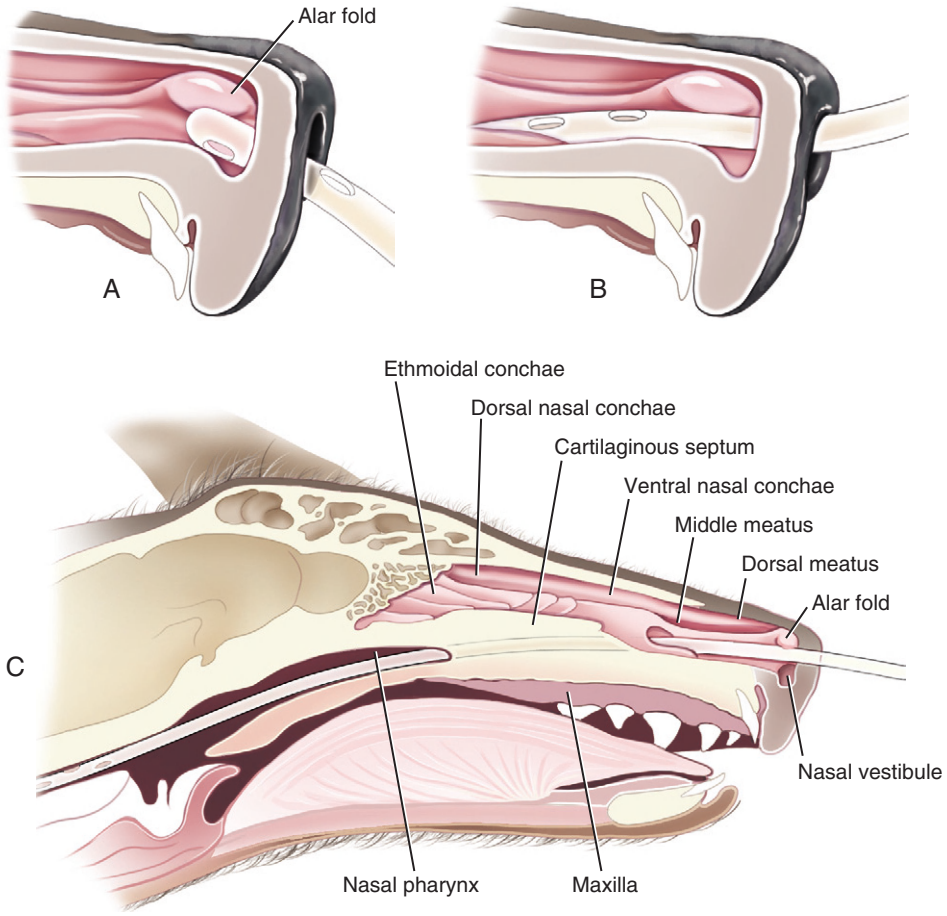

Figure 33-1 Parasagittal section showing stepwise insertion of a nasoesophageal tube through the ventral meatus of a dog. **A,** The presence of a small ventral ridge at the rostral end of the nasal passage necessitates directing the tip of the tube dorsally to clear the protuberance. **B,** Once past the protuberance, the tube is aimed medially and ventrally and advanced into the ventral meatus. **C,** Tube through ventral meatus and nasal pharynx (*NP*). Reprinted with permission from Crowe DT: Clinical use of an indwelling nasogastric tube for enteral nutrition and fluid therapy in the dog and cat. *J Am Anim Hosp Assoc* 22:675–682, 1986.

Products, Inc., New Buffalo, MI), or polyurethane catheter (MILA International, Inc., Florence, KY) should be premeasured from the midcervical esophagus to the seventh or eighth intercostal space, and marked with a permanent marker to ensure the distal end of the catheter terminates in the distal esophagus.[22] The left midcervical area is aseptically prepared from the angle of the mandible to the thoracic inlet. Three basic techniques for placement of a midcervical esophagostomy tube have been described.[24-26]

Technique Using Curved Carmalt, Mixter, or Schnidt Forceps

Advance the right-angle forceps into the midcervical esophagus from the oral cavity. Use the angle of the jaw and the point of the shoulder for landmarks to help ensure that the tip of the forceps can be palpated externally in the midcervical region. Push the curved tips of the forceps laterally at the midcervical esophagus, so they can be palpated below the skin. A number 11 scalpel blade is used to make a stab incision through the skin only, exposing the subcutaneous tissue and muscle layers of the esophagus, and avoiding the jugular and maxillofacial veins. Exteriorize the tip of the forceps from the esophageal lumen through the skin incision. Guide the advancing forceps through the esophageal muscle layers and carefully dissect the esophageal mucosa off the tip of the forceps with a scalpel blade. Use the tip of the forceps to grasp the distal end of the feeding tube, and draw the tube out of the oral cavity. Secure the distal end of the feeding tube using the forceps to ensure that the tube remains exteriorized while the proximal end of the tube is pulled out of the animal's mouth. Retroflex the proximal tip of the feeding tube and advance it in an aboral direction across the pharynx and down the esophagus, while slowly retracting on the external end of the tube 2 to 4 cm. A guidewire can be used to facilitate pushing the proximal tip of the feeding tube into the esophagus. The exteriorized portion of the tube will be observed to rotate in a cranial direction as the tube moves down the esophagus, indicating correct placement of the tube in the esophagus. Retention sutures (Chinese finger-trap suture) using 2-0 polypropylene are used to secure the distal end of the tube to the skin. An additional method of securing the tube involves passing a heavy suture on a taper needle through the skin next to the tube and into the periosteum of the wing of the atlas. Antibiotic ointment and gauze dressing is placed at the incision site, and the tube and entrance site are loosely bandaged with conforming gauze wrap. The correct placement of the tube in the mid to distal esophagus should be confirmed radiographically. It is important to ensure that the tube does not traverse the gastroesophageal sphincter and predispose the patient to gastroesophageal reflux. Feeding can be instituted immediately following full recovery of the patient from anesthesia. The tube

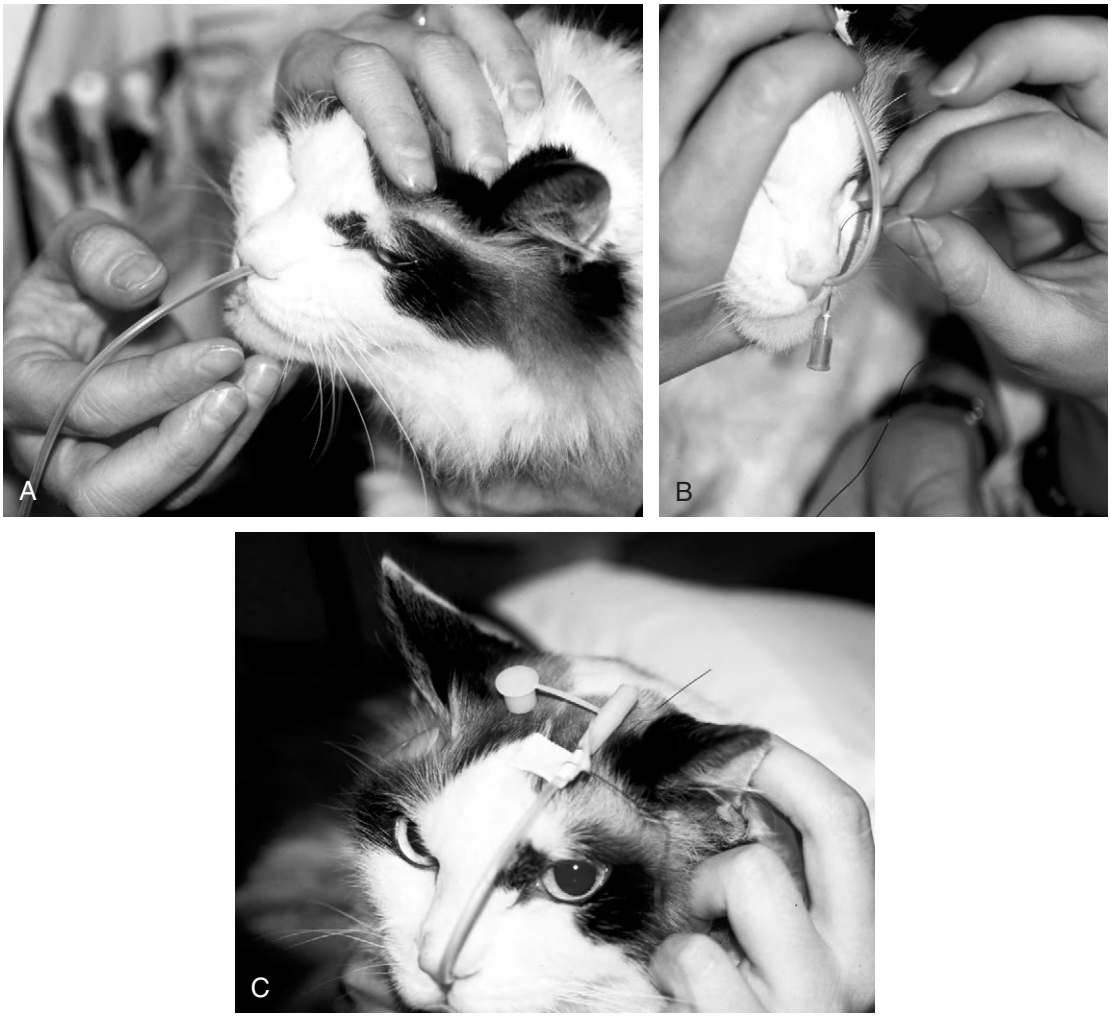

Figure 33-2 **A,** The tip of the nasoesophageal tube has been lubricated and passed into the ventral meatus by positioning the animal's head in a normal angle of articulation. **B,** The tube should be secured as close to the nostril as possible, with either suture material or glue. **C,** The nasoesophageal tube can be secured to the skin on the dorsal midline between the eyes with tape "butterflies."

esophagostomy–skin interphase should be examined at least daily during the first week for evidence of infection or leakage of food or saliva. The stoma site can be kept clean with a topical antiseptic solution (1:100 Betadine solution in 0.9% saline). The tube can be easily removed once nutritional support is no longer needed by cutting the Chinese finger-trap anchoring suture and pulling the tube. The wound should be allowed to heal by second intension.

Percutaneous Feeding Tube Applicator Technique

An alternative tube esophagostomy technique utilizing an ELD percutaneous feeding tube applicator or similar device can be used.[8] The applicator is inserted into the midcervical esophagus via the oral cavity. The distal tip is palpated, and an incision is made through the skin and subcutaneous tissue over the tip of the ELD. Activate the spring-loaded instrument (Fig. 33-3A) to advance the trocar through the esophageal wall and incision (Fig. 33-3B) The distal end of the feeding tube is secured to the eyelet of the trocar with suture material. The ELD device and attached feeding tube are retracted into the esophagus and exteriorized out of the oral cavity. The feeding tube is redirected into the midcervical esophagus after inserting a wire stylet into the distal tip of the feeding tube. The tube is secured to the skin as mentioned above previously.

Percutaneous Needle Catheter Technique

This method incorporates the use of an esophagostomy introduction tube (Van Noort esophagostomy tube set, Global Veterinary Products, Inc., New Buffalo, MI) (Fig. 33-4) that is introduced into the midcervical esophageal area. The slot in the distal portion of the tube is palpated, and a Peel-away sheath needle (Global Veterinary Products, Inc., New Buffalo, MI) is introduced into the distal portion of the tube. The needle is removed from the sheath, and a 10-French catheter is introduced through the sheath to the distal third of the esophagus. The sheath is peeled away and the esophagostomy tube is carefully removed. The feeding tube is secured as described previously. This technique has limitations as the small diameter of the feeding tube (10 French) only allows for the administration of fluids and liquid enteral formulas.

Despite the potential for esophageal scarring and stricture formation, esophageal stricture or a persistent esophagocutaneous fistula have not been reported. The most common minor complication is peristomal inflammation, with peristomal abscessation occurring infrequently.[24-27] Most of the inflammatory reactions are mild and respond to thorough cleansing with topical antibiotics. Other less-common complications include vomiting of the tube into the oral cavity and tube obstruction.[24-27]

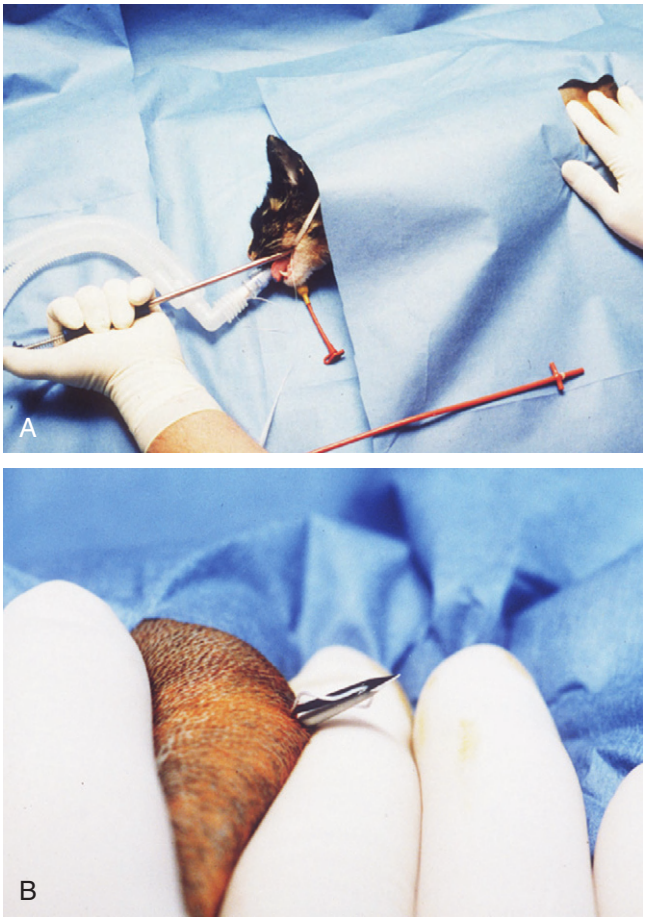

Figure 33-3 **A,** Demonstration of the ELD device for placement of an esophagostomy tube or blind percutaneous gastrostomy technique. Activation of the spring-loaded instrument advances the trocar through the esophageal or gastric wall. **B,** Suture material is attached to the exteriorized eyelet of the trocar, which is retracted into the lumen of the instrument and carefully removed from the esophagus and out the mouth of the animal. The exteriorized suture material is attached to a feeding tube.

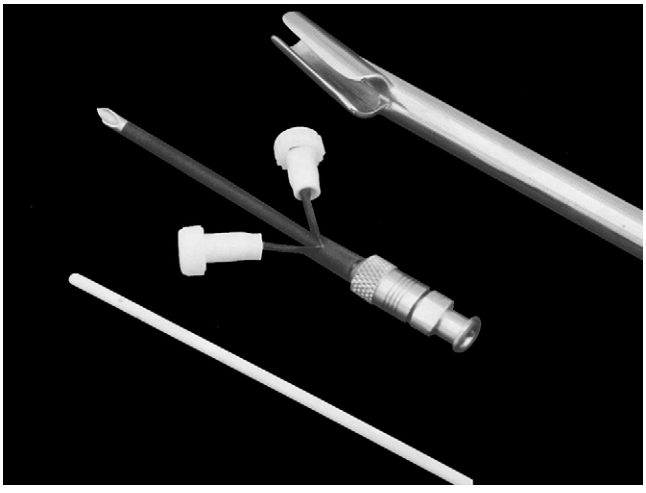

Figure 33-4 Photograph of the esophagostomy tube set, illustrating the esophagostomy introduction tube, 10-gauge, 5-cm-long needle with peel-away sheath needle, and a 10-French silicone catheter.

Gastrostomy Tubes

Gastrostomy tube feeding is indicated for long-term (weeks to months) nutritional support of anorectic or dysphagic animals that have adequate gastrointestinal function to allow digestion and absorption of feeding solutions. Gastrostomy feeding tubes are of comparatively large diameter (20 to 24 French), allowing the economic use of blended pet foods and the direct administration of medications. Gastrostomy tube feeding is contraindicated in animals with persistent vomiting, decreased consciousness, or gastrointestinal obstruction. Caution should be exercised in conditions under which the stomach cannot be apposed to the body wall (severe ascites, adhesions, space-occupying lesions).

Gastrostomy tubes can be placed percutaneously or during laparotomy. Placement is usually accompanied via a percutaneous endoscopic gastrostomy (PEG) technique,[28,29] or a blind percutaneous gastrostomy technique.[30,31] There are a variety of feeding tubes that can be used for gastrostomy feeding, including latex, polyurethane, and silicon tubes with French-Pezzer mushroom, balloon, bumper, or silicone dome tips (Fig. 33-5). The silicone catheters can be purchased from Global Veterinary Inc., New Buffalo, KY and from US Endoscopy, Mentor, OH; polyurethane from MILA International, Inc., Erlanger, KY; and latex catheters from BARD Urological Division, Murray Hill, NJ. One can modify the catheters by cutting off and discarding the flared open end of the catheter and cutting off two 2-cm pieces of tubing (to be used as internal and external flanges) from the same end of the catheter. The end of the catheter opposite the mushroom tip is trimmed to facilitate its introduction into the larger opening of a disposable plastic micropipette. Make a small stab incision through the center of each flange and fit one flange over the cut end of the catheter, sliding it down until it rests against the mushroom tip. Use the other 2-cm piece of tubing as an external flange that lies against the abdominal wall.

Percutaneous Endoscopic Gastrostomy Technique

Endoscopic and blind placement of gastrostomy tubes necessitates brief anesthesia. The animal should be placed in right lateral recumbency so that the stomach tube can be placed through the greater curvature of the stomach and the left body wall. Patient preparation for both percutaneous procedures is identical and involves a surgical prep of the skin caudal to the left costal arch. The endoscope is introduced into the stomach and the stomach is carefully inflated until the abdomen is distended but not drum tight. The left body wall is transilluminated with the endoscope to ensure that the spleen is not positioned between the stomach and body wall. An

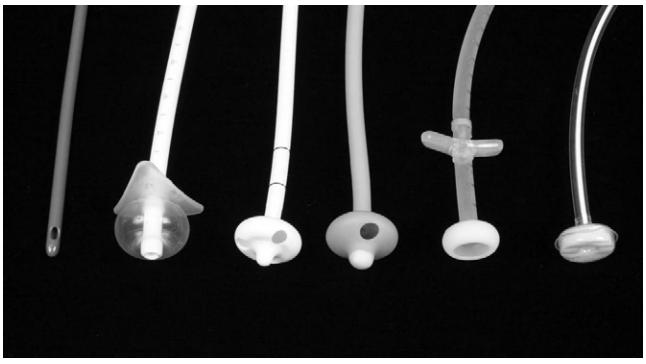

Figure 33-5 Gastrostomy tubes illustrating the various materials and catheter tips. From left to right: French red rubber catheter, silicone balloon catheter, silicone mushroom catheter, latex mushroom catheter, silicone catheter with dome, polyurethane catheter with bumper.

appropriate site for insertion of the tube is determined by endoscopically monitoring digital palpation of the gastric wall. A small incision is made in the skin with a scalpel blade, and an intravenous catheter (16 to 18 gauge, 1.5 to 2 inches) is stabbed through the body wall into the lumen of the stomach (Fig. 33-6A). The stylet is removed and nylon or polyester suture is threaded through the catheter into the lumen of the stomach. The suture material is grasped with the endoscopic biopsy forceps (Fig. 33-6B), and the endoscope and forceps are carefully withdrawn through the esophagus and out of the mouth. The suture material is secured to the feeding tube and gentle traction is applied to the suture material at its point of exit from the abdominal wall (Fig. 33-6C). The feeding tube is pulled out through the body wall allowing the mushroom end to draw the stomach wall against the body wall (Fig. 33-6D). The feeding tube is anchored in this position by the external flange placed over the catheter at the skin surface (Fig. 33-6E). The endoscope is then reinserted into the stomach to verify the correct placement of the mushroom against the gastric mucosa. If blanching of the mucosa is observed, less tension should be applied to the tube, otherwise necrosis of the gastric wall may ensue as a result of ischemia. A plastic clamp is placed over the tube and the tube is capped with a Y-port connector. A jacket made from stockinette (San Jose Surgical Supply, Inc., San Jose, CA) is fitted to protect the tube (Fig. 33-6F).

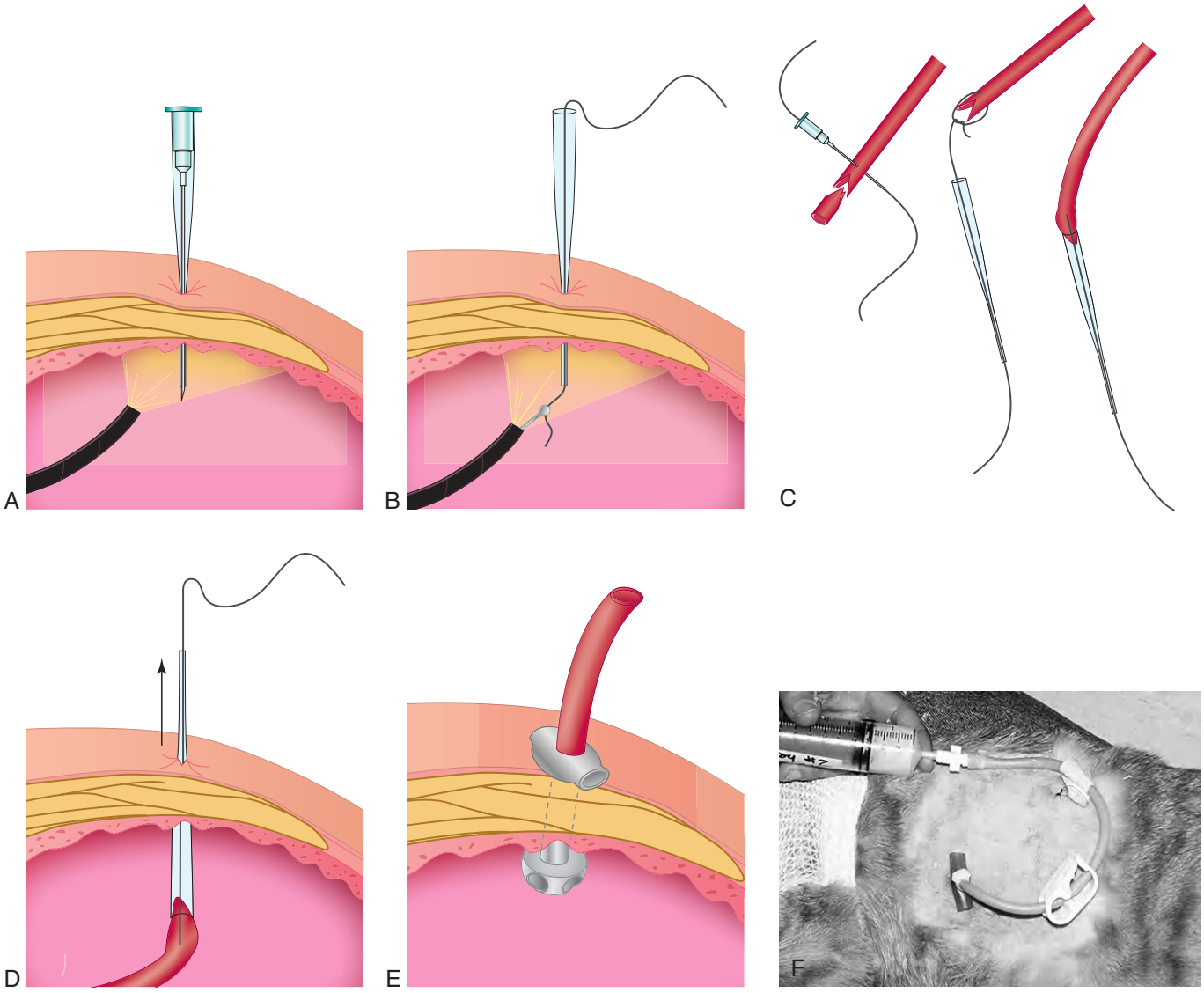

Figure 33-6 Percutaneous endoscopic gastrostomy (PEG) technique. **A,** With the animal in right lateral recumbency, the endoscope is introduced into the stomach, and the stomach is insufflated with air. The left body wall is transilluminated with the endoscope to ensure that the spleen is not between the stomach and the body wall. A 16- to 18-gauge sheathed catheter is pierced transabdominally into the insufflated stomach lumen. **B,** The catheter stylet is removed, and nylon suture is advanced through the catheter until it can be grasped with endoscopic retrieval forceps. The nylon suture is pulled out through the mouth as the endoscope is withdrawn. **C,** The suture material is secured to the feeding tube and water-soluble jelly is applied liberally to the catheter sheath and the mushroom-tip catheter. **D,** The lubricated catheter is drawn down the esophagus and into the stomach as the assistant applies traction on the suture exiting the abdominal wall. **E,** The catheter is advanced until the mushroom tip rests gently against the gastric mucosa. Endoscopy should be repeated to confirm the correct position of the mushroom tip. An external flange is fitted down the tube against the skin to prevent the tube from slipping into the stomach. **F,** Gastrostomy feeding tube in place in a cat, with the clamp in the open position. The stockinette jacket is pulled over the gastrostomy tube once feeding is completed.

Complications related to PEG tubes include those associated with placement of the tube (splenic laceration, gastric hemorrhage, and pneumoperitoneum), and delayed complications such as vomiting, aspiration pneumonia, tube extraction, tube migration, and stoma infection.[28,29,32] Splenic laceration can be minimized by insufflating and transilluminating the stomach prior to placement of the needle or catheter into the abdominal wall. The author has seen a discordant number of large-breed dogs that have had major complications secondary to the stomach falling off the silicone dome at the end of the gastrostomy tube. The stoma appeared normal in all dogs, with the unfortunate consequence that several dogs were fed through the gastrostomy tube. This complication occurred despite the placement of an internal flange between the dome and the gastric mucosa. For this reason, the author recommends that all dogs heavier than 30 kg, particularly those that have delayed wound healing secondary to malnutrition, uremia, or chemotherapy administration, do not have a PEG procedure, and instead have a gastrostomy tube placed surgically or placement of an esophagostomy tube. Minor complications include pressure necrosis at the stoma site and cellulitis.[28,29,32]

Blind Percutaneous Gastrostomy Technique

An alternative technique for nonendoscopic and nonsurgical gastrostomy tube placement has been described.[30,31] The gastrostomy tube placement device can be prepared with a length of vinyl or stainless steel tubing (diameter 1.2 to 2.5 cm) purchased from a hardware store, or an ELD Gastrostomy Tube Applicator (Jorgensen Laboratories, Loveland, CO) or gastrostomy tube introduction set (Global Veterinary Inc., New Buffalo, KY) can be used. The ELD Gastrostomy Tube Applicator is the only device that utilizes an internal trocar, whereas the Cook gastrostomy tube introduction set contains a wire that is threaded through an introduction needle. The distal tip of a stainless steel tube can be flared and deflected 45° to the long axis of the tube to help displace the lateral body wall. The lubricated tube is passed through the mouth and into the stomach. The tube is advanced until the end of the tube displaces the stomach and lateral abdominal wall. Positioning the animal with its head over the edge of the table and lowering the proximal end of the tube will facilitate identifying the tube tip through the body wall. For the Cook gastrostomy introduction set or similarly prepared device, a percutaneous needle is introduced into the lumen of the introduction tube while the assistant firmly holds the distal tip of the tube between two fingers. A skin nick is made over the end of the tube and a 14-gauge needle advanced into the lumen of the introduction tube (Fig. 33-7A). Proper positioning of the needle is confirmed by moving the hub from side to side and feeling the needle tip strike the inside of the tube. A guidewire included in the kit is threaded through the lumen of the needle, into the tube, and out the mouth of the patient. The introduction tube is removed from the patient, and the threaded end of the guidewire is secured to an adapter that fits snugly into the end of a feeding tube (Fig. 33-7B and C). Gentle traction is applied to the guidewire at its point of exit from the abdominal wall, facilitating the placement of the mushroom end of the feeding tube against the gastric mucosa. The feeding tube is secured in an identical fashion to the PEG tube procedure described above.

The reported complication rate for blind percutaneous gastrostomy is similar to that of PEG; however, the risk of penetrating the spleen, stomach, or omentum is greater when the stomach is not insufflated with air prior to positioning the tube against the lateral abdominal wall.[33] Contraindications to using the "blind" technique include severe obesity precluding accurate palpation of the tube against the abdominal wall and esophageal disease. Surgical placement of gastrostomy tubes should be reserved for these patients.

Jejunostomy Tubes

Jejunostomy tubes are indicated in patients unable to tolerate intragastric or intraduodenal feeding, despite having normal distal small

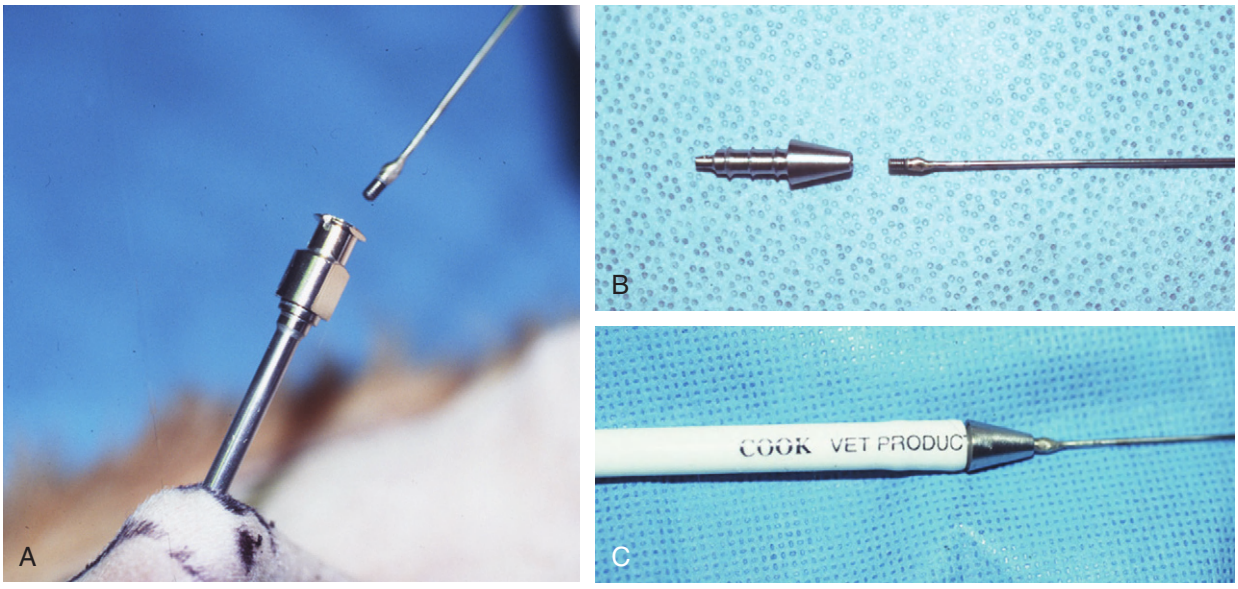

Figure 33-7 **A,** Cook gastrostomy introduction set showing a 14-gauge needle advanced into the lumen of the introduction tube. A guidewire included in the kit is threaded through the lumen of the needle, into the introduction tube, and out the mouth of the patient. **B** and **C,** Following the removal of the introduction tube from the animal, the threaded end of the guidewire is secured to an adapter that fits snugly into the end of the feeding tube. Gentle traction is applied to the guidewire at its point of exit from the abdominal wall to position the mushroom of the tube against the gastric mucosa.

intestine and colon function.[34] Specific indications for feeding via jejunostomy tube include gastric outlet obstruction, gastroparesis, recurrent/potential aspiration, proximal small bowel obstruction, and partial gastrectomy. Jejunal tube feeding minimizes the stimulation of pancreatic secretion and is a viable route for patients with severe pancreatitis.[34] Surgically placed jejunostomy tubes are the most widely used and familiar method for long-term feeding of the small intestine directly. An alternative approach to the surgical jejunostomy technique is the placement of a feeding tube via percutaneous techniques. This includes both percutaneous jejunostomy and percutaneous endoscopic gastrojejunostomy (PEG-J) tubes placed under fluoroscopic or endoscopic guidance. The advantage of the PEG-J technique is that it allows ready access to the stomach for aspiration of gastric luminal contents.

Successful placement of PEG-J tubes has been demonstrated in healthy dogs and cats,[35] according to the method described by Leichus et al.[36] Four sequential steps are followed: (a) routine PEG placement; (b) deep guidewire passage into the small intestine; (c) endoscope retraction leaving the guidewire in place; and (d) jejunostomy feeding tube placement over the guidewire. Briefly, the animal is anesthetized and placed in right lateral recumbency. A PEG tube is routinely placed, and the external portion of the tube trimmed to a length of 6 inches to maximize the amount of jejunostomy tube that can be passed into the small intestine. Placement of a 65-cm jejunostomy tube (Gastro-Jejunal feeding tube, Wilson-Cook Medical Inc., Winston-Salem, NC) works well in cats, whereas a jejunostomy feeding tube 95 cm or larger is recommended for most dogs. A standard loop snare is passed through the PEG tube into the stomach using an endoscope. The snare is opened and the endoscope advanced through the open snare toward the pylorus. The animal is then positioned in left lateral recumbency, and the endoscope is advanced as far down the small intestine as possible. The accessory channel of the endoscope is flushed with water to facilitate rapid passage of a guidewire that is passed down the biopsy channel into the small intestine. As the endoscope is carefully retracted into the stomach, the tip of the endoscope is pulled past the open snare, which is then closed snugly on the guidewire. The endoscope is then removed from the animal with the resultant extension of the guidewire out of the oral cavity. The closed snare is then pulled out through the gastrostomy tube, facilitating the exit of a portion of the guidewire from the opening of the gastrostomy tube. The snare is then released, and an assistant gently pulls on the proximal end of the guidewire. The oral end of the guidewire is pulled through the gastrostomy tube, leaving the distal (aboral) end in the small intestine. The jejunostomy tube is flushed with water, which activates a lubricant on its inner diameter. The jejunostomy tube is threaded over the guidewire under endoscopic guidance until its proximal end is seated in the gastrostomy tube. The guidewire is then removed from the PEG-J tube, and abdominal radiographs are taken to confirm adequate placement of the jejunostomy tube 40 to 60 cm distal to the pylorus. Passage of the jejunostomy tube deeply into the jejunum is deemed critical to prevent retrograde catheter migration into the stomach.

Esophagostomy, Gastrostomy, and Percutaneous Endoscopic Gastrojejunostomy Tube Removal

Unlike gastrostomy tubes, an esophagostomy tube can be removed the same day it is placed if necessary without concern for leakage and development of secondary complications. The dressing and sutures are removed while the tube is held in place. The tube is then occluded by kinking and pulled out using gentle traction. The ostomy site should be cleaned, antibiotic ointment applied, and a light dressing placed around the neck. The dressing should be removed in 24 hours, and the ostomy site inspected. The ostomy site should close within 36 hours. Skin sutures are not needed for closure of the ostomy site. For PEG tubes and PEG-J tubes, it is recommended that the PEG tube be left in place for a minimum of 14 days. Animals receiving immunosuppressive therapy or patients that are severely debilitated may require longer for a peritoneal seal to form. The tube should be removed only when oral food intake is sufficient to meet the patient's caloric requirement. One of two methods of Pezzer PEG tube removal can be applied. The tube can be cut at the body wall and the mushroom tip pushed into the stomach to be passed in the feces. This method is safe in medium- to large-size dogs because the mushroom and internal flange should be easily passed in the stool. Alternatively, a stylet can be inserted into the tube to flatten the mushroom tip, while exerting firm traction on the tube. This method is recommended for cats and small dogs, because the mushroom can cause intestinal obstruction. Removal of the MILA catheter is accomplished by deflating the bumper that occurs once the Y-port adapter is removed. Catheters with a dome (US Endoscopy) are removed by gentle, but firm traction on the tube. The gastrocutaneous tract should seal with minimal or no leakage within 24 hours.

Gastrostomy and Esophagostomy Tube Replacement

The PEG tube may malfunction or be prematurely removed by the patient, requiring replacement. If the gastrostomy tube is removed within 14 days of placement (before establishment of the gastrocutaneous tract), iodinated contrast material can be injected via the stoma site to determine if the gastrocutaneous tract is still intact, or a PEG procedure could be performed to evaluate the gastric mucosa and verify correct positioning of the replacement gastrostomy tube. If the tube is inadvertently removed once the gastrocutaneous tract is well healed, one can replace the original catheter with a balloon-type catheter (Flexiflo Gastrostomy tube, Ross Laboratories, Columbus, OH)[37] or a low-profile gastrostomy device (LPGD, Bard Interventional Products Division, Murray Hill, NJ) (Fig. 33-8A). Both catheter types do not require an endoscopic procedure or anesthesia for placement. The gastrostomy "button" is a small, flexible, silicone device that has a mushroom-like dome at one end and two small wings at the other end that lies flush with the outer abdominal wall (Fig. 33-8B). A one-way antireflux valve prevents reflux of gastric contents through the top of the tube. There are two types of LPGDs: obturated and nonobturated. The obturated device has an enlarged mushroom tip that must be stretched for placement in the stomach by using a special introducer (Fig. 33-8C).[38] The nonobturated tube works like a Foley catheter and does not require forceful entry into the gastrostomy stoma. The length of the gastrocutaneous fistula must be precisely determined to guide correct selection of the appropriate "button" shaft length. This is accomplished with a special stoma-measuring device provided with the kit. The main advantages of the LPGD include their durability because of their silicon material, decreased likelihood of inadvertent removal by the patient, and their aesthetically pleasing appearance to the owners.[39] An alternative low-profile device that can be used in lieu of a regular PEG tube or replacement low-profile device is a one-step or "initial placement" low-profile PEG tube (One Step Button, now renamed as EndoVive Low Profile Percutaneous Endoscopic Gastrostomy kit; Boston Scientific, Natick, MA) (Fig. 33-9A and B). The use of silicon spacers supplied by the manufacturer (Fig. 33-9C) helps ensure that the devices can be adapted to animals with different stoma tract lengths. A recent study evaluating complications

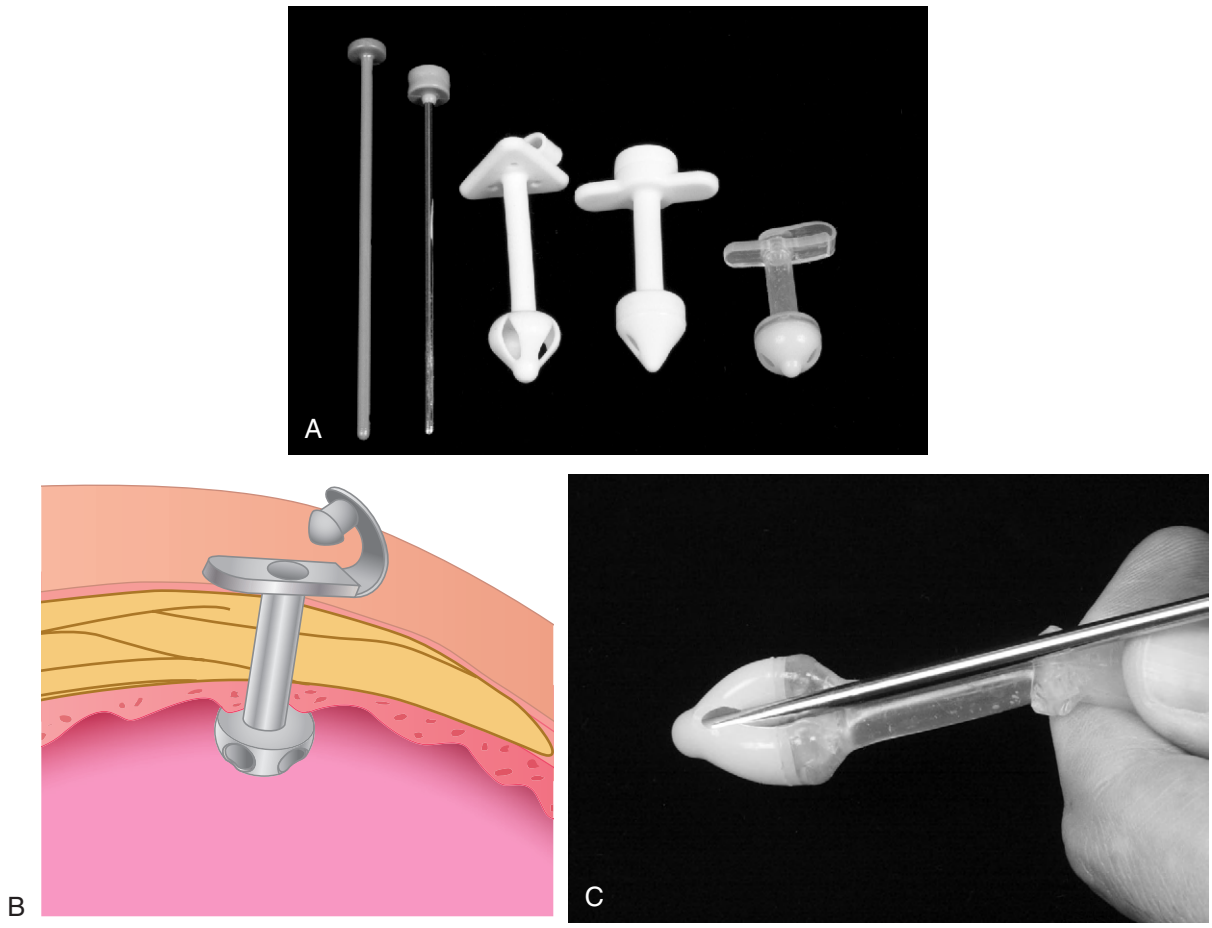

Figure 33-8 **A,** Low-profile gastrostomy devices and obturators used for stretching the dome-shaped tip of the device. From *left*: The Ross Laboratories Stomate low-profile device, the Cook low-profile device, and the Bard "Button" low-profile device. **B,** Low-profile gastrostomy device with small outer wings of the device lying flush against the skin of the abdominal wall. For feedings, the small plastic plug is removed and a feeding adapter is connected to a syringe. **C,** Correct technique for stretching the dome-shaped tip of the low-profile gastrostomy device with an obturator. The dome should not be stretched by passing the obturator through the lumen of the device as it will compromise the integrity of the antireflux valve located adjacent to the dome.

and outcomes of one-step low-profile gastrostomy devices for long-term enteral feeding in dogs and cats found that the devices were well tolerated, with most complications, including peristomal swelling and mucopurulent peristomal discharge, being relatively minor in nature.[40]

Complications of Enteral Feeding

Gastric Pressure Necrosis

Gastric pressure necrosis can occur from either the mushroom of the PEG tube or flange eroding the mucus layer of the stomach because of excessive tension being exerted on the PEG tube during placement. In addition, overzealous traction of the PEG tube followed by placement of the external flange flush against the skin of the patient can also cause pressure necrosis characterized by redness, swelling, and moistness of the skin. To minimize this problem, ensure that the PEG tube can be rotated following its placement and leave a 1-cm space between the external flange and the skin.

Feeding Tube Displacement

This is a relatively common problem, particularly with nasoesophageal and PEG-J tubes. Displacement of the tube can lead to aspiration, diarrhea, or in the case of gastrostomy tubes, peritonitis. Gastrostomy tubes should be marked with tape or a marking pen at the level of the skin to help verify the position of the tube. Detachment of the stomach from the abdominal wall with consequent intraperitoneal leakage of gastric contents can occur in large-breed dogs, and an internal flange should be placed in these animals to minimize dislodgment of the tube.

Tube Obstruction

Obstruction of the feeding tube is one of the most common complications of enteral feeding.[41] Most obstructions are secondary to coagulation of formula, although obstruction by tablet fragments, tube kinking, and precipitation of incompatible medications can also result in tube obstruction. Nasoesophageal tubes are prone to obstruction because of their small diameters, and obstruction also occurs up to three times more frequently in patients fed by continuous versus bolus feedings. Sucralfate and antacids have been reported to precipitate with enteral formulas and cause tube obstruction.[42] Several "remedies" have been advocated to relieve tube obstruction. Warm water injected with gentle pressure and suction will relieve most obstructions. For more unyielding obstructions, carbonated water is instilled into the tube and allowed to sit for

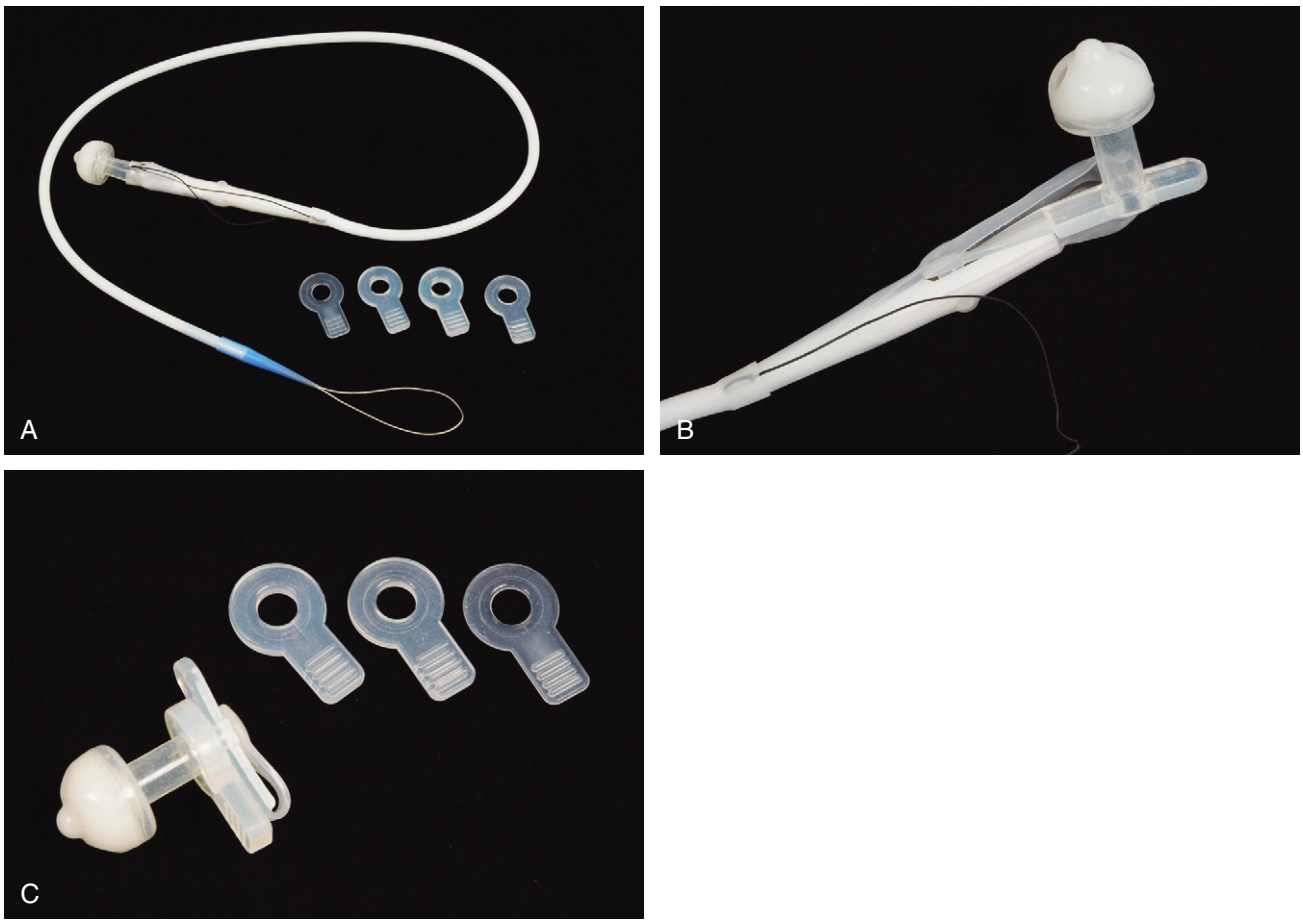

Figure 33-9 **A,** One-step low-profile gastrostomy device with flanges as it comes contained within a catheter sleeve. Four separate silicone spacers are also present. **B,** One-step low-profile gastrostomy device with flanges released after tearing the surrounding catheter sleeve open by pulling on the attached black suture material. **C,** One-step low-profile gastrostomy device separated from catheter sleeve, showing a single 5-mm silicone spacer inserted over the shaft, and three other separate silicone spacers of varying thickness.

1 hour before applying gentle pressure and suction. Pancreatic enzyme infusions[41] and meat tenderizer have also been advocated to dissolve tube obstructions. On rare occasions, the passage of an angiographic wire down the lumen is needed to unclog the tube. Tube obstructions can be minimized by flushing the feeding tube with warm water before and after administering medications or enteral feedings. The tube should also be flushed after checking for gastric residuals, because the acid pH will cause the formula to coagulate in the tube. Elixir forms of medication should be used rather than crushed tablet forms whenever possible. Tablets should be crushed and dissolved in water prior to administration through the feeding tube, if no alternative form of medication is available.

Leakage Through Ostomy Sites

Mild leakage at the stoma site can occur for the first few days following placement of the feeding tube. Persistent leakage may indicate tube dysfunction, peristomal infection, or a stoma site greater than necessary for the tube. Signs of inflammation with or without discharge or fever may indicate infection of the stoma site. These must be differentiated from fasciitis because a simple wound infection can usually be treated locally with dilute Betadine solution and more frequent dressing changes. Systemically administered antibiotics are usually reserved for patients with systemic signs of infection.

Aspiration

Pulmonary aspiration is a common complication of enteral feeding, although the actual incidence of this complication is difficult to determine due to the lack of consistency in how aspiration is defined. Risk factors for aspiration include impaired mental status, neurologic injury, absence of a cough or gag reflex, mechanical ventilation, and previous aspiration pneumonia.[43] The source of the aspirated material should be identified because withholding gastrostomy feedings or placing a jejunostomy feeding tube in a patient will have no benefit if the patient aspirated oropharyngeal secretions. Although controversial, most authors agree that postpyloric feeding reduces the risk of aspiration.[44] In addition, the use of continuous versus bolus feedings has been shown to induce less gastroesophageal reflux than bolus feedings.[45]

Diarrhea

Diarrhea is the most commonly cited complication associated with tube feeding in human and animal patients, with an incidence

ranging from 2.3% to 63%.[46] The clinical implications of enteral feeding–related diarrhea are significant. Severe diarrhea leads to fluid, electrolyte, and nutrient loss, and can cause considerable distress to the patient. Diarrhea in tube-fed patients occurs as a result of multiple factors, including hypoalbuminemia, hyperosmolar or high-fat diets, infected diets, and concomitant antibiotic therapy.[46] The incidence of diarrhea in enterally fed patients taking antibiotics far exceeds the incidence in normally fed patients taking the same antibiotics. Antibiotic-associated diarrhea may arise from overgrowth of enterobacteria (*Klebsiella, Proteus, Pseudomonas*) or from proliferation of *Clostridium difficile*.

Rationale for Parenteral Nutritional Support

CPN refers to the administration of a nutrient admixture into the cranial or caudal vena cava, or directly into the atrium. The term CPN is preferred to the outdated term, TPN, because admixtures used in these formulations are rarely nutritionally complete and balanced for the long-term feeding of patients, even if they supply the full caloric requirement. The indications for CPN have been dramatically altered in people over the past decade following the observation of serious septic and metabolic complications that often worsened patients' outcomes.[47] Deleterious consequences of CPN administration ascertained from results of human and animal studies include intestinal atrophy, decreased mucosal resistance to bacteria, abnormal liver function, increased rate of administration line sepsis, and metabolic complications such as hyperglycemia, blood electrolyte abnormalities, and hyperlipidemia.[2,3] A metaanalysis in which data collected from 27 studies involving 1828 patients were compared, revealed that tube feeding and conventional oral feeding with IV administration of dextrose were associated with a lower rate of infection than that associated with PN in patients with compromised function of the gastrointestinal tract.[3] Administration of CPN to 209 dogs and 75 cats was associated with a high mortality rate of 48% and 52%, respectively.[48,49] The average duration of PN in these studies was between 3 and 5 days, and the poor outcome in these animals was likely a consequence of suboptimal patient selection for PN and the large number of animals with advanced, complex medical disorders. The current use of CPN in people is restricted to the nutritional support of malnourished patients with intestinal failure as a result of extreme short bowel or absolute obstruction, although it might also prove useful to augment nutrition in patients who cannot tolerate sufficient intake by the enteral route. Because of these potential risks and the high cost associated with CPN, veterinary nutritionists have increasingly utilized peripheral parenteral nutrition (PPN) formulations,[50] that contain up to 10% dextrose and are thus not hyperosmolar (osmolality <750 mOsm/L), facilitating their administration via the cephalic or saphenous veins. PPN formulations typically meet 50% to 75% of the animal's RER and are administered for less than 1 week. PPN is thus a practical and beneficial strategy when the clinician anticipates a high likelihood of the patient being able to be weaned onto an enteral formula within days following the initiation of PPN. The major limitation in using PPN is the high incidence of thrombophlebitis.[30]

Parenteral Nutrition Components

The three basic components of parenteral nutrition solutions are amino acids, lipids, and dextrose. Crystalline amino acid solutions, available in concentrations of 3% to 15%, maintain nitrogen balance and replete lean tissue in cachectic patients. The standard amino acid solutions (Travasol 8.5% without electrolytes, Baxter Healthcare Corporation, Deerfield, IL) contain all the essential and dispensable amino acids for dogs and cats, with the exception of taurine. Lipid emulsions provide an intravenous source of fat calories and the essential fatty acids, linoleic and linolenic acid. Cats cannot convert linoleic acid to arachidonic acid, and should thus receive supplementation with an animal fat source if CPN is administered for longer than 2 weeks. Lipid emulsions are isotonic and are available as 10% (1.1 kcal/mL) or 20% (2 kcal/mL) solutions with osmolarities ranging from 270 to 340 mOsm/L, respectively. Lipid emulsions contain soybean oil (Intralipid, Baxter Healthcare Corporation, Deerfield, IL) or a combination of soybean and safflower oil triglycerides (Liposyn II, Hospira, Inc., Lake Forest, IL), egg phosphatides added as an emulsifying agent, and glycerin in water to achieve isotonicity with plasma. Sodium hydroxide is added to these products to adjust the pH to 6 to 9. The emulsified fat particles are comparable in size to chylomicrons and are removed from the circulation via the action of peripheral lipoprotein lipase. A common misconception exists in regards to the use of lipids in cases of pancreatitis. Although hypertriglyceridemia may be a risk factor for pancreatitis, infusions of lipids have not been shown to increase pancreatic secretion or worsen pancreatitis and are therefore considered safe.[51] According to the most recent guidelines provided by the American Society of Parenteral and Enteral Nutrition, human patients with serum triglycerides exceeding 400 mg/dL should have the lipid proportion in PN reduced or eliminated altogether.[51]

Carbohydrate is typically administered in the form of 50% dextrose for CPN, and 10% dextrose for PPN. Providing calories as glucose stimulates insulin secretion, reduces muscle protein catabolism, and inhibits hepatic glucose output, thereby eliminating the need for skeletal muscle protein to provide amino acid precursors for gluconeogenesis. Dextrose is the least expensive intravenous energy source and is available in concentrations ranging from 5% to 70%. The dextrose in intravenous solutions is hydrated, so that each milliliter of dextrose monohydrate provides 3.4 kcal. Standard parenteral maintenance doses of all vitamins should be provided as an additive to the TPN solution. Multivitamin preparations for TPN provide all fat- and water-soluble vitamins with the exception of vitamin K, which may be given subcutaneously once weekly. No formal recommendations are currently available for supplementation of trace minerals to dogs and cats receiving PN.

Parenteral Nutrition Compounding

The preparation and administration of parenteral nutrition solutions may present problems with stability and compatibility. Factors that enhance precipitation include high molar concentrations, increases in solution pH, decreases in amino acid concentration, use of calcium as the chloride salt, increases in temperature, contact with intravenous fat emulsions, and the order of calcium and phosphate addition.[52] Total nutrient admixtures is one term used to describe the combination of dextrose, amino acid, fat emulsion, electrolytes, and multivitamins in one container. These components are aseptically mixed in one bag (up to 3 L) and provide a total nutrient supply for 24 to 48 hours. The advantages of the total nutrient admixture system include decreased nursing time involved in intravenous setup and tubing changes, decreased risk of contamination, and time saved in the pharmacy during preparation. Amino acid solutions should be added to the lipid emulsion before the dextrose solution is added. This prevents deterioration of the emulsion and oiling out that can occur when dextrose (pH approximately

4) is added directly to the lipid emulsion.[52] Ideally, compounding of PN should be done aseptically under a laminar flow hood using a semiautomated, closed-system, PN compounder (e.g., Automix compounder, Clintec Nutrition, Deerfield, IL). Manual compounding can be done in a clean, low-traffic area with strict adherence to aseptic technique using a three-in-one bag if an automated compounder is not available. Formulations of CPN and PPN solutions can be either individualized for each patient according to established worksheets (Boxes 33-1 and 33-2) or, alternatively, preprepared "recipes" are available at many institutions that can save time and prevent the need for calculating individual macronutrients for each formulation. Standardized recipes can be prepared for critically ill dogs and cats with adequate renal and hepatic function (Boxes 33-3 and 33-4) or for hyper- or hypokalemic dogs and cats with altered renal and hepatic function.

Box 33-1 Calculation of Total Parenteral Nutrition in Dogs and Cats

1. Calculate resting energy requirement (RER)
   RER = 70 × (current body weight in kg)$^{0.75}$
   or for animals weighing between 2 and 45 kg:
   RER = (30 × current body weight in kg) + 70 RER
   = _____kcal/day
2. Protein requirements

	Canine (g/100 kcal)	Feline (g/100 kcal)
Standard	4	6
Reduced (hepatic/ renal disease)	2 to 3	3 to 4
Increased (excessive protein losses)	6	6

(RER ÷ 100) × _____ g/100 kcal = _____ g protein required/day
3. Volume of nutrient solutions required
   a. 8.5% amino acid solution = 0.085 g protein/mL
   ____g protein required/day ÷ 0.085 g/mL = _____mL/day of amino acids
   b. Nonprotein calories:
   The calories supplied by protein (4 kcal/g) are subtracted from the RER to get total nonprotein calories needed.
   ____g protein required/day × 4 kcal/g = ____kcals provided by protein
   RER – kcals provided by protein =____total nonprotein kcal/day required
   c. Nonprotein calories are usually provided as a 50:50 mixture of lipid and dextrose
   20% lipid solution = 2 kcal/mL
   To supply 50% of nonprotein calories
   ____lipid kcal required ÷ 2 kcal/mL = ___mL of lipid
   50% of dextrose solution = 1.7 kcal/mL
   To supply 50% of nonprotein calories
   ___dextrose kcal required ÷ 1.7 kcal/mL = ___mL of dextrose
4. Total daily requirements
   ____ mL of 8.5% amino acid solution
   ____ mL of 20% lipid
   ____ mL of 50% dextrose
   ____ total mL of TPN solution to be administered over 24 hours

Note: Given that over 80% of TPN is water, it is important to adjust the IV rates of the patient's IV fluids accordingly.
Rate of administration: Initially start at 25% to 33% of RER, and gradually increase rate over the next 48 hours to meet RER.

Parenteral Nutrition Administration

Cannulation of a large-bore, high-flow central vein, such as the cranial vena cava, permits infusion of hyperosmolar (usually >1600 mOsm/L) nutrient solutions that would not be tolerated by smaller, low-flow peripheral veins. The author prefers to use a multilumen polyurethane catheter for CPN (Arrow International Inc., Reading, PA) that is placed via a surgical cutdown procedure and is dedicated for PN administration. Dressings and tubing connecting the parenteral solutions with the catheter should be changed every 48 to 72 hours. A 0.22-µm filter is inserted between the intravenous tubing and the catheter when lipid-free PN is used and should be changed with the tubing. A 1.2-µm filter should be used when a total nutrient admixture containing a lipid emulsion is infused. Caloric requirements should be based on the animal's RER at initiation of PN. Although some recommendations provide all energy requirements with only dextrose and lipids, others account for the energy provided from amino acids in the calculation and subtract it

Box 33-2 Peripheral Parenteral Nutrition Calculation

1. Calculate resting energy requirement (RER)
   RER = 70 × (current body weight in kg)$^{0.75}$
   or for animals weighing between 2 and 30 kg:
   RER = (30 × current body weight in kg) + 70 RER
   = ____kcal/day
2. Calculate the partial energy requirement (PER)
   Plan to supply 60% of the animal's RER with PPN: PER = RER × 0.60 = ___kcal/day
3. Proportion of nutrient requirements according to body weight:
   (Note that for animals weighing ≤3 kg, the formulation will exceed maintenance fluid requirements.)
   a. Cats and Dogs 3 to 5 kg:
   PER × 0.20 = ____kcals/day carbohydrate required
   PER × 0.20 = ____kcals/day protein required
   PER × 0.60 = ____kcals/day lipid required
   b. Cats and Dogs 6 to 10 kg:
   PER × 0.25 = ____kcals/day carbohydrate required
   PER × 0.25 = ____kcals/day protein required
   PER × 0.50 = ____kcals/day lipid required
   c. Dogs 11 to 30 kg:
   PER × 0.33 = ____kcals/day carbohydrate required
   PER × 0.33 = ____kcals/day protein required
   PER × 0.33 = ____kcal/day lipids required
   d. Dogs >30 kg:
   PER × 0.50 = ____kcals/day carbohydrate required
   PER × 0.25 = ____kcals/day protein required
   PER × 0.25 = ____kcals/day lipid required
4. Volumes of nutrient solutions required:
   a. 5% dextrose solution = 0.17 kcals/mL
   ____kcals carbohydrate required/day ÷ 0.17 kcals/mL = ____ mL/day dextrose
   b. 8.5% amino acid solution = 0.34 kcals/mL
   ____kcals protein required/day ÷ 0.34 kcal/mL = ____ mL/day amino acids
   c. 20% lipid solution = 2 kcal/mL
   ____kcals lipid required/day ÷ 2 kcal/mL = ___ mL/day lipid
   = ____ total mL of PPN to be administered over 24 hours

Box 33-3 Standardized Central Parenteral Formula for Dogs

300 mL	50% Dextrose
500 mL	20% Intralipid
1000 mL	8.5% Travasol without electrolytes
10 mL	Vitamin B complex (by Vedco)
36 mEq	Potassium phosphate
Provides:	1.0 kcal/mL (1129 mOsm/L)

Macronutrient composition: 17% protein (4.9 g protein/100 kcal), 54% lipid and 29% CHO, on ME basis. 20 mEq potassium/L.
1800 mL total volume (sufficient for 30-kg dog at RER for 48 hours or 75-kg at RER for 24 hours)

Box 33-4 Standardized Central Parenteral Formula for Cats

100 mL	50% Dextrose
200 mL	20% Intralipid
500 mL	8.5% Travasol without electrolytes
5 mL	Vitamin B complex (by Vedco)
16 mEq	Potassium phosphate
20 mEq	Potassium/L
Provides:	0.9 kcal/mL (1096 mOsm/L)

Macronutrient composition: 21% protein (6.1 g protein/100 kcal), 55% lipid and 24% CHO on ME basis
800 mL total volume (sufficient for 7-kg cat RER for 48 hours)

from the daily RER to estimate the total nonprotein calories required (see Boxes 33-1 and 33-2). The administration set and fluid bag must be protected from UV light to prevent degradation of B vitamins. The PN solution and entire administration set should be changed every 48 hours regardless of the volume remaining to decrease risk of bacterial growth in the solution and risk of sepsis. The administration line should be dedicated for PN administration and should not be broken (keep attached for walks and client visits) unless changing the administration set. The PN flow rate should be gradually increased over 48 hours to meet the patient's RER. Likewise, PN should be gradually tapered over 48 hours before discontinuation to prevent rebound hypoglycemia.

Monitoring

A complete blood count and serum biochemical profile should be performed prior to initiation of PN support. Body weight, fluid intake, and fluid output should be measured daily, whereas serum electrolytes, phosphorus, and glucose concentrations can be determined every 48 hours until stable and then rechecked weekly. Serum triglyceride concentrations should be evaluated early in the course of parenteral nutrition to document adequate triglyceride clearance. Triglyceride concentrations greater than 400 mg/dL necessitate either reduction of the rate of infusion or complete discontinuation of lipid supplementation. Providing 30% to 40% of total calories as lipid, however, does not stimulate the pancreas and can attenuate the hyperglycemia of pancreatitis.[53]

Complications

A total of 473 complications were recorded in 209 dogs receiving TPN over an 84-month period at the University of California, Davis, Veterinary Medical Teaching Hospital.[48] Metabolic complications were the most commonly encountered problems occurring during TPN administration (70% of complications), with transient hyperglycemia being the most common metabolic complication. Hyperglycemia was also the most commonly identified medical complication in a retrospective study of 75 cats administered TPN, and a significant association was identified between hyperglycemia and increased mortality rate at 24 hours.[49] Effective control of glycemia in critically ill human patients has been associated with a marked reduction in the incidence of bloodstream infections, and intensive insulin treatment in critically ill human patients partially prevents the anticipated postoperative decrease in neutrophil phagocytic function, ameliorates the depression in oxidative function in the alveolar macrophages, and reverses the decreased intracellular bacteriocidal activities in leukocytes.[54,55] Other less-common metabolic complications included hyperbilirubinemia, increased alkaline phosphatase activity, and hyperlipemia. Mechanical complications comprised 25% of the complications observed and included inadvertent catheter removal, catheter occlusion, disconnection or breakage of the line, and venous thrombosis. Mechanical complications can be reduced with meticulous catheter care and close patient monitoring. Catheter or solution-related sepsis was a relatively infrequent complication (5% of complications) because of scrupulous catheter care and insertion technique.

Summary

The field of interventional tube feeding is rapidly expanding, and is being matched by the proliferation of innovative enteral access techniques and the development of specialized feeding tubes. There has been a progressive downward trend in the use of CPN in veterinary institutions, predominantly as a consequence of the cost and recognition that this nutritional modality is no longer the "holy grail" in our nutritional armamentarium. Human and veterinary nutritionists have become increasingly aware of the detriments associated with the withholding of enteral nutrition in our hospital patients, and are more proactive in trickle-feeding patients enterally to preserve the integrity of the intestinal tract, while relying upon PN to augment the patient's energy intake. Peripheral PN represents a practical and relatively safe method for providing the bulk of the patient's nutritional needs for the short-term (<1 week), and can be effectively used alone or combined with enteral nutrition.

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CHAPTER 34

Antidiarrheal Agents

Robert J. Washabau

Pathogenesis of Diarrhea

When clinical signs are acute and there are no systemic signs of illness, symptomatic therapy often takes precedence over achieving a precise diagnosis. When the duration of clinical signs is chronic (>3 weeks), or if there are systemic signs of illness, a determined effort should be made to achieve a specific diagnosis. Diarrhea in companion animals may develop through one or more pathophysiologic mechanisms,[1] but one mechanism tends to predominate.[1,2]

Luminal Maldigestion

Small intestinal bacterial overgrowth (SIBO) and Exocrine pancreatic insufficiency (EPI) are the best examples of luminal maldigestion in companion animals. SIBO (or antibiotic-responsive diarrhea) and EPI induce maldigestion, steatorrhea, and diarrhea because of bacterial degradation of pancreatic enzymes (SIBO) or insufficiency of enzyme secretion (EPI). Fat maldigestion and steatorrhea may also result from deficiencies in bile salt secretion (e.g., intra- or extrahepatic cholestasis) or abnormalities in the enterohepatic recirculation of bile salts (e.g., portosystemic vascular shunts).

Villous Atrophy

Atrophy of the villous absorptive surface area occurs with many pathologic processes. Atrophy is caused by accelerated loss of enterocytes or decreased production of enterocytes by stem cells in the crypts. Stem cells retain the ability to reconstitute the overlying mucosa, but regeneration may take days to weeks depending upon the pathologic process. Viral infections (e.g., parvovirus, coronavirus, rotavirus) are the most important causes of damage to villus enterocytes in dogs and cats. Viral enteritides are usually acute, self-limiting infections that resolve over a matter of a few days to 1 to 2 weeks. Villous atrophy may result from immune-mediated processes such as gluten-sensitive enteropathy in the Irish Setter dog,[3] or as a consequence of food sensitivity reactions in both dogs and cats.[4] Food sensitivity reactions are increasingly recognized as an important cause of villous atrophy, malassimilation, and diarrhea in companion animals. Immunosuppressive drugs (e.g., glucocorticoids, vincristine, azathioprine, cyclophosphamide) may also cause severe villous atrophy. Glucocorticoids are frequently prescribed in the management of inflammatory bowel disease (IBD). Antiinflammatory doses of glucocorticoids appear to have minimal effect on epithelial cell turnover, but immunosuppressive doses may abolish epithelial cell renewal. These effects are usually reversible with discontinuation of therapy.

Enterocyte Dysfunction

Enterocyte dysfunction is a common finding in many of the primary gastrointestinal disorders of dogs and cats. Enterocyte dysfunction may be seen with inflammation, infection, malnutrition, malignancy, ischemia, and with certain drug therapies (e.g., misoprostol). Gastrointestinal tract pathology induces enterocyte dysfunction by impeding Cl^- transport, the Na^+/glucose cotransporter, the voltage-dependent calcium channel, or any other component of the cell's signal transduction pathways.[2]

Brush-Border Membrane Maldigestion

SIBO is the major cause of brush-border membrane damage in the canine intestine. Hydrolase and other brush-border transport proteins are degraded by bacteria, particularly anaerobes, during proliferation of small intestinal bacteria. Damage to the brush-border is usually reversible following appropriate antimicrobial therapy. Similar brush-border membrane maldigestion has been documented in canine IBD, but these changes are also readily reversible with resolution of IBD.[1,2] A specific brush-border membrane malabsorption has been documented in Giant Schnauzers with cobalamin deficiency and malabsorption.[5]

Mucosal Barrier Disruption

Just as the stomach has evolved with mucosal barrier properties to reduce the deleterious effects of gastric acidity, the intestine has evolved with mucosal barrier properties to exclude bacterial pathogens and to maintain oral tolerance.[6-9] Barrier disruption may be caused by moderate to severe inflammation, ulceration, ischemia, cytotoxic drugs, and certain protein-losing states. Inflammatory mediators such as interferon-γ, tumor necrosis factor-α, and platelet-activating factor mediate some of the effects on mucosal barrier disruption.[10]

Hypersensitivity

The role of dietary hypersensitivity reactions in the pathogenesis of canine and feline chronic diarrhea is incompletely understood, although recent studies suggest that adverse reactions to food antigens are common in dogs and cats with chronic diarrhea.[4] True allergy or immunoglobulin E–mediated reactions appear to be rare

in companion animals.[4] Food hypersensitivity reactions may evoke more generalized inflammatory responses involving histamine, leukotrienes, prostaglandins, substance P, or 5-HT (serotonin) effects on gastrointestinal absorption, secretion, permeability, and motility.

Mucosal Inflammation

Inflammation is a major cause of chronic diarrhea in both dogs and cats. Although gut inflammation may be induced by many different inciting causes (e.g., dietary antigens, bacterial pathogens, toxins, neoplasia), experimental studies suggest that the immune response is initiated and sustained as a result of exposure to dietary antigens and/or indigenous gut bacteria. Cellular components (T and B lymphocytes, plasma cells, macrophages) and molecular elements (prostaglandins, leukotrienes, complement, platelet-activating factor, nitric oxide, and oxygen-derived free radicals) contribute to the mucosal inflammatory response. The clinical signs of IBD (diarrhea, vomiting, anorexia) are somewhat related to the severity of the mucosal cellular infiltrates and inflammatory mediators.[11,12] (Functional abnormalities, e.g., changes in the permeability or motility of the gut, may contribute to the clinical signs in many animals.)

Neoplasia

Intestinal neoplasia may induce diarrhea by several pathophysiologic mechanisms, including obstruction-induced fluid secretion, release of bioactive substances (e.g., histamine with diffuse mast cell disease, 5-HT with intestinal carcinoid, and gastrin with gastrinoma), bacterial proliferation and overgrowth, protein and lipid exudation, and reduction of the normal villous absorptive surface area.

Lymphatic Transport Disorders

Lymphangitis and intestinal lymphangiectasia are the most common lymphatic transport disorders in the dog. Lymphangiectasia is fairly common in the dog, but rare in the cat. Lymphangiectasia may occur as a primary congenital disorder, or more frequently, it may develop secondarily to IBD,[13] neoplastic infiltration, or right-sided heart failure.

Multiple Pathophysiologic Mechanisms of Diarrhea

Some diarrheal disorders result from one pathogenic mechanism, but others may have several concurrent pathogenic mechanisms, for example, maldigestion, malabsorption, excessive secretion, changes in permeability, protein and lipid exudation, and disordered motility.[2] EPI is often regarded as a classic maldigestive disorder. In the absence of pancreatic enzyme secretion, undigested protein, lipid, or carbohydrate cannot be further absorbed. Affected animals develop diarrhea, steatorrhea, and severe protein-calorie malnutrition. These same animals develop SIBO, gastric acid–induced injury to the intestinal mucosa, cobalamin malabsorption, and hypersecretion of fluid and electrolytes. It is for these reasons that pancreatic insufficient animals may have incomplete response with pancreatic enzyme replacement therapy. Bacterial infection is another example of a diarrheal disorder with multiple pathophysiologic mechanisms. The heat-stable enterotoxin of enteropathogenic *Escherichia coli* stimulates guanylate cyclase production of cyclic guanosine monophosphate (cGMP) and activation of cGMP-dependent protein kinases, culminating in secretory-type diarrhea. At the same time, platelet-activating factor, prostaglandins, and leukotrienes produced during bacterial infection may contribute to the malabsorption and disordered motility of *E. coli* infections.

Specific Therapy of Diarrhea

The best clinical outcomes will be obtained with definitive diagnosis and specific therapy (see Section VI). A cat with intestinal lymphoma, for example, will have a better outcome if it is correctly diagnosed and treated with chemotherapy. Similarly, a German Shepherd dog with diarrhea, steatorrhea, weight loss, and ravenous appetite will have a much better outcome if it is correctly diagnosed with EPI and appropriately medicated with pancreatic replacement enzymes. Table 34-1 outlines other examples of definitive diagnoses and specific therapies.

Nonspecific Therapy of Diarrhea

Definitive diagnosis and specific therapy may not be possible in all cases. This is especially true of cases of IBD in which sequential, nonspecific therapy may be needed to control mild to severe clinical signs (Box 34-1).[2,11,12,14] The pet owner may not permit a detailed medical investigation, or a definitive diagnosis may not be reached despite a detailed and appropriate medical investigation. In these cases, it would be entirely appropriate to consider nonspecific forms of therapy. The criteria for commencing nonspecific therapy should include: (a) the diarrhea is chronic, frequent, and/or severe; (b) definitive diagnosis is not forthcoming; and (c) the client does not desire definitive diagnosis.[2,12,14]

Dietary Therapy

The precise immunologic mechanisms of canine and feline IBD have not yet been determined, but a prevailing hypothesis for the development of IBD is the loss of immunologic tolerance to the normal bacterial flora or food antigens. Accordingly, dietary modification may prove useful in the management of canine and feline IBD. Several nutritional strategies have been proposed for the management of gastrointestinal tract disease including novel proteins, hydrolyzed diets, antioxidant diets, prebiotics, medium-chain

Table 34-1 Examples of Definitive Diagnoses and Specific Therapies

Pathogenesis	Specific Therapy
Food sensitivity reaction	Dietary modification
Bacterial infection	Antibiotics
Parasitic infection	Anthelmintic agents
Fungal infection	Antifungal agents
Pancreatic insufficiency	Pancreatic enzymes
Intestinal cancer	Chemotherapy
Lymphangiectasia	Dietary fat modification
Hyperthyroidism	Chemo- or radiotherapy

Box 34-1 Sequential, Nonspecific Therapy in Inflammatory Bowel Disease

1. Dietary modification
2. Physical exercise
3. Antibiotics
4. Probiotics
5. Antidiarrheal agents
6. Restoration of motility
7. Immunosuppressive agents
8. Behavioral modification

triglyceride supplementation, low-fat diets, modifications in the omega-6-to-omega-3 fatty acid ratio, and fiber supplementation. Of these strategies, some evidence-based medicine has emerged for the use of novel protein, hydrolyzed, antioxidant supplemented, and prebiotic diets.[2,11,14]

Novel Proteins

Food sensitivity reactions were suspected or documented in 49% of cats presented because of gastroenterologic problems (with or without concurrent dermatologic problems) in a prospective study of adverse food reactions in cats.[4] Beef, wheat, and corn gluten were the primary ingredients responsible for food sensitivity reactions in that study, and most of the cats responded to the feeding of a chicken- or venison-based selected-protein diet for a minimum of 4 weeks. The authors concluded that adverse reactions to dietary staples are common in cats with chronic gastrointestinal problems and that they can be successfully managed by feeding selected-protein diets. Further support for this concept comes from studies in which gastroenterologic or dermatologic clinical signs were significantly improved by the feeding of novel proteins.

Hydrolyzed Diets

Evidence is accruing that hydrolyzed diets may be useful in the nutritional management of canine IBD. The conceptual basis of the hydrolyzed diet is that oligopeptides are of insufficient size and structure to induce antigen recognition or presentation.[15] In one preliminary study, dogs with IBD showed significant improvement following the feeding of a hydrolyzed diet, although they had failed to respond to the feeding of a novel protein.[16] Clinical improvement could not be solely attributed to the hydrolyzed nature of the protein source because the test diet had other modified features; that is, high digestibility, cornstarch rather than intact grains, medium chain triglycerides, and an altered ratio of omega-6-to-omega-3 polyunsaturated fatty acids. Additional studies will be required to ascertain the efficacy of this nutritional strategy in the management of IBD.

Physical Exercise

Experimental IBD in the dog is accompanied by significant abnormalities in the normal gastrointestinal motility. Physical exercise has been shown to disrupt the jejunal, ileal, and colonic migrating motor complexes and to increase the total duration of contractions that are organized as non-migrating motor complexes during the fed state. Exercise also induces giant migrating contractions, defecation, and mass movement in both the fasted and fed states. The increased motor activity of the intestine and colon and extra giant migrating contractions that result from physical exercise may aid in normal gastrointestinal motor function.[17]

Antibiotics

Some IBD cases are initiated by true enteric pathogens, whereas others are complicated by SIBO. Some IBD cases may show short-term responsiveness to one or more antibiotics, for example, tylosin, metronidazole, or oxytetracycline.

Probiotics

Probiotics are living organisms with low or no pathogenicity that exert beneficial effects (e.g., stimulation of innate and acquired immunity) on the health of the host. The Gram-positive commensal lactic acid bacteria (e.g., lactobacilli) have many beneficial health effects, including enhanced lymphocyte proliferation, innate and acquired immunity, and anti-inflammatory cytokine production. *Lactobacillus rhamnosus* GG, a bacterium used in the production of yogurt, is effective in preventing and treating diarrhea, recurrent *Clostridium difficile* infection, primary rotavirus infection, and atopic dermatitis in humans.[18] *L. rhamnosus* GG has been safely colonized in the canine gastrointestinal tract, although probiotic effects in the canine intestine have not been firmly established.[19] The probiotic organism, *Enterococcus faecium* (SF68), has been safely colonized in the canine gastrointestinal tract, and it has been shown to increase fecal immunoglobulin A content and circulating mature B ($CD21^+$/major histocompatibility complex class II^+) cells in young puppies.[20] It has been suggested that this probiotic may be useful in the prevention or treatment of canine gastrointestinal disease. This organism may, however, enhance *Campylobacter jejuni* adhesion and colonization of the dog intestine, perhaps conferring carrier status on colonized dogs.[21] *Lactobacillus acidophilus* has also been shown to safely colonize the canine gastrointestinal tract.

Antidiarrheal Agents

The major physiologic functions of the small intestine are luminal and brush-border digestion, secretion, and absorption (see Chapter 1). Other physiologic properties of the small intestine, for example, motility and blood flow, have evolved to regulate digestion, secretion, and absorption. The anatomic structures in support of these functions include the serosa, longitudinal smooth muscle, myenteric or Auerbach's plexus, circular smooth muscle, submucosal or Meissner's plexus, muscularis mucosa, and mucosa. Epithelial cells in the intestinal mucosa are specialized primarily for membrane brush-border enzymatic (e.g., disaccharidases, peptidases) digestion, fluid and electrolyte secretion, and absorption. The crypt is the germinal center of the intestinal epithelium. Crypt epithelial cells are primarily secretory in function—water, solutes, and bicarbonate are secreted into the intestinal lumen to solubilize the chyme, neutralize gastric acid, and reduce the bacterial microflora. As cells migrate up the intestinal villi, they mature into absorptive cells. Villus epithelial cells are primarily absorptive in function—water, solutes, glucose and other monosaccharides; amino acids and small peptides; free fatty acids and glycerol; minerals and vitamins; and other nutrients are absorbed from the lumen into villus epithelial cells. Submucosal plexus neurons innervate the overlying mucosa and regulate absorption and secretion by the villus and crypt epithelial cells, respectively. Myenteric plexus neurons innervate the longitudinal and circular smooth muscle layers and regulate intestinal motility. Contraction of longitudinal smooth muscle stimulates peristaltic type activity and net fluid transit, while contraction of circular smooth muscle mediates segmentation type activity and delay in fluid transit.

In health, villus epithelial cells actively absorb Na^+ and Cl^-, and passively absorb H_2O (see Fig. 1-17). In malabsorptive disorders, Na^+, Cl^-, and H_2O absorption are often markedly reduced in villus epithelial cells. Absorption may be inhibited through a number of mechanisms, including the effects of prostaglandins (e.g., prostaglandin E_2), leukotrienes, cyclic nucleotides (cyclic adenosine monophosphate, cGMP), serotonergic (serotonin or 5-hydroxytryptamine), and vasoactive intestinal polypeptide receptor activation. Stimulation of absorption by these cells, on the other hand, is mediated by noradrenergic (norepinephrine) and opioid (μ,δ-opioid) receptor activation. The pathophysiology of malabsorptive disorders serves as the basis for medical therapy such as prostaglandin synthetase inhibitors, μ,δ-opioid agonists, serotonergic antagonists, and noradrenergic agonists (see Fig. 1-17).

In health, crypt epithelial cells actively secrete Cl^- or HCO_3^-, and H_2O (see Fig. 1-17). In hypersecretory disorders, Cl^- and H_2O secretion is often markedly increased in crypt epithelial cells. The

pharmacology of the secretory crypt cell is remarkably similar to that of the absorptive villus cell. Thus, crypt epithelial cell secretion may be stimulated by prostaglandins (e.g., prostaglandin E_2), leukotrienes, cyclic nucleotides (cyclic adenosine monophosphate and cGMP), serotonergic (serotonin or 5-hydroxytryptamine), and vasoactive intestinal polypeptide receptor activation (see Fig. 1-17). Inhibition of secretion by these cells, on the other hand, is mediated by noradrenergic (norepinephrine) and opioid (μ,δ-opioid) receptor activation. The pathophysiology of hypersecretory disorders serves as the basis for medical therapy, for example, prostaglandin synthetase inhibition, serotonergic receptor antagonism, noradrenergic receptor agonism, and μ,δ-opioid receptor agonism (see Fig. 1-17).

Prostaglandin Synthetase Inhibitors

Sulfasalazine is a highly effective prostaglandin synthetase inhibitor that has proven efficacy in the therapy of large bowel IBD in the dog.[2,14] Sulfasalazine is a compound molecule of mesalamine (formerly 5-aminosalicylate) and sulfapyridine linked in an azo chemical bond. Following oral dosing, most of the sulfasalazine is transported to the distal gastrointestinal tract where cecal and colonic bacteria metabolize the drug to its component parts. Sulfapyridine is largely absorbed by the colonic mucosa, but much of the 5-aminosalicylate remains in the colonic lumen where it inhibits mucosal lipoxygenase and the inflammatory cascade. Sulfasalazine has been recommended for the treatment of canine large bowel IBD at doses of 10 to 30 mg/kg PO q8-12h for 4 to 6 weeks. With resolution of clinical signs, sulfasalazine dosages are gradually decreased by 25% at 2-week intervals and eventually discontinued while maintaining dietary management. Salicylates are readily absorbed and induce toxicity in cats, therefore this drug classification should be used with great caution in cats.[22] If used in cats, some authors have recommended using half of the recommended dog dose (i.e., 10 to 30 mg/kg PO q8-24h). Sulfasalazine usage has been associated with the development of keratoconjunctivitis sicca in the dog, so tear production should be assessed subjectively (by the pet owner) and objectively (by the veterinarian) during usage.[23,24]

Other 5-Aminosalicylates

This drug classification was developed to reduce the toxicity of the sulfapyridine portion of the parent molecule (sulfasalazine) and to enhance the efficacy of the 5-aminosalicylate. Mesalamine (Dipentum, Asacol) and dimesalamine (olsalazine) are available for use in the treatment of canine large bowel IBD. Olsalazine has been used at a dosage of 10 to 20 mg/kg PO q8h in the dog. Despite the formulation of sulfa-free 5-aminosalicylate preparations, instances of keratoconjunctivitis sicca have still been reported in the dog.

μ,δ-Opioid Agonists

These drugs stimulate circular smooth muscle contraction and therefore intestinal segmentation. Loperamide concurrently stimulates absorption, and inhibits secretion of, fluid and electrolytes. Loperamide, at a dose of 0.1 mg/kg PO q8-12h, is the preferred drug in this category.

5-HT_3 Serotonin Antagonists

Antagonists of the neuronal 5-HT_3 receptor inhibit Cl^- and H_2O secretion from intestinal epithelial cells. Examples of drugs in this classification include ondansetron (Zofran, Glaxo) at a dose of 0.5 to 1 mg/kg BID PO; granisetron (Kytril, SmithKline Beecham) at a dose of 0.1 to 0.5 mg/kg PO or IV q12h; tropisetron (Navoban, Novartis) at a dose of 0.5 to 3 mg/kg BID PO; and dolasetron (Anzemet, Sanofi-Aventis) at a dose of 0.6 to 1 mg/kg BID PO, IV, SQ.

α_2-Adrenergic Antagonists

These drugs must be used carefully as they can activate α_2-adrenergic receptors in the chemoreceptor trigger zone and cause vomiting. Clonidine, at a dose of 5 to 10 μg/kg BID-TID SQ/PO, is the best example in this classification.

Restoration of Normal Motility

The mixed μ,δ-opioid agonist, loperamide, stimulates fluid and electrolyte absorption while stimulating segmentation-type intestinal motility. Loperamide (0.1 mg/kg PO q8-12h) may be beneficial in the treatment of difficult or refractory cases of IBD.

Immunosuppressive Therapy

Glucocorticoids

Antiinflammatory to immunosuppressive doses of prednisone or prednisolone may be used to treat IBD in dogs that have failed to respond to dietary management, sulfasalazine, or metronidazole, and as adjunctive therapy to dietary modification in feline IBD.[14] Prednisone or prednisolone are used most frequently, as both have short durations of action, are cost-effective, and are widely available. Equipotent doses of dexamethasone are equally effective but may have more deleterious effects on brush-border enzyme activity. Prednisone should be used for 2 to 4 weeks depending upon the severity of the clinical signs. Higher doses of prednisone (e.g., 2 to 4 mg/kg PO daily) may be needed to control severe forms of eosinophilic colitis or hypereosinophilic syndrome in cats. Combination therapy with sulfasalazine, metronidazole, or azathioprine may reduce the overall dosage of prednisone needed to achieve remission of clinical signs. As with sulfasalazine, the dose of glucocorticoid may be reduced by 25% at 1- to 2-week intervals, while hopefully maintaining remission with dietary modification.

Budesonide

Because of steroid side effects and suppression of the hypothalamic–pituitary–adrenal axis, several alternative glucocorticoids have been developed that have excellent topical (i.e., mucosal) antiinflammatory activity but are significantly metabolized during first pass hepatic metabolism. Budesonide has been used for many years as an inhaled medication for asthma, and an enteric-coated form of the drug is now available for treatment of IBD in humans (and animals). There is little evidence-based medicine in support of the use of this medication in canine or feline IBD, but doses of 3 mg/m^2 Po once daily every other day have been used with some success in anecdotal cases.

Azathioprine

Azathioprine is a purine analogue that, following DNA incorporation, inhibits lymphocyte activation and proliferation. It is rarely effective as a single agent, and it should instead be used as adjunctive therapy with glucocorticoids. Azathioprine may have a significant steroid-sparing effect in IBD. Doses of 2 mg/kg PO q24h in dogs and 0.3 mg/kg PO q48h in cats have been used with some success in IBD. It may take several weeks or months of therapy for azathioprine to become maximally effective. Cats particularly should be monitored for side effects, including myelosuppression, hepatic disease, and acute pancreatic necrosis.

Cyclosporine

Cyclosporine has been used in the renal transplantation patient for its inhibitory effect on T-cell function. In more recent times, cyclosporine has been used in a number of immune-mediated disorders, including keratoconjunctivitis sicca, perianal fistula (anal furunculosis), and immune-mediated hemolytic anemia. Anecdotal reports

suggest that cyclosporine (3 to 7 mg/kg PO daily) may be useful in the treatment of some cases of refractory IBD. Evidence-based medicine studies are needed to establish efficacy, but anecdotal experience suggests that cyclosporine may be useful in some of the more difficult or refractory cases of IBD. Modified formulations of cyclosporine (i.e., cyclosporine-modified) are preferable to the original (unmodified) formulation.

Chlorambucil

Chlorambucil (1.5 mg/m^2 PO every other day) has been used in place of azathioprine in some difficult or refractory cases of feline IBD.

Behavior Modification

IBD and irritable bowel syndrome very likely have underlying behavioral components. Abnormal personality traits and potential environmental stress factors were identified in 38% of dogs in one study. Multiple factors were present in affected households, including travel, relocation, house construction, separation anxiety, submissive urination, noise sensitivity, and aggression.[25] The role of behavior in the pathogenesis and therapy of canine and feline gastrointestinal disorders remains largely unexplored (see Chapter 42).

Prognosis

Most reports indicate that the short-term prognosis for control of IBD is good to excellent.[12,14] Following completion of drug therapy, many animals are able to maintain remission of signs with dietary management alone. Treatment failures are uncommon and are usually a result of (a) incorrect diagnosis (it is especially important to rule out alimentary lymphosarcoma), (b) presence of severe disease such as histiocytic ulcerative colitis and protein-losing enteropathy or irreversible mucosa lesions such as fibrosis, (c) poor client compliance with appropriate drug/dietary recommendations, (d) use of inappropriate drugs or nutritional therapy, and (e) presence of concurrent disease such as SIBO or hepatobiliary disease. The prognosis for cure of IBD is poor, and relapses should be anticipated.

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CHAPTER 35

Antiemetic Agents

Robert J. Washabau

Vomiting or emesis is a complex reflex pathway that has evolved to protect animals from ingested toxins, but it holds greater importance because of the large number of medical conditions that may cause or be associated with it.[1,2] Emesis may occur with such diverse conditions as systemic (e.g., septicemia, multiple organ failure), metabolic (e.g., uremia, liver failure), and endocrine (e.g., hyperthyroidism, hypoadrenocorticism) disease, as well as with the inflammatory, infectious, neoplastic, obstructive, and toxicologic disorders of the primary gastrointestinal tract, pancreas, liver, and biliary tract. In each of these circumstances, vomiting is believed to be activated through a neural or humoral mechanism.[3,4]

Physiology of Vomiting: Humoral and Neural Pathways

The first mechanistic studies of vomiting were carried out by Borison and Wang in the early 1950s.[3,4] Those authors postulated a two-component model of vomiting involving activation of a humoral or neural pathway. In the Borison-Wang model, vomiting was postulated to occur through activation of the chemoreceptor trigger zone (CRTZ) by bloodborne substances (*humoral pathway*), or through activation of the emetic center by vagosympathetic, CRTZ, nucleus tractus solitarius, vestibular, or cerebrocortical neurons (*neural pathway*). Through a complicated series of experiments, Borison and Wang showed that activation of the CRTZ by circulating emetogenic substances (e.g., uremic toxins, cardiac glycosides, endotoxins, and apomorphine) could be abolished by CRTZ antagonism, but not by vagotomy, sympathectomy, or emetic center antagonism. At the same time, neural activation of the emetic center by gastrointestinal disease (e.g., inflammation, infection, obstruction, toxicity) could be abolished by vagotomy, sympathectomy, and emetic center antagonism, but not by CRTZ antagonism. Thus, vomiting was most easily explained by two independent mechanisms: one mechanism involving an essentially neural pathway, the other mechanism operating through a humorally dependent pathway.[3,4] The Borison-Wang two-component model has helped to explain many of the vomiting disorders of animals and humans. The model is not without challenge, however, and it has been suggested that there are parallel mechanisms for the initiation of emesis in response to any stimulus, and it is the sum of the inputs that drives the emetic response.[5] In other words, emesis need not be simply an either/or response. The concept of a discrete emetic center has also been seriously challenged. Based on more recent electrophysiologic studies, a model of sequential activation of a series of effector nuclei (e.g., nucleus tractus solitarius, retrofacial nucleus, dorsal motor nucleus of the vagus) has been proposed that doesn't require a discrete emetic center.[5] Despite contemporary reexamination, there still is good agreement on two general patterns of emesis, one humoral and the other neural (Figure 35-1).

The essential component of the *humoral* pathway is the CRTZ located within the area postrema, which is sensitive to activation by bloodborne substances. The CRTZ is located anatomically outside of the blood–brain barrier and is readily perfused by substances in the systemic circulation. Receptors within the CRTZ may be activated by many endogenous (e.g., uremic-, hepatoencephalopathic-, or endotoxins) or exogenously derived (e.g., digitalis glycosides, *cis*-platinum, apomorphine) bloodborne substances. Many pharmacologic approaches to antiemetic therapy are based on receptor interactions at the CRTZ, emphasizing the *humoral* pathway of emesis.[1,4]

Although many antiemetic agents are based on CRTZ pharmacology, many spontaneous vomiting disorders result from activation of the *neural* pathway. Vomiting associated with primary gastrointestinal tract disease (e.g., inflammation, infection, malignancy, toxicity) results from activation of an afferent neural pathway, nucleus tractus solitarius neurons, and the emetic center. Efferent information transmitted back to the gastrointestinal tract stimulates the motor correlates of vomiting; that is, retrograde duodenal and gastric contractions, relaxation of the gastroesophageal sphincter, gastroesophageal reflux, opening of the proximal esophageal sphincter, and evacuation of gastrointestinal contents.[7] A *neural* pathway can also be involved in vomiting associated with motion sickness. Although there are important species differences,[8-10] motion within the semicircular canals is transduced to vestibulocochlear neurons that ultimately synapse in the CRTZ (dog) or emetic center (cat). Finally, a *neural* pathway involving cerebrocortical neurons is very likely involved in vomiting disorders associated with anxiety or anticipation, but its importance in companion animals has not yet been established.

Pharmacology of Vomiting: Neurotransmitters and Receptors

Chemoreceptor Trigger Zone

Neurochemical studies have demonstrated the presence of several neurotransmitters: dopamine, norepinephrine, 5-hydroxytryptamine (5-HT, serotonin), acetylcholine, histamine, substance P, and enkephalins; their respective receptors or binding sites: D_2 dopaminergic, α_2 adrenergic, 5-HT_3 serotonergic, M_1 cholinergic, H_1 and

H_2 histaminergic, NK_1 neurokininergic, and ENK_μ and ENK_δ enkephalinergic; and their respective synthetic or degradative enzymes: DOPA (dihydroxyphenylalanine) decarboxylase, dopamine β-hydroxylase, 5-hydroxytryptophan decarboxylase, choline acetyltransferase, histidine decarboxylase, aminopeptidase N, and enkephalinase (Figure 35-2).[11] Some neurotransmitter-receptor signal transduction pathways are probably more important than others. For example, apomorphine, a D_2-dopamine receptor agonist, is a potent emetic agent in the dog, but it does not readily induce emesis in the cat.[12] This finding has two important implications: (a) CRTZ D_2-dopamine receptors may not be as important in mediating humoral emesis in the cat, and (b) D_2-dopamine receptor antagonists (e.g., metoclopramide) may not be as effective as an antiemetic agent in the cat. Xylazine, an α_2-adrenergic agonist, is a more potent emetic agent in the cat than in the dog.[12,13] Xylazine's effect suggests that α_2-adrenergic antagonists may be more useful antiemetic agents than D_2-dopamine antagonists in the cat.[9] Cancer chemotherapy (e.g., *cis*-platinum, doxorubicin, cyclophosphamide)-induced emesis is mediated by activation of 5-HT_3 receptors in the CRTZ of the cat,[11,14-16] while visceral and vagal afferent 5-HT_3 receptors may be more importantly involved in the dog.[17] Antagonists of the 5-HT_3 receptor are efficacious in the prevention of emesis associated with *cis*-platinum and other chemotherapy in cats[14-16] and dogs.[18] NK_1 receptor antagonists represent a unique new class of antiemetic agents that are based on substance P pharmacology at the CRTZ, as well as the nucleus tractus solitarius. This group of antiemetic agents may have advantages over other antiemetic classifications in that they may inhibit vomiting through both pathways (humoral and neural).[19,20] Finally, although histamine and H_1- and H_2-histaminergic receptors have been demonstrated in the CRTZ of the dog, they have not yet been demonstrated in the cat. Histamine is a potent emetic agent in the dog, but the cat seems resistant to its emetic effects.[11,12] H_1-histaminergic antagonists (e.g., diphenhydramine, dimenhydrinate) are ineffective antiemetic agents for motion sickness in the cat (Table 35-1).[10]

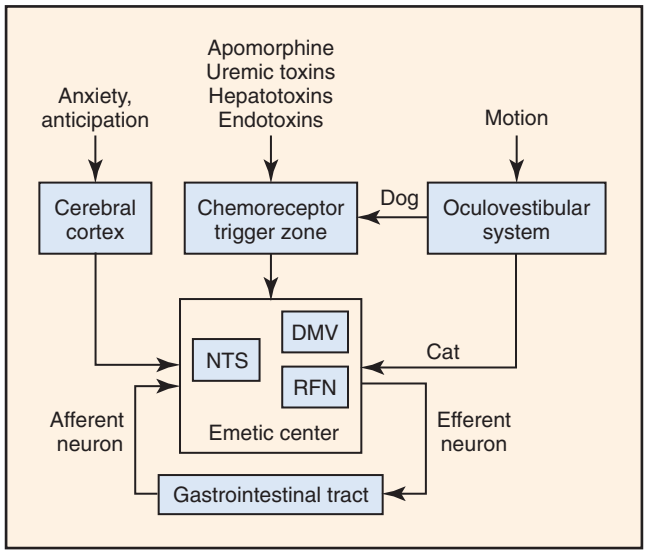

Figure 35-1 Physiology of vomiting: humoral and neural pathways. *Humoral pathway*—Vomiting is initiated through activation of the chemoreceptor trigger zone by bloodborne substances. *Neural pathway*—Vomiting is initiated through activation of the emetic center by a vagosympathetic, chemoreceptor trigger zone, nucleus tractus solitarius, vestibular, or cerebrocortical neurons. NTS, nucleus tractus solitarius.

Emetic Center

Emetic center pharmacology is complicated; indeed, some experimental results may not be reflective of pharmacology at one site. At the present time, the 5-HT_{1A}, α_2-adrenergic, and NK_1 receptors are the only documented receptors involved in the regulation of emesis at the level of the emetic center for which there are clinically available antiemetic agents. It has been shown that 5-HT_{1A} receptor agonists (e.g., flesinoxan, 8-OH-DPAT, buspirone) suppress emesis associated with motion sickness in cats.[21] The emetic center α_2

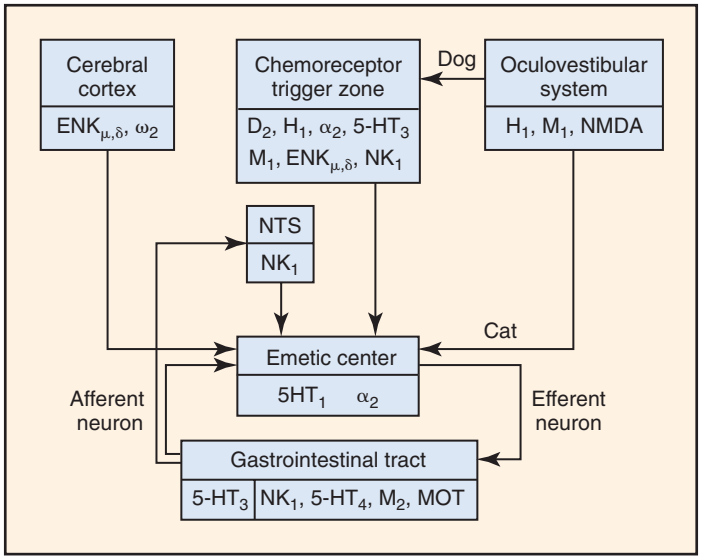

Figure 35-2 Pharmacology of vomiting: neurotransmitters and receptors. α_2, Alpha$_2$-adrenergic receptor; D_2, dopamine$_2$ receptor; ENK$_{\mu,\delta}$, enkephalin$_{\mu,\delta}$ receptor; H_1, histamine$_1$ receptor; 5-HT_{1A}, 5-hydroxytryptamine$_{1A}$ receptor; 5-HT_3, 5-hydroxytryptamine$_3$ receptor; 5-HT_4, 5-hydroxytryptamine$_4$ receptor; M_1, muscarinic$_1$ cholinergic receptor; M_2, muscarinic$_2$ cholinergic receptor; MOT, motilin receptor; NK_1, neurokinin$_1$ receptor; NTS, nucleus tractus solitarius; ω_2, benzodiazepine ω_2 receptor.

Table 35-1 Antiemetic Classifications

Classification	Examples	Site(s) of Action	Dosage	Side Effects
α_2-Adrenergic antagonists	Prochlorperazine	CRTZ, emetic center	0.1 to 0.5 mg/kg q6-8h SQ, IM, IV	Hypotension, sedation
	Chlorpromazine	CRTZ, emetic center	0.2 to 0.4 mg/kg q8h SQ, IV	Hypotension, sedation
	Yohimbine	CRTZ, emetic center	0.25 to 0.5 mg/kg q12h SQ, IM	Hypotension, sedation
D_2-dopaminergic antagonists	Metoclopramide	CRTZ, GI smooth muscle	0.2 to 0.4 mg/kg q6h PO, SQ, IM, IV	Extrapyramidal signs
	Domperidone	CRTZ, GI smooth muscle	0.1 to 0.5 mg/kg q6-8h SQ, IM, IV	Extrapyramidal signs
	Prochlorperazine	CRTZ, emetic center	0.5 mg/kg q6-8h SQ, IM	Hypotension, sedation
	Chlorpromazine	CRTZ, emetic center	0.2 to 0.4 mg/kg q8h SQ, IV	Hypotension, sedation
H_1-histaminergic antagonists	Diphenhydramine	CRTZ	2 to 4 mg/kg q8h PO, IM	Sedation
	Dimenhydrinate	CRTZ	4 to 8 mg/kg q8h PO	Sedation
	Prochlorperazine	CRTZ, emetic center	0.1 to 0.5 mg/kg q6-8h SQ, IM, IV	Hypotension, sedation
	Chlorpromazine	CRTZ, emetic center	0.2 to 0.4 mg/kg q8h SQ, IV	Hypotension, sedation
M_1-cholinergic antagonists	Pirenzepine	Vestibular apparatus, CRTZ	25 to 50 mg q24h PO	None reported
	Aminopentamide	Multiple CNS and PNS sites	0.01 to 0.03 mg/kg q8 to 12 h PO, IM, SQ	GI dysmotility
	Prochlorperazine	CRTZ, emetic center	0.1 to 0.5 mg/kg q6-8h SQ, IM, IV	Hypotension, sedation
	Chlorpromazine	CRTZ, emetic center	0.2 to 0.4 mg/kg q8h SQ, IV	Hypotension, sedation
5-HT_3 serotonergic antagonists	Ondansetron	CRTZ, vagal afferent neurons	0.5-1.0 mg/kg q12h PO	Sedation, head-shaking
	Granisetron	CRTZ, vagal afferent neurons	0.1 to 0.5 mg/kg q12h PO, IV	Sedation, head-shaking
	Tropisetron	CRTZ, vagal afferent neurons	0.5 to 3.0 mg/kg q12h PO	Sedation, head-shaking
	Dolasetron	CRTZ, vagal afferent neurons	0.6 to 1 mg/kg q12h PO, IV	Sedation, head-shaking
5-HT_4 serotonergic agonists	Cisapride	Myenteric neurons	0.1 to 0.5 mg/kg q8-12h PO	Cardiac arrhythmia
$ENK_{\mu,\delta}$ enkephalinergic	Butorphanol	CRTZ	0.2 to 0.4 mg/kg q12h IM	Sedation antagonists
NK_1 neurokinin antagonists	Maropitant	CRTZ, emetic center	1 mg kg q24h SQ	Injection irritant

Abbreviations: CNS, central nervous system; CRTZ, chemoreceptor trigger zone; GI, gastrointestinal; 5-HT, 5-hydroxytryptamine; IM, intramuscular; PNS, peripheral nervous system; SQ, subcutaneous, PO, per os; q, every.

receptor, as well as the CRTZ α_2 receptor, may be antagonized by a pure α_2-antagonist, for example, yohimbine, or by mixed α_1/α_2-antagonists, for example, prochlorperazine and chlorpromazine.[13] It is likely, however, that most of the antiemetic effect of the α receptor antagonists results from antagonism at the level of the CRTZ (Table 35-1).[21,22]

Vestibular Apparatus

Muscarinic M_1 receptors and acetylcholine have been demonstrated in the vestibular apparatus of the cat. Mixed M_1/M_2 antagonists, for example, atropine, and pure M_1 antagonists, for example, pirenzepine, inhibit motion sickness in the cat. It is not clear, however, whether the antiemetic effect of these drugs is solely a result of M_1 receptor antagonism at the vestibular apparatus. Other sites (e.g., cerebral cortex, reticular formation, area postrema) of antagonism are possible.[11] More recently, NK_1 receptors have been shown to be involved in pathogenesis of motion sickness, and NK_1 receptor antagonists (e.g., maropitant) prevent motion sickness in both dogs and cats (Table 35-1).[23,24]

Cerebral Cortex

Opioids, cannabinoids (e.g., nabilone) and benzodiazepines (e.g., diazepam, lorazepam) have been used to reduce anticipatory nausea and vomiting in human beings undergoing cytotoxic drug therapy. Cerebrocortical opioid and benzodiazepine receptors have been implicated but have not been very well characterized pharmacologically. The importance of these receptors in the pathogenesis of nausea and vomiting disorders in the dog and cat has not yet been established.[4,11,12]

Gut Afferents

There are a number of different mechanisms by which stimuli arising from the gastrointestinal tract activate the vomiting reflex. Ingested toxins, cell degeneration or necrosis, inflammation, luminal distention, chemotherapy, and radiation therapy all induce emesis. Of the many receptors found in the gastrointestinal tract, 5-HT_3 receptors likely play an important role in the initiation of emesis.[11] It is now well established that cytotoxic drugs provoke 5-HT release from enterochromaffin cells in the gastrointestinal tract which then activates 5-HT_3 receptors in afferent vagal fibers (dog)[17] or CRTZ (cat).[14,15] Vomiting induced by 5-HT release and 5-HT_3 receptor activation is abolished by pretreatment with 5-HT_3 antagonists, for example, ondansetron, granisetron, tropisetron, and dolasetron.[14,18] Metoclopramide is a weak antagonist of 5-HT_3 receptors but does not seem to be very effective in preventing chemotherapy-induced emesis (see Table 35-1).[25] It remains to be determined whether other gastrointestinal tract pathologies (e.g., inflammation, infection, malignancy, toxicity) are mediated via 5-HT_3 receptor activation.

Gut Efferents

Vagal efferent and myenteric neurons initiate the complex excitation and inhibition of visceral smooth muscle (e.g., retrograde duodenal and gastric contractions, relaxation of the gastroesophageal sphincter, gastroesophageal reflux, opening of the cricoesophageal

sphincter, and evacuation of gastrointestinal contents) that culminates in emesis. A number of receptors have been identified on myenteric neurons and gastrointestinal smooth muscle cells that regulate gastric emptying and/or intestinal transit. These include 5-HT_4 serotonergic (neuronal),[26] D_2-dopaminergic (neuronal),[27] M_2-cholinergic (smooth muscle),[28] and motilin (smooth muscle—dog only)[29] receptors. Cisapride and other 5-HT_4 agonists facilitate gastric emptying by activating presynaptic neuronal 5-HT_4 receptors.[26,20] Metoclopramide is a weak gastric prokinetic agent in the dog and cat, and is believed to facilitate gastric emptying via agonism of 5-HT_4 serotonergic receptors,[26] or via antagonism at D_2 dopamine receptors.[27] Canine gastric emptying is also regulated by motilin, a hormone that is released episodically from gastrointestinal endocrine cells. Motilin initiates phase III of the migrating myoelectric complex and facilitates gastric emptying during the fasting state. Low doses of erythromycin (0.5 to 1 mg/kg q8h PO, IV) stimulate motilin release and facilitate gastric emptying in the dog.[29,31] The role of motilin in the regulation of feline gastric emptying is incompletely understood. Motilin-like macrolide antibiotics increase tone in the feline caudal esophageal sphincter,[32] but their role in the regulation of gastric, intestinal, and colonic motility is incompletely understood (Table 35-1).

Treatment and Management

General Principles

Each vomiting patient will likely have a unique clinical presentation, some that are benign and require little in the way of intervention, others requiring extensive stabilization, therapy, and rehabilitation. Efforts should be made to identify and eliminate inciting agents, sustain blood and plasma volume, restore blood pressure, correct acid–base, electrolyte, and fluid deficits, and treat complications as they develop.

Nutrition

Short periods of fasting are appropriate to reduce the severity and frequency of the central emetic response. Fasting in cats should be implemented only in those instances in which there is severe vomiting and risk of aspiration pneumonia. As obligate carnivores, cats develop fat mobilization and hepatic lipidosis during even short periods of starvation. With chronic vomiting disorders, esophagostomy, gastrostomy, and enterostomy tubes may be placed to facilitate nutrition in anorectic animals (see Chapter 32).

Fluids

Severe vomiting will likely result in serious fluid, electrolyte, and acid/base disturbances. The goal of fluid therapy is to restore the volume and composition of body fluids to normal and, once this is achieved, to maintain external fluid and electrolyte balance so that input by treatment matches fluid losses (see Chapter 49). Electrolyte solutions can be divided into replacement and maintenance solutions. Replacement solutions provide 130 to 147 mEq/L of sodium, similar to values in the extracellular fluid. Maintenance electrolyte solutions provide 40 to 77 mEq/L of sodium, about one-half or less of values in the extracellular fluid. Supplementation of replacement fluids may be required to correct acid/base imbalance and potassium deficits, particularly in animals suffering from vomiting and diarrhea. In the absence of cardiopulmonary disease, intravenous fluids can be safely administered to dogs and cats at 90 mL/kg/h. Animals with mild volume depletion can be treated with lower fluid rates (10 to 20 mL/kg/h, as needed).

Antiemetic Agents

Antiemetic therapy should be formulated on the basis of most likely underlying pathogenesis, that is, neural or humoral pathway. The NK_1 neurokinin antagonists, α_2-adrenergic antagonists, 5-HT_3 serotonergic antagonists, and D_2-dopaminergic antagonists appear to be the most effective antiemetic agents in the dog and cat, although the D_2-dopaminergic antagonists appear to be less efficacious in the cat (see Table 23-1).

Antisecretory Agents

The histamine H_2 receptor antagonists and H^+,K^+-adenosine triphosphatase (ATPase) inhibitors are best clinical examples of gastric acid secretory inhibitors. It may be difficult, if not impossible, to determine the pathogenesis of gastric injury in an individual animal. Most cases will likely result from the combined effects of acid injury and disruption of the gastric mucosal barrier. Acid suppression and restitution of the gastric mucosal defense mechanisms are the cornerstones of treatment (see Chapter 46).

Prokinetic Agents

Gastrointestinal prokinetic agents should be considered in patients that fail to respond to dietary and antiemetic therapy. Combination antiemetic/prokinetic therapy are particularly effective in refractory vomiting patients. The most effective prokinetic agents are the 5-HT_4 serotonergic agonists, of which cisapride, tegaserod, and mosapride are the best examples. D_2-dopaminergic antagonists, motilides, and cholinomimetic agents have also been used to stimulate propagating gastrointestinal motility in companion animals (see Chapter 53).

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CHAPTER 36

Antifungal Drugs

Robert J. Washabau

Introduction

Indigenous Fungal Organisms

The gastrointestinal (GI) tract is readily colonized by small numbers of fungal organisms that become part of the indigenous microflora, maintain stable populations, and may even contribute to the nutrient economy of the host. Many of these organisms are undetectable by routine microbiology standards. With the advent of molecular fingerprinting techniques, the role of these organisms in the health of the mammalian host is becoming more readily apparent (see Chapter 2).

Opportunists

Most fungal species, whether transitory or part of the permanent habitat of the gut, appear to be of low pathogenicity. Given appropriate circumstances, however, commensal organisms may become pathogenic to the host. Inflammatory bowel disease, for example, is accompanied by an increase in the number and type of fungal organisms found in the GI tract, although it is still unknown whether this is cause or effect. *Candida* spp. are dimorphic fungi that are normal inhabitants of the GI tract, but they too can become opportunistic infections in some patients.[1] Other opportunistic organisms are sometimes isolated from immunosuppressed patients. Reported opportunists are typically from the Zygomycetes class (zygomycosis), and include members of the Entomophthoraceae (e.g., *Basidiobolus* spp., *Conidiobolus* spp.) and Mucoraceae (e.g., *Absidia* spp., *Rhizopus* spp., *Mucor* spp., and *Mortierella* spp.).[1]

True Pathogens

Rare cases of aspergillosis and mucormycosis involving the GI tract have been reported in the veterinary literature, but the most important pathogens are *Histoplasma capsulatum*, a true fungal organism, and *Pythium insidiosum*, an oomycete.

Pathogenic Fungal Infection of the Gastrointestinal Tract

Histoplasma capsulatum

Etiology

Histoplasmosis is a systemic fungal disease of dogs and cats caused by *H. capsulatum*. In the environment, *H. capsulatum* organisms are mycelial, saprophytic soil fungi. In infected tissue or when cultured at 30°C to 37°C (86°F to 98.6°F), the organism is a yeast. The fungus is endemic throughout most of the temperate and subtropical regions of the world. Most cases of histoplasmosis in the United States occur in the central states, with the geographic distribution following the Mississippi, Ohio, and Missouri Rivers.[2,3]

Pathophysiology

Infection is probably via inhalation or ingestion of infective conidia from the environment. The respiratory system is thought to be the primary route of infection in cats and dogs, although the GI tract may also be an important route in the dog. After inhalation or ingestion, conidia transform from the mycelial phase and are phagocytized by macrophages, where they grow as facultative intracellular organisms. Hematogenous and lymphatic dissemination results in multisystemic disease. Organisms can be disseminated to any organ system, but the lungs, gastrointestinal tract, lymph nodes, liver, spleen, bone marrow, eyes, and adrenal glands are the most common organs of dissemination in the dogs; lungs, liver, lymph nodes, eyes, and bone marrow are most commonly affected in cats. Cell-mediated immunity induces a granulomatous inflammatory response in most infections.[4]

Clinical Examination

Dogs with gastrointestinal histoplasmosis are typically presented with mild fever, anorexia, lethargy, weight loss, vomiting, diarrhea, hematochezia, and tenesmus. Cachexia is a common physical examination finding. Other historical and physical examination findings (dyspnea, cough, ascites, lameness, oropharyngeal ulceration, chorioretinitis, neuropathy) will depend upon organ and tissue involvement.

Diagnosis

Organism identification is required for definitive diagnosis. The most common means of organism identification is cytology. Cytology from affected tissue reveals pyogranulomatous inflammation, often with numerous small, round to oval intracellular yeast cells (2 to 4 μm in diameter) characterized by a basophilic center and a light halo. Exfoliative cytology during colonoscopy (or upper GI endoscopy) is considered useful in diagnosing the disease.[5] Histopathology is helpful if cytology is nondiagnostic or inconclusive. Multiple endoscopic colonic biopsies are usually sufficient to diagnose the disease. The yeast form does not stain well with routine hematoxylin and eosin stains, periodic acid-Schiff and Gomori methenamine silver stain are often used. Fungal culture from affected tissue can be used for diagnosis, but is rarely needed in clinical cases. Currently available serologic tests have poor specificity and sensitivity.[4]

Table 36-1 Antifungal Drug Classifications

Example (Generic)	Trade Name	Mechanism of Action	Dose	Route	Frequency
Amphotericin B	Fungizone	Binds cell membrane sterols; activates tissue macrophages	Dog: 0.5 to 0.1 mg/kg	IV	q48h
			Cat: 0.25 mg/kg	IV	q48h
Lipid amphotericin B	Abelcet complex		Dog: 1 to 3 mg/kg	IV	q48h
Ketoconazole	Nizoral	Inhibits 14-α-demethylase and ergosterol biosynthesis	Dog: 10 to 30 mg/kg	PO	divided q12h
Itraconazole	Sporanox		Dog: 5 to 10 mg/kg	PO	q24h
			Cat: 10 mg/kg	PO	q24h
Fluconazole	Diflucan		Dog/Cat: 2.5 to 10 mg/kg	PO	q12h
Posaconazole	Noxafil		Dog/Cat: 5 mg/kg	PO	q24h
Voriconazole	Vfend		Dog/Cat: 5 mg/kg	PO	q12h
Flucytosine	Ancobon	Inhibits DNA & RNA synthesis	Dog: 25 to 50 mg/kg	PO	q6h
Terbinafine	Lamisil	Inhibits squalene epoxidase and ergosterol biosynthesis	Dog/Cat: 10 to 20 mg/kg	PO	q24h
Caspofungin	Cancidas	Glucan synthase inhibition	Dog/Cat: Safe and effective doses not yet established		

Treatment

Itraconazole (5 mg/kg PO BID for 2 to 4 months) is considered the treatment of choice (Table 36-1) for feline histoplasmosis. In one study, itraconazole therapy cured histoplasmosis infections in all eight study cats.[6] Ketoconazole and amphotericin B have been described as the treatments of choice for canine histoplasmosis. With GI tract involvement, additional GI therapy may be useful in affected dogs, for example, dietary modification, treatment for small intestinal bacterial overgrowth, and direct antidiarrheal therapy. Corticosteroids may have been used successfully in the treatment of airway obstruction secondary to hilar lymphadenopathy in chronically infected dogs.[7]

Prognosis

There may be important species differences in prognosis although the paucity of reports, especially of prospective clinical trials, makes it difficult to generalize. It would seem that the prognosis is guarded in dogs, but fair to good in cats.

Oomycete Infection

Pythium insidiosum

Etiology

P. insidiosum is an aquatic oomycete that causes severe GI pathology in a range of hosts in tropical and subtropical climates.[8] Based on ribosomal RNA gene sequence data, members of the class Oomycetes are phylogenetically distinct from the kingdom Fungi, and are more closely related to algae than to fungi.[9] The oomycetes differ from fungi in two important properties: cell wall and cell membrane composition. Chitin is an essential component of the fungal cell wall, but it is generally lacking in the oomycete cell wall. Oomycetes also differ from fungi in that ergosterol is not a principal sterol in the oomycete cell membrane. This difference may explain why ergosterol-targeting drugs like the azoles (e.g., itraconazole) are less effective in the medical treatment of pythiosis.[9]

Pathophysiology

The infective state of *P. insidiosum* is thought to be the motile zoospore, which is released into stagnant water in warm environments, and likely causes infection either by encysting in the skin, or by being ingested into the GI tract. Ingested zoospores encyst and adhere to the gastric, jejunal, and colonic epithelium with a polarity oriented toward the submucosa for rapid tissue penetration following germ tube eruption. *Pythium* induces a chronic pyogranulomatous response in the GI tract and mesenteric lymph nodes. The gastric outflow tract and ileocolonic junction are the most frequently affected portions of the GI tract, and it is not uncommon to find two or more segmental lesions in the same patient.[10] Inflammation in affected regions is typically centered on the submucosa, with variable mucosal ulceration and occasional extension of disease through serosal surfaces, resulting in adhesion formation and peritonitis.

Clinical Examination

Weight loss, vomiting, diarrhea, and hematochezia are the most important clinical signs. Physical examination often reveals emaciated body condition and a palpable abdominal mass. Signs of systemic illness such as lethargy and depression are not typically present unless intestinal obstruction, infarction, or perforation occurs.

Diagnosis

Ileocolonic wall thickening, obliteration of the normal layered appearance, and regional lymphadenopathy are common ultrasonographic features of canine intestinal pythiosis.[11] Of course, these findings cannot be readily differentiated from those associated with intestinal malignancy. Definitive diagnosis requires histologic demonstration or immunohistochemical labeling of the organism and/or positive enzyme-linked immunosorbent assay (ELISA) or polymerase chain reaction (PCR) assays. The histologic findings associated with pythiosis generally are characterized by eosinophilic granulomatous to pyogranulomatous inflammation with fibrosis. Affected tissue typically contains multiple foci of necrosis surrounded and infiltrated by neutrophils, eosinophils, and macrophages. Discrete granulomas composed of epithelioid macrophages, plasma cells, multinucleate giant cells, and neutrophils and eosinophils may also be observed. *Pythium* zoospores may be cultured directly from affected tissue in antibiotic-containing (e.g., streptomycin and ampicillin) media. More recently, sensitive and specific ELISA and PCR assays were developed for the accurate diagnosis of pythiosis in dogs.[12-14]

Treatment

Aggressive surgical resection remains the treatment of choice (see Table 36-1) for pythiosis in dogs. Because it provides the best opportunity for a long-term cure, complete resection of infected tissue should be pursued whenever possible. Segmental lesions of the GI tract should be resected with 3- to 4-cm margins whenever possible. Medical therapy for the oomycetes has not been very promising. This may relate to the absence of ergosterol (cell membrane target of most currently available antifungal drugs) in the oomycete cell membrane. Clinical and serologic cures have been obtained in a small number of dogs following therapy with amphotericin B lipid complex (2 to 3 mg/kg QOD administered to a cumulative dose of 24 to 27 mg/kg) or itraconazole (10 mg/kg q24h for 6 to 9 months).

Prognosis

Unfortunately, most dogs with GI pythiosis are not presented to the veterinarian until late in the course of the disease, when complete excision is not possible. The anatomic site of the lesion (e.g., pylorus or ileocolic sphincter) may also prevent complete excision. Consequently, the prognosis is usually grave in most animals.[9]

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CHAPTER 37

Anthelmintic Agents

Michael R. Lappin

There are a number of cestodes, nematodes, and trematodes that are associated with gastrointestinal disease in dogs and cats. Chapters 55 to 58 provide an in-depth discussion of the clinical applications of anthelmintic drugs for these disease states. Some helminths can also be associated with clinical illness in humans and therefore management of infections in dogs and cats is part of a comprehensive public health program. This is particularly important for some of the hookworm (e.g., *Ancylostoma* spp., *Uncinaria* spp.) and roundworm (e.g., *Toxocara* spp., *Baylisascaris procyonis*) species. Approximately 3% to 5% of client-owned dogs and cats in the United States are currently shedding roundworm or hookworm eggs, with much higher shedding rates being detected in specific regions.[1-5]

This chapter provides information concerning the drugs most frequently used to remove or control helminth infections in dogs and cats. The majority of the compounds discussed are available in multiple countries. However, formulations and combinations of drugs may vary between countries. In addition, some of the drugs are used off-label for some parasites and label claims and dosages may change. Thus readers should always consult recent publications for potential changes. The majority of the comments in this chapter are written using resources and experiences from practice in the United States. Information is also drawn from the recommendations of the Companion Animal Parasite Council in the United States (www.capcvet.org) and the Compendium of Veterinary Products (CVP) drug label database in the United States.

Benzimidazoles

Historically, many drugs in the benzimidazole class (albendazole, fenbendazole, flubendazole, mebendazole, oxibendazole, thiabendazole) or probenzimidazole drugs (febantel) have been used as broad-spectrum anthelmintics in dogs and cats.[6-11] There is no information available to suggest that albendazole, flubendazole, mebendazole, oxibendazole, or thiabendazole are more effective against gastrointestinal parasites in dogs or cats than fenbendazole or febantel. Mebendazole is associated with hepatic necrosis in dogs and albendazole is associated with bone marrow suppression in dogs and cats, which are additional reasons fenbendazole and febantel are prescribed more frequently.[12,13] These drugs are considered among the best broad-spectrum agents because of activity against a variety of different parasites of the gastrointestinal system and other systems (Tables 37-1 and 37-2).

Mechanism of Action

The benzimidazole and probenzimidazole drugs are believed to inhibit energy metabolism in susceptible parasites leading to energy exchange breakdown and inhibition of glucose uptake. The drugs also bind to tubulin molecules, which binding inhibits microtubule formation and cell death of susceptible parasites through disruption of cell division.

Dose and Toxicity

If a labeled product containing fenbendazole or febantel is available, the label should be followed for each respective parasite. In general, fenbendazole at the dosage of 50 mg/kg, PO, daily for 3 days, is considered safe and effective against most of the target helminths of both dogs and cats (see Tables 37-1 and 37-2). In the United States, febantel is labeled only for oral administration in dogs. However, the drug has been administered safely to cats in several studies at dosages as high as 56.5 mg/kg (adult cats).[11,14] Side effects at the recommended dosages in dogs and cats are rare, and if side effects occur, generally salivation or vomiting, they are usually mild and self-limiting.

Clinical Application

Fenbendazole and febantel are prescribed frequently for the target helminths as discussed (see Tables 37-1 and 37-2). However, neither compound is effective for the treatment of *Dipylidium caninum* or *Echinococcus* spp. infections. Febantel is combined with praziquantel (see "Isoquinolones" section), which effectively treats the other tapeworms and pyrantel (see "Tetrahydropyridimines" section), which increases its activity against hookworms and roundworms (Drontal Plus, Bayer Animal Health). Benzimidazoles also treat *Trichuris vulpis* infections, which is an advantage over some of the drugs in other classes with anthelmintic activity.

Fenbendazole or febantel are also commonly prescribed to dogs or cats with small bowel diarrhea for potential activity against *Giardia* spp. (see Chapter 57).[14-17] Fenbendazole is one of the anthelmintics that is believed to have activity against the trematodes that can be associated with gastrointestinal disease (*Alaria* spp., *Nanophyetus salmincola*, *Heterobilharzia americana*, *Platynosomum fastosum*).[18] However, optimal protocols have not yet been established and fenbendazole is not labeled for this use.

Table 37-1 Drugs Used in the Management of Common Helminth Infections of the Gastrointestinal System of Dogs

	NEMATODES			CESTODES		
Drug and Class	**Hookworms**	**Roundworms**	**Whipworms**	***Dipylidium***	***Echinococcus***	***Taenia***
Benzimidazoles						
Febantel	Yes	Yes	Yes	No	No	Yes
Fenbendazole	Yes	Yes	Yes	No	No	Yes
Cyclic depsipeptide						
Emodepside	Yes	Yes	Yes	No	No	No
Isoquinolones						
Epsiprantel	No	No	No	Yes	No	Yes
Praziquantel	No	No	No	Yes	Yes	Yes
Macrocyclics						
Ivermectin	Variable[#]	Variable[#]	No	No	No	No
Milbemycin oxime	Yes	Yes	Yes	No	No	No
Moxidectin	Yes	Yes	Yes	No	No	No
Selamectin	No	No	No	No	No	No
Piperazines						
Piperazine	No	Yes	No	No	No	No
Tetrahydropyrimidines						
Pyrantel	Yes	Yes	No	No	No	No

Hookworms = *Ancylostoma caninum* and *Uncinaria stenocephala* infections; roundworms = *Toxocara canis* and *Toxascaris leonina* unless stated otherwise in the text; whipworms = *Trichuris vulpis.*
[#]The dose of ivermectin used in heartworm preventatives is unlikely to remove or control intestinal nematodes but higher doses may be effective.

Table 37-2 Drugs Used in the Management of Common Helminth Infections of the Gastrointestinal System of Cats

	NEMATODES		CESTODES	
Drug and Class	**Hookworms**	**Roundworms**	***Dipylidium***	***Taenia***
Benzimidazoles				
Febantel	Yes	Yes	No	Yes
Fenbendazole	Yes	Yes	No	Yes
Cyclic depsipeptide				
Emodepside	Yes	Yes	No	No
Isoquinolones				
Epsiprantel	No	No	Yes	Yes
Praziquantel	No	No	Yes	Yes
Macrocyclics				
Ivermectin	Yes	Variable[#]	No	No
Milbemycine oxime	Yes	Yes	No	No
Moxidectin	Yes	Yes	No	No
Selamectin	Yes	Yes	No	No
Piperazines				
Piperazine	No	Yes	No	No
Tetrahydropyrimidines				
Pyrantel	Yes	Yes	No	No

Hookworms = *Ancylostoma tubaeforme;* roundworms = *Toxocara cati* and *Toxascaris leonina.*
[#]The dose of ivermectin used in heartworm preventatives controls hookworm infections but not roundworms. Higher doses may be effective for roundworms.

Cyclic Depsipeptide

Emodepside is the only drug in this class currently prescribed to dogs or cats. It has been evaluated for oral (dogs) or topical (cat) administration and is considered safe and effective for use in the management of several nematode infections in dogs or cats (see Tables 37-1 and 37-2).[19-23] Emodepside is combined with praziquantel (Profender, Bayer Animal Health). The oral formulation for use in dogs is not currently available in the United States.

Mechanism of Action

The emodepside mechanism of action is considered unique to the drugs with anthelmintic activity. The drug binds to the latrophilin receptor presynaptically, which activates a complex signal transmission cascade that eventually results in the release of inhibitory neuropeptides into the synaptic gap. The resulting ion influx that occurs postsynaptically results in the inhibition of pharyngeal pump function that leads to paralysis and death of susceptible nematodes.

Dose and Toxicity

Based on the label in the United States, the emodepside-containing topical solution should be applied to cats older than 8 weeks of age and greater than 1 kg of body weight. The drug has been applied to small numbers of pregnant queens and 4-week-old kittens in a research study without apparent side effects.[19] Adverse effects associated with administration of the topical solution to 606 cats in a controlled, double-masked field safety study reported by Bayer Animal Health were infrequent, mild, and self-limited. The reactions reported were licking/excessive grooming in 18 cats (3.0%), scratching treatment site in 15 cats (2.5%), salivation in 10 cats (1.7%), lethargy in 10 cats (1.7%), alopecia in eight cats (1.3%), agitation/nervousness in seven cats (1.2%), vomiting in six cats (1.0%), diarrhea in three cats (0.5%), eye irritation in three cats (0.5%), respiratory irritation in one cat (0.2%), and shaking/tremors in one cat (0.2%).[21-23] Salivation, vomiting, and mild neurologic effects induced by administering the topical solution orally to cats were self-limited. Side effects induced by administration of the oral preparation to dogs have also been minimal.[21-23]

Clinical Application

In addition to the label indications, administration of emodepside to a small number of pregnant queens that were experimentally infected with *Toxocara cati* apparently blocked lactogenic transmission to the kittens.[19] Combining emodepside with praziquantel expands the spectrum of activity to include cestodes and, potentially, trematodes (see "Isoquinolones" section).[23] Emodepside also has effects against helminths of other body systems like feline lungworm.[24]

Isoquinolones

Praziquantel and epsiprantel are the isoquinolones currently used for the treatment of a number of cestode and trematode infections in dogs and cats.

Mechanism of Action

The exact mechanisms of action of the isoquinolones are unknown but may relate to inhibition of organism attachment. At low concentrations in vitro, praziquantel appears to impair the function of the cestode suckers and stimulates parasite motility. At higher concentrations in vitro, praziquantel increases the contraction of the worm's strobila, which can be irreversible at very high concentrations. Isoquinolone administration may cause damage to the integument of susceptible cestodes and trematodes, which may impart increased vulnerability to digestion by the host.

Dose and Toxicity

In dogs and cats in the United States, epsiprantel (Cestex, Pfizer) is labeled for use at 5.5 mg/kg or 2.75 mg/kg PO once, respectively. The company recommends use of the epsiprantel in dogs and cats older than 7 weeks of age. Praziquantel is available alone for oral administration, alone for injection, combined with pyrantel (see "Tetrahydropyridimines" section) for oral administration, combined with pyrantel and febantel for oral administration (see "Benzimidazoles" section), or combined with emodepside for topical administration to cats (see "Cyclic Depsipeptides" section). For treatment of susceptible cestodes, the label dosage of praziquantel based on the formulation used should be followed. Side effects, even at extremely high doses, are unusual for epsiprantel or praziquantel. Discomfort may occur during administration of praziquantel for injection.

Clinical Application

Praziquantel and epsiprantel are commonly prescribed by veterinarians for the treatment of current infections by susceptible cestodes. Some praziquantel-containing products are also labeled for the removal and control of *Echinococcus granulosa* and *Echinococcus multilocularis* in dogs in some countries. In *E. multilocularis* endemic areas, dogs continually exposed to wild rodents can be administered praziquantel every 21 to 26 days to lessen potential for shedding infective eggs into the human environment.

Praziquantel is one of the anthelmintics with activity against the trematodes that can be associated with gastrointestinal disease (*Alaria* spp., *N. salmincola, H. americana, P. fastosum*).[18] Praziquantel administration after fenbendazole administration has also be used successfully to treat peritoneal larval cestodiasis.[25] However, optimal protocols are unknown and praziquantel is not labeled for these infections.

Macrolides

There are several macrolides (macrocyclic lactones) with toxic effects against gastrointestinal nematode infections of dogs and cats and these include ivermectin, milbemycin oxime, moxidectin, and selamectin.[6,26-31] These drugs also have the advantage of preventing *Dirofilaria immitis* infections and some also can be used in the management of *Ctenocephalides felis* and other external parasite infections (see Clinical Application).

Mechanism of Action

The macrolides are antibiotics produced by *Streptomycetes* and the basic mechanism of action of action is likely similar for each of the drugs. Contact of the drugs with susceptible nematodes triggers a calcium ion influx that results in hyperpolarization of the nematode neurons. This ultimately prevents initiation and propagation of normal action potentials and results in paralysis and death.[6]

Dose and Toxicity

There are multiple products containing ivermectin, milbemycin oxime, moxidectin, or selamectin for use in the removal or control of some nematodes in dogs or cats (see Tables 37-1 and 37-2). Some products are for oral administration (ivermectin and milbemycin), injection (moxidectin; dogs only), or topical administration (moxidectin and selamectin). The drug label for each product should be consulted for specific dose recommendations and toxicity. Accidental high doses of macrocyclic lactones can cause toxicity.[32] Some dogs are at increased risk for ivermectin toxicity (in particular, Collies and Shelties) and this risk is genetically determined.[33,34] In general, this drug class is considered extremely safe when used as directed, even in ivermectin-sensitive dogs.[34,35]

Clinical Application

Tables 37-1 and 37-2 list the usual indications for the macrolide drugs for gastrointestinal helminth infections in dogs and cats. When used monthly for heartworm prevention, some of the

products also can be used as strategic deworming for hookworms and roundworms. Heartworm preventatives that contain ivermectin alone do not have a high enough concentration to effectively treat or prevent roundworm infections in dogs or cats or hookworm infections in dogs. Consequently, ivermectin is combined with pyrantel in some products to achieve this purpose (see "Tetrahydropyridimines" section). Some of the macrolides have effect against some external parasites at the heartworm prevention doses (selamectin); others are combined with other drugs like imidacloprid (Advantage Multi, Bayer Animal Health) or lufenuron (Sentinel, Novartis Animal Health).

Some of the macrolides are also being evaluated for the management of other less common gastrointestinal helminth infections. For example, milbemycin has been shown to be effective for the treatment of *Baylisascaris procyonis* in dogs, and moxidectin has been shown to be effective for prevention of *Spirocerca lupi* in dogs.[36,37]

Piperazines

Piperazine and the piperazine analogue diethylcarbamazine have activity against some helminths. Diethylcarbamazine administered by mouth daily can be used as a heartworm preventive, but has no activity against helminths associated with gastrointestinal disease when used alone. The anthelmintic spectrum of piperazine is narrow, but the drug has been used widely for the treatment of ascarid infections in dogs and cats because of wide availability and minimal side effects.

Mechanism of Action

Piperazine is thought to paralyze susceptible nematodes by disrupting acetylcholine or γ-aminobutyric acid neurotransmission.

Dose and Toxicity

Although multiple doses have been recommended over the years for the treatment of adult roundworms, a dose range of 45 to 65 mg/kg of the base drug is frequently prescribed and given orally to dogs or cats. As there is no effect of tissue stages, treatment is usually recommended at 2-week intervals. Clinical side effects are almost never recognized at recommended doses. However, self-limiting vomiting, diarrhea, and ataxia have been reported in some dogs and cats. If a massive overdose occurs, clinical signs related to anticholinergic effects may be noted and include depression, weakness, ataxia, muscle fasciculations, hypersalivation, slowed papillary light responses, and nystagmus.

Clinical Application

Piperazine should be used exclusively for the treatment of adult roundworm infections in dogs and cats. As coinfections with other helminths are common in dogs and cats, many veterinarians now recommend the use of other products with a more broad spectrum of activity.

Tetrahydropyridimines

Pyrantel is the only tetrahydropyridine currently used in dogs and cats. The drug is safe, effective, and tolerated by most dogs and cats and so is currently one of the most frequently used anthelmintics in small animal practice.[38]

Mechanism of Action

Susceptible parasites are paralyzed by pyrantel, which acts as a depolarizing, neuromuscular-blocking agent owing to cholinesterase inhibition.

Dose and Toxicity

Pyrantel is available in several products labeled for dogs or cats around the world. For labeled indications, the product label can be followed. Published oral doses used for roundworms and hookworms in dogs have varied from 5 to 15 mg/kg and in cats have varied from 5 to 10 mg/kg orally. Treatments are usually repeated several times in infected animals and in puppies and kittens during strategic deworming programs because of minimal effects on tissue phases (see Chapter 38 and www.capcvet.org). Side effects are almost never reported at clinical doses and when they occur generally consist of mild, self-limited vomiting. Overdoses result in clinical signs consistent with excess cholinergic stimulation (increased respiratory rate and ataxia). Because of competing mechanisms of action, pyrantel should not be administered with piperazine.

Clinical Application

Pyrantel is widely used in hookworm and roundworm strategic deworming protocols in puppies and kittens (www.capcvet.org). The drug is also well tolerated by dogs and cats and is used frequently when hookworm or roundworm infections are suspected based on clinical signs of disease. Some products have pyrantel combined with praziquantel (Drontal for Cats, Bayer Animal Health) or with febantel and praziquantel (Drontal Plus, Bayer Animal Health). Pyrantel has also been used to treat *Physaloptera* infections in vomiting dogs or cats at 5 mg/kg PO once (see also Chapters 55 to 58).

Miscellaneous

Other drugs with anthelmintic activity that were used historically in dogs and cats include dichlorophene, *N*-butyl chloride, toluene, levamisole (imidazothiazole), and dichlorvos (organophosphate). Some products containing these substances are still available in the United States but are less commonly prescribed by small animal veterinarians than the other drugs discussed in this chapter because of issues associated with safety or efficacy.

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CHAPTER 38

Nonsteroidal Antiinflammatory Analgesics

Karol Mathews and Sarah Boston

Nonsteroidal antiinflammatory analgesics (NSAIAs) are a group of pharmaceutical agents that possess both analgesic and antiinflammatory properties. The NSAIAs are frequently used in human and veterinary medicine to relieve mild, moderate and severe pain associated with surgery, inflammatory conditions, and osteoarthritis. The efficacy of many NSAIAs are equal or superior to the pure μ-opioid agonists (e.g., oxymorphone, morphine, hydromorphone, meperidine), and butorphanol or buprenorphine in managing postoperative pain.[1-15] When used in combination with opioids, a synergistic effect is achieved and may allow for reduced dosing of the opioid in mild to moderate, but not in severe, pain states where higher opioid dosages may still be necessary. In addition to their centrally acting antinociceptive effect, NSAIAs concentrate in inflamed joints and tissues with a duration of effect of 12 to 24 hours.[16] The duration and efficacy of the NSAIAs make them ideal for treating acute[1-15] and chronic pain[17-28] in veterinary patients; however, because of their potential for harm, patient and NSAIA selection must be considered prior to administration. More detailed reviews of NSAIAs have been published elsewhere.[29-39]

Pharmacology of Eicosanoid

Cyclooxygenase (COX) enzymes oxidize arachidonic acid to various eicosanoids and related compounds—prostanoids, prostacyclin, thromboxanes, and leukotrienes (Fig. 38-1).[40] COX-1 and COX-2 are constitutively expressed throughout the body. Their functions are determined by the specific sites and locations within tissues and cells, and the stimulus triggering their production. Canine and human COX-1 and COX-2 isoenzymes share 96% and 93% DNA sequence homology, respectively. The isoenzyme distribution does differ amongst the species, therefore extrapolation to specific anatomic function may not be appropriate.

COX-1, present in all tissues, ultimately converts arachidonic acid into prostanoids, thromboxanes, and prostaglandins (PGE_2, PGF_2, PGI_2, and PGD_2), which are involved in many homeostatic functions and which are organ specific.[46] For example, prostaglandin (PG) activity throughout the body is important in maintaining smooth muscle tone, modulation of vascular tone, and regulation of body temperature[46,52]; PGE_2 maintenance of the gastric mucosal barrier properties; and thromboxane A_2 (TXA_2), released by platelets in response to vessel injury is responsible for primary plug formation, thrombosis, and primary hemostasis.

COX-2 is involved in many pain and inflammatory states, and as an essential enzyme in many constitutive functions. Prostacyclin (PGI_2) is a COX-2 metabolite that, when released from the endothelium, is antithrombotic in modulating TXA_2 and maintains a nonthrombotic barrier between the vessel wall and the blood. Prostacyclin is a potent vasodilator that is regulated in several organ systems. In the kidney, for example, this includes the structures that play an essential role in renal blood flow associated with renin activity, fluid–electrolyte homeostasis,[31,53,57] and nephron maturation.[53,56] COX-2 enzyme also has important constitutive functions in bone metabolism; nerve, brain, ovarian, and uterine function; and intestinal mucosa healing.[52,55]

COX-3, a COX-1 variant, is expressed in the brain and its microvasculature in the dog.[46,49,50] Its importance in humans has not yet been established. The COX-3 isoenzyme is associated with generation of fever and appears to be more sensitive to NSAIAs that are analgesic and antipyretic, but which have low antiinflammatory activity.[44]

PGs serve as both inflammatory and antiinflammatory mediators where COX-2–derived PG (the PGJ_2) functions in resolution of inflammation.[47,50,51] PGJ_2 interacts with nuclear receptors that comprise the peroxisome proliferator-activating receptor (PPAR) family, particularly PPAR-γ. Activation of PPAR-γ transrepresses the activation of many transcription factors, including nuclear factor κβ (NF-κβ), an important promoter in many inflammatory responses. PPAR-γ is found in macrophages, dendritic cells, and B and T lymphocytes with potential roles in regulating inflammation and immunomodulation.[50,51]

Leukotrienes produced in the 5-LOX (5-lipoxygenase) cascade are also involved in the inflammatory response. Arachidonic acid is converted in a two-step process into the conjugated triene epoxide leukotriene (LT) A_4, the most biologically important form of LT (see Fig. 38-1).[47,62-64] LTA_4 is subsequently metabolized to LTB_4, LTC_4, and LTD_4. Cells known to express 5-LOX include circulating polymorphonuclear leukocytes (PMNs), monocytes, basophils, eosinophils, tissue macrophages, and mast cells. These cells release LTA_4 and participate in the transcellular biosynthesis of either LTC_4 or LTB_4.[65] As with the prostanoids, it is impossible to list all the activities of the LTs as their function is also dependent on organ involvement. With inhibition of COX-1 or COX-2 by NSAIAs, there is the potential of conversion of arachidonic acid into leukotriene B_4 via the 5-LOX pathway.[39,47,66-68]

In addition to the antiinflammatory functions of the PGs, endogenous antiinflammatory mechanisms in the LOX pathway also exist. These consist of small chemical mediators, or autacoids, that play a key role in controlling inflammation by inhibiting PMN recruitment

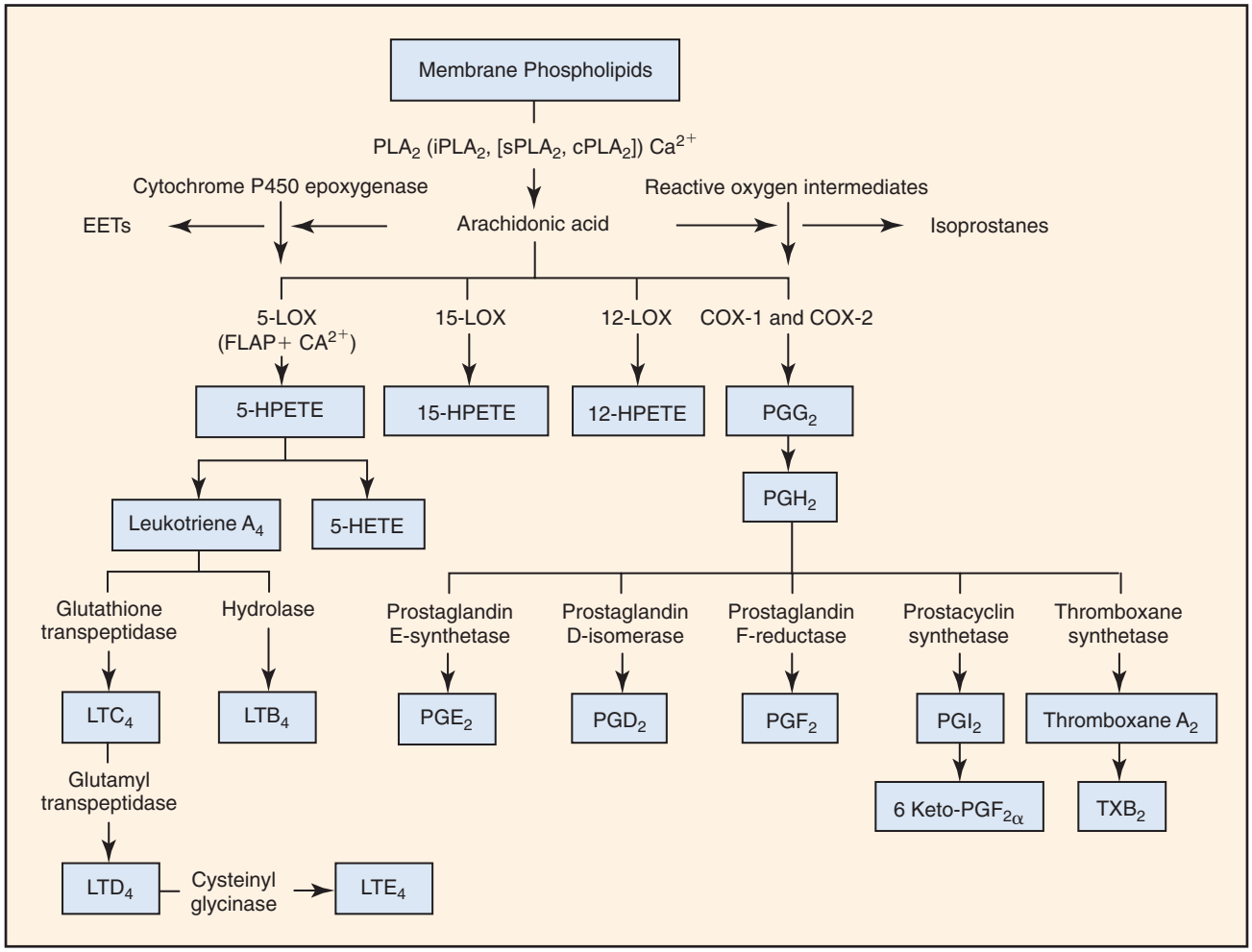

Figure 38-1 The arachidonic cascade. COX, cyclooxygenase; EETs, epoxyeicosatrienoic acids; FLAP, 5-lipooxygenase-activating protein; HETE, hydroxyeicosatetraenoic acid; HPETE, hydroperoxyeicosatetraenoic acid; LOX, lipoxygenase; LT, leukotriene; PG, prostaglandin; PLA_2, phospholipase A_2; TXB_2, thromboxane B_2. (From Mathews KA, Nonsteroidal anti-inflammatory analgesics. In: Ettinger SJ, Feldman EC, eds. *Textbook of Veterinary Internal Medicine*, ed 7, St. Louis, Saunders, 2010.)

and enhancing monocyte activity.[64] Arachidonic acid–derived lipoxins (LXs), particularly LXA_4, have been identified as antiinflammatory mediators, illustrating that the LOX pathway also has a dual proinflammatory and antiinflammatory role. These endogenous "antiinflammatory" products are also referred to as resolvins.[51] Resolvins, by definition, are endogenously generated within the inflammatory resolution phase and downregulate leukocytic exudate cell numbers.[51,82]

Cyclooxygenase and the Gastrointestinal Tract

Chapters 45 and 56 describe the mechanisms of gastric and intestinal mucosal protection. The prostaglandin-conferred component is extremely important in the overall protection of the gastrointestinal tract. Many of the effects of the prostaglandins in the gastric mucosa were discovered retrospectively as a result of the side effects associated with NSAIA administration.

Cyclooxygenase-1

The COX-1–derived prostaglandins are responsible for gastric mucosal protection through vasodilation, stimulation, and secretion of gastroduodenal mucus and bicarbonate, and forming a protective barrier to acid injury. These prostaglandins help protect the stomach's mucosal integrity during periods of vasoconstriction and the daily "trauma" of ingestion, digestion, and emptying. The cytoprotective and trophic functions are important in wound healing secondary to mucosal damage of foods transiting through the stomach. Exogenous administration of prostaglandins have been shown to inhibit gastric acid secretion, stimulate gastroduodenal mucus and bicarbonate secretion, maintain or enhance gastric mucosal perfusion, and have a trophic effect on the gastric mucosa.[51a]

Cyclooxygenase-2

Some studies also show a protective role for COX-2 in the maintenance of gastrointestinal integrity. For example, upregulation of COX-2 is identified in the duodenum in response to mucosal injury.[52,54]

Pathophysiology of Nonsteroidal Antiinflammatory Analgesic–Induced Gastritis and Gastric Ulcers

NSAIA gastropathy describes the subepithelial hemorrhages, gastroduodenal erosions, and ulcerations that can occur secondary to NSAIA administration.[54a] Lesions range from simple erosions affecting only the mucosal layer of the stomach to ulceration affecting the submucosa and deeper layers. There are several studies in dogs

reporting gastric ulceration associated with aspirin, flunixin meglumine, phenylbutazone, meclofenamic acid, piroxicam, naproxen and ibuprofen,[54b] and more recently in association with combination or sequential therapy, or inappropriate dosing of deracoxib[73] and meloxicam.[74] The inhibition of COX-1 is the principal mechanism responsible for the development of gastric lesions. When a synthetic PGE_1 (misoprostol) and an NSAIA (aspirin) with known COX-1 selectivity were administered concurrently, dogs developed significantly fewer gastroduodenal lesions than dogs receiving aspirin alone, but mild gastroduodenal lesions still developed in some of the dogs despite the administration of misoprostol.[54c,54d] Despite the importance of COX-1, COX-2 inhibition may also contribute to the pathophysiology of gastric ulceration. A study evaluating the effects of various COX inhibitors (a selective COX-1 inhibitor, a selective COX-2 inhibitor, a preferential COX-2 inhibitor, and nonselective inhibitor) showed that prolonged healing and a decrease in gastric blood flow were noted in all treatment groups compared with controls. The effect was most profound in the selective COX-1 and nonselective inhibitor treatment groups. The coadministration of synthetic PGE_2 in similar treatment groups facilitated healing. Analysis of mucosal (COX-1) and (COX-2) of the saline-treated group revealed stable levels of COX-1 at all times during the study; but COX-2 levels were not detectable in intact mucosa. In the ulcerated mucosa of the NSAIA-treated rats, COX-2 was present at all times and peaked on day 7 of a 14-day test period.[54e] This study suggests that COX-2 may play an important role in protection during response to inflammation. In a later study COX-2 was found to be constitutively expressed in canine pyloric and duodenal mucosa. NSAIAs may amplify or decrease the endogenous antiinflammatory response. Aspirin is more COX-1 selective and can impair many components of mucosal defense and enhances leukocyte adherence within the gastric and mesenteric microcirculation.[54f] However, with chronic use of aspirin there is an adaptation of the gastric mucosa, which occurs at approximately 14 days, and is associated with a marked upregulation of COX-2 expression and lipoxin production. This lipoxin is termed *aspirin-triggered lipoxin* (ATL). Aspirin is unique among current therapies in that it acetylates the COX-2 enzyme thereby enabling the biosynthesis of 15(R)-hydroxyeicosatetraenoic acid (15[R]-HETE), which is converted to ATL by 5-LOX. Inhibition of either of the COX-2 or 5-LOX enzymes results in blockade of ATL synthesis. LXA_4 and ATL (a carbon-15 epimer of LX) attenuates aspirin-induced leukocyte adherence, whereas selective COX-2 inhibitors augment aspirin-induced damage and leukocyte adherence to the endothelium of mesenteric venules in rats.[54f]

NSAIAs are excreted at varying rates, depending upon the metabolic pathway and extent of enterohepatic circulation. There are many species differences in drug elimination among the NSAIAs. For some drugs, the enterohepatic cycling may increase the risk of toxicosis because of the persistent local effects of the drug on the intestinal mucosa through repeated cycling in the biliary system.[34]

For NSAIAs that are administered orally, a topical or local effect on the gastric mucosa may also be responsible for the development of erosions/ulcers. In the acidic environment of the stomach, NSAIAs exist in a nonionized form, which are relatively lipophilic and will readily permeate gastric mucosal cells. Here the NSAIA is effectively trapped and can lead to an increase in osmotic pressure causing swelling and cell lysis. The disruption of the gastric mucosal barrier, may allow the diffusion of gastric acid into the submucosa, contributing to further damage.[54b] The effect of NSAIAs on the microcirculation to the stomach may be another component of the pathogenesis of gastropathy. Aspirin has been shown to cause a focal decrease in mucosal blood flow at the sites of subsequent ulcer formation.[54g] Some of these alterations in blood flow are likely mediated through the systemic inhibition of PG synthesis, or local effects of NSAIAs. Another potential mechanism affecting the microcirculation is the increase in neutrophil adherence to the vascular endothelium after NSAIA administration resulting in direct obstruction of the microvasculature, or by causing damage to the endothelium and epithelium by releasing proteases and free radicals.[54b]

Signs of Gastric Ulceration

Clinical signs of gastric ulceration in dogs include vomiting, hematemesis, melena, abdominal pain, pallor of the mucous membranes, lethargy, weakness, collapse and anorexia. Interestingly, experimental studies of NSAIAs reported clinical signs of gastric ulceration to be inconsistently present in dogs with endoscopic or gross evidence of gastrointestinal lesions.[54h] Some dogs remained bright and alert with no signs of abdominal pain. These findings are consistent with reports in humans where most cases of NSAIA-induced gastric ulceration go undiagnosed until they are life-threatening, complicated ulcers. The delay between the development of gastric ulceration and the observation of clinical signs may be related to unique properties of the NSAIA, or clinical signs may not develop until a deep ulcer erodes into a large blood vessel. Poor correlation between gastrointestinal lesions observed by endoscopy and clinical signs following treatment with carprofen, ketoprofen, or meloxicam have been reported in other studies. These lesions were mild to moderate in severity and did not differ statistically from placebo. The initial signs of vomiting and anorexia are frequently due to gastric irritation or inflammation. Because of the requirement of a severe lesion prior to the presence of hemorrhage or acute kidney injury, it is essential that owners be warned to stop NSAIA administration and seek immediate advice from the family veterinarian should the dog or cat develop vomiting or anorexia.

Role of Prostaglandins and Antiprostaglandins in Nociception

Nonsteroidal antiinflammatory analgesics inhibit COX-1, COX-2, or both, or COX-3 resulting in reduced PG synthesis. COX-2 is inducible and synthesized by macrophages and inflammatory cells, potentially increasing by 20-fold over baseline, especially in injured tissue and inflammatory conditions such as osteoarthritis.[42] Increased COX expression stimulates prostanoid production and these compounds serve as mediators of inflammation and amplifiers of nociceptive input in the peripheral and central nervous systems.[42] By this mechanism, COX-2 is responsible for a significant amount of pain and hyperalgesia following tissue injury. COX-1 is increased approximately two- or threefold during tissue injury, and may also generate PGs at sites of inflammation (e.g., joints, skin, gastrointestinal tract). COX-1 is present within the central nervous system and active in pain transmission. In addition to the peripheral effect, a significant part of the NSAIA antinociceptive effect is exerted at the spinal cord and supraspinal levels.[41-47] This action, in addition to pain relief, may account for the observed overall well-being and improved appetite of patients receiving injectable NSAIAs for relief of acute pain.

Pain management should be considered in its physiologic context as pain pathways involve COX-1 or COX-2 genes predominantly, both of which are differentially expressed. COX-1 selective NSAIAs, for example, are superior to COX-2 selective NSAIAs at inhibiting visceronociception and visceronociception is also greatly reduced in COX-1 but not COX-2 knockout mice. Visceral pain may be mediated by intraperitoneal receptors on sensory fibers by COX-1–produced prostacyclin. These studies concluded that peripheral COX-1 mediates nociception in slowly developing pain in mice,

such as in visceral pain, and central COX-1 may be involved in rapidly transmitted, nonvisceral pain, such as that caused by thermal stimulation. Interestingly, there may be gender differences, as in Ballou's mouse model, COX-2 was also found to mediate visceral nociception, but only in female mice.[47a] The analgesic potency of a range of NSAIAs in relieving tooth-extraction pain in humans correlates closely with increasing selectivity toward COX-1 rather than COX-2. These findings highlight the importance of both COX-1 and COX-2 contributing to pain and the selectivity of NSAIAs in treating painful conditions. The veterinary COX-2 preferential (COX-2 inhibition with some COX-1 sparing) NSAIAs may have similar activity.

Early research emphasis was placed on development of medications that inhibit COX-2 activity and spare constitutive COX-1 function. Theoretically, COX-2–selective NSAIAs should be effective, with potentially fewer adverse effects in the management of pain. Unfortunately, this complex biologic system is still not clearly defined and current knowledge indicates a role for both in nociceptive transmission and constitutive functions,[47,48] and the notion of "good versus bad COX" is probably too simplistic.[34] In addition to the COX-2 role in inflammation, aberrantly upregulated COX-2 expression is increasingly implicated in the pathogenesis of a number of epithelial cell carcinomas, including those of the colon and esophagus.[58,59] COX-2 inhibitors are being studied as potential anticarcinogenic agents. Although glucocorticoids are not analgesics, the COX-2 gene is glucocorticoid sensitive, in that it is reduced following administration of glucocorticoids, which may partially explain the antiinflammatory and analgesic effects of this class of medications.[47,58,60]

The COX-3 isoenzyme has been proposed as a target of the analgesic/antipyretic agents acetaminophen and dipyrone.[46,49,50] Both acetaminophen and dipyrone have minimal effect on COX-1 and COX-2,[46] and are frequently used to reduce fever in animals with little gastrointestinal or renal adverse effects. The COX-3 isoenzyme is more sensitive to NSAIAs that are analgesic and antipyretic, but which have low antiinflammatory activity. This fact emphasizes the different niche for NSAIA therapy in managing pain of differing etiology. As the COX-3 isoenzyme is derived from the COX-1 gene, this suggests that the COX-1 gene plays an integral role in pain and/or fever depending on the physiologic context.[44]

Adverse Effects of Nonsteroidal Antiinflammatory Agents

The breadth and severity of organ dysfunction depends on the COX selectivity of the NSAIA (Table 38-1). All NSAIAs require accurate dosing to avoid potential adverse effects, especially when used long-term. The recommended dosages for the various NSAIAs rarely compromise these functions; however, should a patient be in a prostaglandin-dependent pathologic state, administration of NSAIAs frequently result in adverse effects. However, even in health, the NSAIAs may result in gastrointestinal, renal, or hepatic abnormalities, or rarely coagulopathy (predominately non-selective NSAIAs). Some patients may be receiving other medications and NSAIA interaction with these must be considered prior to administration.[71]

Gastrointestinal Tract

COX-2–specific inhibitors appear to have fewer GI adverse effects than COX-1 inhibition, but long-term use in some people has resulted in gastrointestinal problems similar to those experienced with the COX-1 inhibitors, thereby identifying individuals intolerant to NSAIAs. Although the incidence of gastrointestinal signs may be reduced with COX-2–specific targeted NSAIAs, adverse effects may also occur in dogs and cats, as COX-2 is protective in the intestinal mucosa. COX-2 expression has been identified in the duodenum of dogs, which increased significantly following 3 days of aspirin (10 mg/kg q12h for 3 days), when compared with carprofen and deracoxib.[72] Duodenal ulceration has been identified in dogs receiving appropriate dosing of deracoxib and meloxicam; therefore it cannot be assumed that COX-2–specific inhibitors will be a "safe" treatment for all dogs with chronic administration. Frequently, dosages higher than those recommended or in association with corticosteroids resulted in gastric or duodenal ulceration.[73,74] This highlights the importance of contraindications for NSAIA administration. Some reports of meloxicam toxicity have been associated with the use of Mobicox, the human formulation.[74]

When given per os, NSAIAs should be given with food to protect the gastric mucosa from high, localized drug concentrations. Another potential cause for gastric ulceration is the fact that most NSAIAs that inhibit COX have been shown to result in diversion of arachidonate to the 5-LOX pathway (see Fig. 38-1). This results in an excessive production of leukotrienes, which have been implicated in many pathologic states, including hyperalgesia and the formation of NSAIA-induced ulcers.[46,61-64]

Liver

An elevation in serum alanine aminotransferase (ALT) can potentially occur with all NSAIAs, and is usually reversible with NSAIA withdrawal. Rare, acute, idiosyncratic hepatic necrosis after carprofen administration has been recognized in dogs.[75] Hepatotoxicity occurs in cats where acetaminophen has been administered. *N*-Acetylcysteine 140 mg/kg initially, then 70 mg/kg IV q4h × 12 to 24 h with IV fluid support is recommended.

Kidney

Where malaise, inappetence, and vomiting occur, serum creatinine should be measured to rule out renal injury as a cause of signs. As both the COX-1– and COX-2–selective NSAIAs deplete PG production in the kidney there is potential for renal injury where a PG-dependent state exists. Animals with renal disease, various degrees of volume depletion, hypotension, and increased sympathetic tone could experience an increased release of angiotensin II and norepinephrine. Renal PGs modulate such vasoconstrictive influences of the renal vessels thereby preserving renal blood flow and glomerular filtration rate (GFR).[76] In a study assessing potential alterations in GFR, serum urea and creatinine, following NSAID administration to young healthy dogs; carprofen, meloxicam, or saline was administered one hour prior to anesthesia and painful stimulus.[78] The findings of this study showed that meloxicam or carprofen produce no clinically significant alteration of renal function when compared with a saline placebo. However, should an unrecognized or untreated ischemic event occur, this may result in injury to the proximal tubule, increased solute delivery to the distal nephron, which in turn stimulates tubuloglomerular feedback and further vasoconstrictive effects. Damage to endothelial cells and subsequent activation of leukocytes also contribute to impaired GFR by physically impeding blood flow.

Table 38-1 Nonsteroidal Analgesic Dosing Regimen Per Lean Body Weight*

Drug	Indication	Species, Dose, Route	Frequency
Ketoprofen	Surgical pain	Dogs: ≤2 mg/kg, IV, SC, IM, PO	Once postoperative
COX-1 & COX-2 selective		Cats: <2 mg/kg, SC	Repeat q24h
	Chronic pain	Dogs: & cats <1 mg/kg	cats; no more than 5 days dogs: 1 mg/kg PO up to 5 days, 0.25 mg/kg for up to 30 days
		Dogs: & cats ≤2 mg/kg, PO ≤1 mg/kg	Repeat q24h
Meloxicam	Surgical pain	Dogs: <0.2 mg/kg IV, SC	Once
COX-2 preferential		<0.1 mg/kg IV, SC, PO	Repeat q24h
	Chronic pain	Dogs: <0.2 mg/kg PO	Once
		<0.1 mg/kg PO	Repeat q24h
	Surgical pain	Cats: <0.2 mg/kg SC, PO	Once
		0.05 mg/kg SC, PO	Daily × 2 to 3 days
	Chronic pain	Cats: ≤0.05 mg/kg SC, PO	Once daily
		Titrate reduction to comfort ~0.025 mg/kg ASAP	Daily or 3 to 5× weekly
Carprofen	Surgical pain	Dogs: <4 mg/kg, IV, SC	Once upon induction
COX-2 preferential, however, mechanism not clear		<2.2 mg/kg PO	Repeat q12h-24h PRN
	Chronic pain	Cats: <2 mg/kg SC	Once upon induction
		Dogs: <2.2 mg/kg PO	q12 to 24h
Etodolac	Chronic pain	Dogs: <10 to 15 mg/kg PO	Once daily
Deracoxib	Perioperative pain	Dogs: 3.0 mg/kg PO	Once daily × ≤7 days
COX-2 selective	Chronic pain	Dogs: 1 to 2 mg/kg PO	Once daily
Firocoxib	Chronic pain	Dogs: 5 mg/kg PO	Once daily
COX-2 selective			
Tepoxalin	Chronic pain	Dogs: 10 mg/kg PO	Once daily
Dual LOX-COX inhibitor			
Tolfenamic acid	Acute & chronic pain	Cats: <4 mg/kg SC, IM	SC, IM dose: once
COX-1 COX-2 selective		Dogs: <4 mg/kg PO	Oral dosing: once daily for 2 to 4 days consecutive days per week, repeat weekly cycle
Flunixin meglumine	Pyrexia	Dogs & cats: 0.25 mg/kg SC	Once
COX-1 COX-2 selective	Ophthalmologic procedures	Dogs & cats: 0.25 to 1 mg/kg SC	q12 to 24h PRN for 1 or 2 treatments
Ketorolac	Surgical pain	Dogs: 0.3 mg/kg PO	Twice daily along with misoprostol
		Cats: 0.25 mg/kg IM	q12h for 1 to 2 treatments
COX-1 COX-2 selective	Panosteitis	Dogs: 10 mg/dog >30 kg, PO 5 mg/dog >20 kg but <30 kg, PO	Once daily for 2 to 3 days
Piroxicam	Inflammation of the lower urinary tract	Dogs: 0.3 mg/kg, PO	q24 to 48h
		Cats: 0.3 mg/kg, PO	q24 to 72h
Acetaminophen	Acute or chronic pain	Dogs: only 15 mg/kg PO	q8h
weakly inhibit both COX-1 and COX-2 but have greater inhibition of COX-3			
Aspirin	Acute or chronic pain	Dogs: 10 mg/kg PO	q12h
COX-1 COX-2 selective			
Dipyrone	Antipyresis	Dogs & cats 10 mg/kg IV	q12h
weakly inhibit both COX-1 and COX-2, but have greater inhibition of COX-3	Analgesia	Dogs & cats 25 mg/kg IV	q12h

*See text for details on the contraindications for use.
PRN, As required.
(From Mathews KA, Nonsteroidal anti-inflammatory analgesics. In: Ettinger SJ, Feldman EC, eds. *Textbook of Veterinary Internal Medicine*, ed. 7, St. Louis, Saunders, 2010, p. 610.)

Hemostasis and Cardiovascular

Alteration of COX-1 and COX-2 disrupts vascular homeostasis. Platelets contain solely COX-1. NSAIAs with COX-1 selectivity have anti-TXA_2 activity thereby reducing platelet aggregation. Poor platelet function results in hemorrhage in susceptible patients. Conversely PGI_2, a modulator of thrombosis, is affected by the NSAIAs with COX-2 selectivity resulting in a reduction in vasodilation and antithrombosis.[84] A study examining the effect on coagulation in dogs with osteoarthritis and receiving aspirin, deracoxib, carprofen, or meloxicam revealed changes in platelet aggregation and the thrombelastogram associated with the COX selectivity of these NSAIDs.[75a]

Because of the opposing effects of prostacyclin and TXA_2 on hemostasis, the degree of hemorrhage in any individual patient may vary. Patients with occult von Willebrand disease have been

identified by severe hemorrhage following a single dose of a non-selective COX inhibitor. In this setting, the effects of COX-1 inhibition were demonstrated in the vulnerable patient. The potential for proliferation of thrombi due to unopposed TXA_2 activity may be a potential problem in specific situations in dogs taking highly selective COX-2 inhibitors. This, in addition to unopposed vasoconstriction, was the reason for withdrawal of some COX-2–selective NSAIAs implicated in myocardial infarction and stroke in humans.

Summary of Adverse Effects

When summarizing the common adverse effects noted in animals following administration of NSAIAs (e.g., gastrointestinal ulceration, hepatic necrosis, renal perturbations, and hemorrhage), hemorrhage is the only one that appears to be spared with COX-2–selective and COX-2–preferential NSAIAs in animals with normal platelet numbers and function. The majority of reported adverse effects secondary to NSAIA administration appear to be iatrogenic and other pre-existing pathology and drug usage should have been considered.

General Considerations

As a group, NSAIA effects are not reversible, making it imperative that the general health of the patient be considered prior to prescribing NSAIAs. With large-animal formulations, dilutions and estimations are ill-advised, as a very small volume may easily result in serious overdose. Dosing should be calculated based on the ideal weight of a patient. Overdose requires short-term, gastric protection and IV fluids to support renal function. Because cats and dogs are more susceptible to the adverse effects of NSAIA administration, the reported safety of any NSAIA approved for the human patient is not easily transduced to the veterinary patient. The potential for toxicity with certain NSAIAs is greater in cats than other species as a result of their limited ability to glucuronidate NSAIAs, resulting in a prolonged duration of effect.[38] Therefore, only NSAIAs approved for use in cats should be administered to this species (see Table 38-1).[77] Of note, meloxicam (Metacam) is approved for use in cats in many countries. A single dose of 0.3 mg/kg is approved in the United States; however, it is the opinion of this author and others[38] that a loading dose of no more than 0.1 or 0.2 mg/kg IV, SC, PO, depending on degree of surgical pain, and lower for chronic pain, is effective, allowing repeated daily dosing. In general, NSAIAs should be restricted to animals older than 6 weeks of age. If a particular NSAIA appears ineffective in managing pain, prescribing a different NSAIA may be effective because of individual variation in response to the different analgesics. However, caution is advised when switching from one NSAIA to another as COX-2 dysregulation within the duodenal mucosa may predispose to ulceration. Currently it is difficult to predict in the individual patient what is a "safe" time to wait prior to starting a different NSAIA. In a recent study where the COX-2 inhibitor firocoxib was administered to dogs after a wash-out period from 1 to 7 days (most commonly >2 days) following discontinuation of another NSAIA, there was no increased risk when compared to a longer washout period.[81] The study examined only administration of firocoxib after another NSAID; therefore, the results cannot be extrapolated to other NSAIDs. In another study where dogs were administered injectable carprofen followed by oral deracoxib within 24 hours, there was no evidence of NSAIA treatment–related lesions in the gastrointestinal tract.[83] Again, based on the individual intolerance and susceptibility to adverse effects of the NSAIAs, veterinarians and owners must be aware of the potential for gastrointestinal pathology when switching from one NSAIA to another, especially where intolerance to one is the reason for change, and not efficacy.

Contraindications for the Use of Nonsteroidal Antiinflammatory Analgesics

There are many potential interactions between NSAIAs and other medications.[71] Prior to prescribing an NSAIA to a patient receiving other medications, it is essential to review the interactions to ensure there are no contraindications for coadministration. Concurrent use of any other NSAIAs or corticosteroids has resulted in gastroduodenal perforation. NSAIAs should not be administered to patients in shock, trauma cases upon presentation or where hemorrhage is evident (e.g., epistaxis, hemangiosarcoma, head trauma). Likewise, those animals with acute renal insufficiency, hepatic insufficiency, dehydration, hypotension, conditions associated with low "effective circulating volume," coagulopathies (i.e., factor deficiencies, thrombocytopenia, von Willebrand disease), or evidence of gastrointestinal pathology, should not receive NSAIAs. NSAIAs must be avoided in animals with spinal injury, including herniated intervertebral disk, as most of these patients receive corticosteroids with medical or surgical management. A study using healthy beagles simulated such a scenario where dexamethasone (0.25 mg/kg q24h) and meloxicam (0.1 mg/kg q 24h) were administered for 3 days pre- and post-sham surgery. When compared with lesions in dogs receiving saline, dexamethasone, or meloxicam combined with saline, the total endoscopic score of the dexamethasone-meloxicam group was significantly greater than the other groups. Scores for the dexamethasone group were significantly greater than the scores for the saline and meloxicam groups, with no significant difference found between the saline and meloxicam groups. The location of lesions were consistent with previous findings where the pylorus and pyloric antrum appear more susceptible to the effects of combination NSAIAs and corticosteroids.[71a]

NSAIAs should not be administered to patients with severe or poorly controlled asthma, or other moderate to severe pulmonary disease, as they may deteriorate with COX-1–inhibiting NSAIAs, especially aspirin. As COX-2 induction is necessary for ovulation and subsequent implantation of the embryo,[52] NSAIAs should be avoided in breeding females during this stage of the reproductive cycle. NSAIAs also block PG activity in pregnant animals resulting in cessation of labor, premature closure of the ductus arteriosus in the fetus, and disruption of fetal circulation.[52] If administered prior to birth, or during lactation, a permanent nephropathy may result.

Over several years, many studies have reported the safety and efficacy of NSAIAs in various clinical settings. The NSAIAs are very effective analgesics in both the acute and chronic clinical settings. Millions of dogs and cats worldwide benefit from these analgesics on a daily basis. Due diligence on behalf of the veterinarian will reduce the potential for harm.

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CHAPTER 39

Antimicrobial Drugs

Mark G. Papich

Antimicrobial drugs used for gastrointestinal disease are primarily used to treat infections of the intestine and occasionally stomach (e.g., treatment of *Helicobacter*-like organisms). These drugs are used to treat a primary infection of the gastrointestinal tract (GIT) or prevent a more serious systemic infection disseminating from the GIT. Once an infection of the GIT has disseminated, producing sepsis and a general inflammatory reaction, systemic antimicrobials are needed. Although antimicrobial drugs technically also include antiviral drugs, antiprotozoal drugs (anticoccidial drugs), and anthelmintic drugs—all of which can be important to treat diseases of GIT—these drugs are discussed in other sections of this book. More detailed information about the pharmacology of these drugs and prescribing information can be found in other publications.[1,2] Principles of antibiotic therapy can be found in another chapter.[3]

Antimicrobial Drugs

Macrolide Antibiotics

The macrolide antibiotics include erythromycin and tylosin. More recent derivatives include clarithromycin and azithromycin. The macrolide antibiotics are protein synthesis inhibitors that bind to the 50-S ribosomal subunit and interfere with the translocation reaction necessary for RNA-dependent protein synthesis in bacteria. The macrolides may be bactericidal for some Gram-positive bacteria, but for other bacteria these drugs are bacteriostatic. Their action is considered time-dependent. Their pharmacokinetics favor a time-dependent action because many in this class have long half-lives that produce drug concentrations above the minimum inhibitory concentration (MIC) in plasma, cells, or tissue for an extended time after dosing.

The activity of these drugs is better for Gram-positive bacteria than Gram-negative bacteria. Gram-positive bacteria accumulate macrolides to a greater extent than Gram-negative bacteria (as much as 100× for erythromycin). Subsequently, activity is almost nonexistent against Gram-negative bacteria, especially those of the Enterobacteriaceae (e.g., *Escherichia coli*). Their activity also includes GIT pathogens such as *Campylobacter jejuni* and *Clostridium* spp.

The clinical use of macrolides involves the use of erythromycin, tylosin, and occasionally azithromycin, administered orally. In some instances, such as with tylosin-responsive diarrhea this chapter (see "Tylosin-Responsive Diarrhea" section), the pathogens that are the target of successful treatment are not known.

Macrolide pharmacokinetics have been studied in most animals. Oral absorption of erythromycin is inconsistent because it is not stable in the stomach. Oral absorption is less than 20%. Various attempts have been made to improve stability in the stomach, including salts of erythromycin, poorly soluble esters, and enteric coating. Azithromycin requires some buffering of oral formulation, but its oral absorption is much higher than for erythromycin.

The poor oral absorption of erythromycin is probably responsible for one of its most common adverse effects; that is, diarrhea. This has obvious importance when treating diseases of the GIT. Usually, gastrointestinal adverse effects in small animals are fewer following administration of tylosin or azithromycin, but this is based on anecdotal experiences and has not been investigated in a controlled study.

The most common adverse effect reported from administration of erythromycin is vomiting in dogs. This may be caused either by irritation of the stomach, or stimulation of stomach contraction. In one study, erythromycin oral administration produced the most frequent adverse effects in comparison with other drugs.[4] Stimulation of gastric motility occurs via an increase in activation of motilin receptors, via release of endogenous motilin, or via cholinergic mechanisms in the upper GIT and gallbladder.[5,6] This effect has been utilized therapeutically (see "Other Uses for Antimicrobials" section).

Lincosamides

Clindamycin and lincomycin are the most common drugs from this class. They are not related to the macrolides by chemical structure, but there are many overlapping properties such as pharmacokinetics and antimicrobial activity. Clindamycin differs from lincomycin by only the addition of chlorine on the parent molecule. This addition produces a more active drug against bacteria and some protozoa. Because clindamycin is the most often used from this group in small animals, lincomycin is not discussed further.

Like macrolides, these drugs are inhibitors that bind to the 50-S ribosomal subunit and interfere with protein synthesis. They are traditionally considered bacteriostatic (time-dependent in action), but more recent evidence shows that there is some bactericidal activity as well.

Susceptible bacteria important for the GIT include streptococci, *C. jejuni*, *Clostridium* spp., and some mycobacteria. There is little activity against most Gram-negative organisms, particularly the enteric bacteria (Enterobacteriaceae). Clindamycin has good activity against most anaerobic bacteria, but resistance has been documented among bacteria of the *Bacteroides fragilis* group.

For clindamycin, tablets, capsules, and an oral liquid (clindamycin hydrochloride) are available for small animals (Antirobe and generic) and clindamycin palmitate liquid (Cleocin), an ester that must be hydrolyzed in the GIT. Oral absorption of clindamycin hydrochloride is high in small animals.

The adverse effects are noteworthy because they predominantly affect the GIT. Clindamycin usage has been associated with bacterial overgrowth (especially *Clostridium difficile*) in the colon. Serious and fatal diarrhea has been reported in humans, rabbits, ruminants, and horses from oral administration. In people, clindamycin-associated diarrhea is common and a serious disease known as *pseudomembranous colitis* can occur as a consequence of clindamycin administration. Fortunately, such serious adverse effects have not been reported in dogs and cats, although mild diarrhea certainly is possible.

The other adverse effect that may affect the GIT in cats is esophageal injury caused by the oral administration of the hydrochloride formulation.[7] Hydrochloride formulations of other drugs (e.g., doxycycline hyclate) also have been reported to produce esophageal injury to cats (see "Tetracyclines" section).

Fluoroquinolone Antibiotics

These drugs include enrofloxacin, marbofloxacin, orbifloxacin, and difloxacin. This class also includes ciprofloxacin, which is an approved human drug that is frequently administered to dogs. (Enrofloxacin is partially metabolized to ciprofloxacin in most animals.) For treatment of GIT disease, the fluoroquinolones owe their usefulness to the high activity against Gram-negative bacilli, particularly the Enterobacteriaceae. These drugs also have the favorable property of weak activity against anaerobic bacteria. Without anaerobic activity, these drugs are less likely than other oral antimicrobials to disrupt the anaerobic intestinal bacterial population.

The fluoroquinolones have a unique mechanism of action. They inhibit the DNA gyrase enzyme (also called topoisomerase type II), which catalyzes the conversion of relaxed closed circular DNA to the superhelical form. There are A and B subunits of this enzyme and quinolones usually inactivate the A subunit. As a result of this activity, the fluoroquinolones are highly bactericidal.

The fluoroquinolones are highly absorbed after oral administration. A summary of their individual pharmacokinetics is available in a recent book chapter.[8] The exception to this generalization is the human drug ciprofloxacin. In cats the oral absorption of ciprofloxacin is low, and in dogs it is highly variable, ranging from approximately 30% to 80%. An advantage of fluoroquinolones is that they are excreted both by hepatic and renal mechanisms. Renal or hepatic insufficiency is not a contraindication to their use nor requires a dose adjustment.

The fluoroquinolones have a good safety record and can be used in a wide range of patients. The most notable adverse effects are arthropathy in young dogs (ages 4 to 28 weeks are the most susceptible) with high doses, and blindness in cats if the dose of enrofloxacin exceeds 5 mg/kg per day. Other adverse effects such as neurologic problems (seizures, tremors) are rare at the doses used for GIT diseases.

The formulation most often used is the tablet, which is available for every drug listed previously. Enrofloxacin is also available in an injectable formulation, which may be necessary in animals that cannot tolerate oral medications. When oral treatments are used, drug interactions are possible. The fluoroquinolones can be inactivated by di- and trivalent cations, producing poor oral absorption. This may be important for treatment of some GIT diseases because drugs known to contain these cations include antacids (magnesium, aluminum, and calcium), sucralfate (aluminum), and nutritional supplements (supplements containing magnesium or iron).

Tetracyclines

The tetracyclines include tetracycline, oxytetracycline, doxycycline, and minocycline. For small animals, the use is almost exclusively that of doxycycline. Tetracyclines are protein synthesis inhibitors. They bind to the 30-S ribosomal subunit and block the aminoacyl-transfer RNA from binding to the messenger RNA (mRNA) ribosome complex.

The tetracyclines are broad-spectrum drugs that are active against Gram-negative and Gram-positive bacteria, as well as *Chlamydia*, rickettsia, spirochetes, mycoplasma, L-form bacteria, and some protozoa (e.g., *Plasmodium, Entamoeba)*. The family Rickettsiaceae includes *Rickettsia* and *Ehrlichia* and tetracyclines, particularly doxycycline, are considered the drug of first choice for these infections.

The oral route is the most common method of administration and doxycycline hyclate tablets, and occasionally doxycycline monohydrate, are the formulations most often administered to small animals. Oral absorption is sometimes erratic and unpredictable, but high enough for oral treatment in most animals. Calcium and other divalent cations will chelate tetracyclines and inhibit oral absorption (note that in "Fluoroquinolone Antibiotics" section, drugs were listed to treat GIT diseases contain these cations), although this is less of a problem for doxycycline than for other tetracyclines.

Most tetracyclines are metabolized minimally and rely on glomerular filtration for elimination. However, doxycycline and minocycline are metabolized more than the other tetracyclines and the renal excretion may not be as high as for other tetracyclines. Doxycycline and minocycline differ from the other tetracyclines because they are excreted into the intestinal lumen, which may be important for treatment of some intestinal diseases.

Tetracyclines can produce changes in the gastrointestinal microflora. This has been a problem in some animals (horses especially), but less so for small animals. Nevertheless, diarrhea can occur from oral administration. The other important adverse effect related to the GIT is esophageal injury. Doxycycline entrapped in the esophagus from a broken tablet or incompletely dissolved capsule can cause injury to the esophagus and stricture. In cats, a capsules or broken tablets can lodge in the esophagus unless administered with water. Therefore, one should be cautious about giving oral doxycycline medications to cats. This problem has been primarily associated with doxycycline hyclate (the form most common in the United States), rather than doxycycline monohydrate.

Ampicillin and Amoxicillin

Ampicillin and amoxicillin are aminopenicillins, derived semisynthetically from the parent drug penicillin. They have advantages over penicillin that include better oral absorption (although amoxicillin is better absorbed than ampicillin in small animals), and slightly better activity against Gram-negative bacilli. They are also active against many of the anaerobic bacteria and some enterococci.

The aminopenicillins are available in a variety of formulations, including tablets, capsules, liquid oral suspensions, and injectable forms. Their absorption is variable. In dogs the systemic availability for ampicillin is 30% to 40%, and for amoxicillin it is approximately 60% to 80%. A relatively high amount remains in the intestinal lumen and this forms the basis for the oral use of these drugs for

treating GIT diseases. These drugs may also produce diarrhea in animals by disrupting the oral flora.

Chloramphenicol

Chloramphenicol is highly active against many pathogens that cause GIT disease. Chloramphenicol is a protein synthesis inhibitor that acts by binding to the 50-S subunit of the ribosome. This is the same site of action as macrolide antibiotics, therefore antagonism is possible. Binding to this subunit is reversible and results in inhibition of protein synthesis.

Chloramphenicol has been considered bacteriostatic, but some evidence suggests a more bactericidal action. Chloramphenicol has a wide spectrum of activity that includes both Gram-positive and Gram-negative bacteria, as well as some atypical organisms. The bacterial spectrum includes organisms that are important for GIT disease, including *Salmonella*, anaerobes (including *Bacteroides*), and enterococci.

Adverse effects must be considered whenever prescribing chloramphenicol. Dose-related anemia and pancytopenia may be associated with chronic treatment. This effect has been well-documented in cats and can occur after 14 days of therapy with standard dosages.[9] Because of the potential injury to bone marrow cells, use in neonatal animals or pregnant animals should be avoided. The more serious effect of idiosyncratic aplastic anemia has been described in humans only. The incidence is rare but the consequences are severe. This can potentially occur by direct exposure from handling the medication; therefore, pet owners should properly be advised when receiving a prescription for their pets. Chloramphenicol also can be involved in drug–drug interactions. It decreases the clearance of other drugs that are metabolized by the same metabolic enzymes (e.g., barbiturates).

Florfenicol (Nufluor) is a chloramphenicol derivative used as an injectable formulation in pigs and cattle. It has been examined only experimentally in small animals. The requirement for frequent administration and poor absorption make it an impractical choice for treating dogs. The lack of a palatable oral formulation and inexperience with clinical use is a disadvantage for the use in cats.

Metronidazole

Metronidazole (Flagyl and generic) is of the group of nitroimidazoles. Metronidazole is the most common drug prescribed from this group. Tinidazole (Tindamax) tablets are approved in people for treating *Giardia*, *Trichomonas*, and *Entamoeba*. Similar drugs, not available presently in the United States, are nimorazole (Naxogin), ornidazole (Tiberal), ronidazole, and benznidazole (Rochagan). Ronidazole is not a registered drug in the United States, but compounded formulations have been used in the United States to treat infections caused by intestinal *Tritrichomonas* in cats.

Metronidazole is a unique antimicrobial in that it has very little effect on aerobic Gram-positive and Gram-negative organisms, but is highly effective against anaerobic bacteria (e.g., *Bacteroides, Fusobacterium, Clostridium, Peptococcus*, and *Peptostreptococcus*). It is not effective against bacteria that may be facultative anaerobes. It has good activity against many protozoa (e.g., *Giardia lamblia, Entamoeba, Trichomonas*). Metronidazole has been used in people, in combination with other drugs, to treat *Helicobacter pylori*.

Metronidazole is rapidly taken up by bacteria, followed by a reaction in the cell in which it is metabolized by a reduction process to cytotoxic derivatives (short-lived free radical compounds). These cytotoxic compounds damage DNA and other critical intracellular bacterial macromolecules. Aerobic bacteria lack the reductive pathway necessary to produce a cytotoxic compound.

Metronidazole is rapidly and highly absorbed in small animals (59% to 100% in dogs) following oral administration. An injectable preparation is available, but seldom used. Peak concentrations occur 1 to 2 hours following oral administration. The related drug, ronidazole, is also highly absorbed. In cats, the oral absorption of ronidazole is rapid and complete (almost 100%).

The most significant adverse effect is neurotoxicity. The reactions appear to be caused by inhibition of the γ-aminobutyric acid neurotransmitter. At high doses (67 to 129 mg/kg/day) that exceed the recommended dose, metronidazole has caused ataxia, lethargy, proprioceptive deficits, nystagmus, and seizure-like signs in dogs. Dogs have recovered if drug administration was discontinued, but recovery may take 1 to 2 weeks.[10,11] Recovery is much faster if diazepam is administered.[12] Neurotoxicosis also has been observed in cats with high doses.

Metronidazole has caused nausea, vomiting, and diarrhea in animals, but it is rare. Palatability is a problem in most animals because of its bitter taste. Cats are particularly susceptible to the unpleasant taste of broken or crushed tablets. This problem can be alleviated by administration of the ester metronidazole benzoate.[13]

Aminoglycosides

The aminoglycosides are administered orally. They are used occasionally for diseases of the GIT because they retain their activity in the lumen of the GIT without systemic absorption and risk of systemic adverse effects.

Aminoglycosides are protein synthesis inhibitors. They irreversibly bind to the 30-S ribosomal subunit and cause misreading of the genetic code and inhibit bacterial protein synthesis. The aminoglycosides are rapidly bactericidal. They are concentration-dependent drugs for which the activity is predicted by the peak concentration (C_{MAX}) in relation to the MIC. The clinical protocols that administer these drugs orally retain high concentrations in the GIT lumen; therefore, their pharmacodynamics are ideally suited for this application.

Aminoglycosides are active against most Gram-negative bacteria, including Enterobacteriaceae. Their action against streptococci and enterococci is limited unless they are combined with a β-lactam antibiotic. Anaerobic bacteria are inherently resistant because drug transport into bacteria is oxygen dependent.

Oral absorption of aminoglycosides is poor, but if any systemic absorption occurs, these drugs rely almost exclusively on renal clearance, primarily glomerular filtration. If there is any risk of systemic absorption caused by a compromised GIT mucosa (e.g., severe enteritis), systemic absorption may occur, and dosage adjustments must be considered in patients with renal insufficiency or failure. If systemic absorption occurs, the most serious toxic effect associated with aminoglycoside therapy is renal tubular injury. These drugs are actively taken up by proximal tubular cells. Animals that are dehydrated have electrolyte imbalances (e.g., low Na^+ or K^+), have endotoxemia, or have existing renal disease, are at a higher risk for toxicity than are healthy animals.

Drugs used for GIT disease in this class include gentamicin oral formulations (developed for pigs), neomycin oral (e.g., Biosol), and paromomycin. Paromomycin has been administered orally to people and small animals for treatment of intestinal infections. Its primary use has been in oral treatment of enteric protozoa and aerobic bacteria. It has also been used as a treatment for cryptosporidiosis, but efficacy is questionable. Caution is advised when using paromomycin for intestinal disease because it has caused acute renal failure in cats at high doses.[14]

Antimicrobial Drugs for Treatment of Diarrhea

The routine use of antimicrobials to treat diarrhea has been questioned by gastroenterologists. Therapy for diarrhea should include fluid therapy, electrolyte replenishment, maintaining acid–base balance, and control of discomfort. But drugs are sometimes used such as antimicrobials, motility modifiers, and intestinal protectants. Drugs used to treat diarrhea caused by intestinal parasites are covered in another section. In most cases of diarrhea in small animals, a bacterial etiology cannot be identified. A recent review[15] provides a critical overview of the lack of proven efficacy for many antimicrobials that are FDA-approved for treating diarrhea. In those patients, fluid therapy and supportive measures are often the most widely recommended treatment.

The preferred drugs for treatment of diarrhea are those that are poorly absorbed or nonabsorbed antibiotics, because the goal of treatment is to restrict the drug activity to the gastrointestinal lumen. For treatment of diarrhea, these drugs have been combined with motility modifiers, adsorbents, and intestinal protectants. These drugs have been combined in commercial preparations, but some of these are irrational combinations and no longer have a place in companion animal medicine.

Important points that are essential to understanding the use of antimicrobial drugs for treatment of diarrhea include: (a) sometimes administration of oral antibiotics can be a *cause* of diarrhea.[16,17] (b) Selection of drugs is often empirical and based on anecdotal experience, reports by experts, or extrapolated from the use of the drug in human medicine. (c) It is unusual for therapy to be guided by culture and susceptibility testing. In addition to the challenges of culturing and isolating bacteria that may be the cause of diarrhea, standardized susceptibility testing methods are not available. Ordinarily, when bacteria are cultured a susceptibility test can be performed according to standards developed and published by the Clinical Laboratory Standards Institute (CLSI).[18] However, these standards, and particularly the breakpoints that define susceptibility and resistance, only apply to the systemic use of the agents. The antibacterial MICs for organisms isolated from the intestine may not apply to drugs that are delivered locally (i.e., orally). Therefore, a susceptibility test may not correlate to the efficacy of the drug when used to treat the diseases discussed in this section, unless the treatment is targeted to a systemic infection.

Campylobacter Enteritis

This disease is caused by C. *jejuni*, which has public health significance because it may be transmitted to people. This organism is the most common cause of foodborne infectious diarrhea in people. The treatment is aimed primarily at maintaining fluid and electrolyte balance. If antimicrobials are considered, the following drugs have been used: erythromycin (10 to 20 mg/kg q8h for 5 to 7 days), azithromycin (7 to 10 mg/kg once a day × 3 days), fluoroquinolones, tylosin, clindamycin, tetracycline, or chloramphenicol (40 to 50 mg/kg PO q8h). Although erythromycin has been cited as the treatment of choice, bacterial shedding may resume once therapy is stopped.[19]

Intestinal Bacterial Overgrowth Caused by *Escherichia coli or Clostridium* spp.

Treatments that have been used include antimicrobial treatment and administration of probiotics. Probiotics are formulations of specific bacteria that will restore a healthy population of bacteria in the intestine (discussed in more detail elsewhere). When antibiotics are considered, one should administer an oral drug that is active in the gastrointestinal lumen. For treatment of infections caused by *Clostridium* spp. the drug should have activity against anaerobic bacteria and may include metronidazole or clindamycin. Oral ampicillin or amoxicillin also has been used. Vancomycin is used orally in people when resistance to other drugs is suspected, but this use has not been described for small animals. For *E. coli*, fluoroquinolones are recommended.

Tylosin Responsive Diarrhea

Because some forms of chronic diarrhea in animals have been responsive to the antimicrobial tylosin (Tylan), the disease has been characterized as "tylosin-responsive chronic diarrhea in dogs."[20,21] This disease, affecting both large and small bowel, is most likely caused by a bacterial pathogen, but the specific etiology has not been identified. C. *jejuni* and *Clostridium perfringens* have been identified in some of the affected animals. Tylosin has been effective at improving clinical signs that occur with or without organisms being identified. When administered at 7 to 15 mg/kg/q12-24h (average dose) response was prompt.[20] Some dogs respond within 24 hours; others respond within 3 days. Other studies by the same investigators showed that a dose of 20 mg/kg/day was effective, but other drugs (metronidazole, trimethoprim-sulfonamides, doxycycline, or prednisolone) were not.[21]

Sources of Tylosin

The powdered form for livestock (Tylan) has been mixed with the animal's food at a dosage of 40 to 80 mg/kg/day. One teaspoon contains approximately 3 g (3000 mg); consequently, one-quarter teaspoon contains 750 mg, enough for many dogs. Because some animals may find the bitter taste unpleasant and refuse their food, the administration should be tested to identify the method of administration that is best tolerated. Tablets for small animals are available in other countries.

Metronidazole Responsive Diseases

Metronidazole (Flagyl) is active against the protozoan *Giardia* and it is for this use that metronidazole has traditionally been administered to treat diarrhea in small animals. Veterinarians discovered that metronidazole also was effective in patients that did not have giardiasis. Bowel inflammation may be caused by metronidazole-sensitive bacteria, which act as a chemoattractant for neutrophils. The efficacy of metronidazole may be related to this antibacterial activity. Oral administration of metronidazole at 20 mg/kg to cats decreased the number of anaerobic and aerobic bacteria and altered the indigenous bacterial population.[22] In addition, metronidazole may have an immunosuppressive effect on the gastrointestinal mucosa (decreased cell-mediated response). Metronidazole (with and without combination with ampicillin) has been effective for histiocytic ulcerative colitis in dogs.[23] Doses have been as high 60 mg/kg/day for 2 to 4 weeks, but many animals will respond to low doses of 30 mg/kg/day (in divided doses). Cats can receive one-quarter of a 250 mg tablet, two to three times daily (10 to 25 mg/kg). Cat owners should be cautioned that broken tablets have an unpleasant taste.

Ronidazole

Ronidazole, from the same chemical group as metronidazole, has greater in vitro activity against, and is the preferred treatment for, intestinal infections in cats caused by the organism *Tritrichomonas foetus*. It has been administered at a dose of 30 mg/kg once or twice daily for 14 days, and studies in cats demonstrate

that is one of the few drugs associated with eradication of this organism.[24]

Although central nervous system reactions are associated with ronidazole treatment in cats, these are usually associated with high doses. Because of the long half-life, it may be possible to administer this drug once daily and avoid adverse effects.

Ulcerative Colitis in Dogs

In some dogs, particularly Boxer dogs, ulcerative colitis is associated with *E. coli* infection of the colonic mucosa.[25] In these dogs there is evidence of mucosal infiltration with large numbers of macrophages that induce an inflammatory reaction, leading to ulcerative colitis. The invasive bacteria evoke production of inflammatory reactions and produce cytokines that are responsible for clinical signs. Successful treatment has been accomplished with oral administration of fluoroquinolones, which are highly active against *E. coli*. One of the regimens includes enrofloxacin at 7 mg/kg, once a day × 9 weeks.

Salmonellosis

The primary goal when treating *Salmonella* is to maintain fluid balance and prevent electrolyte losses. The patients should be isolated to prevent spreading of infection and strict containment procedures should be instituted in the hospital. Antibiotics are discouraged unless absolutely necessary for patients with salmonellosis. Antibiotic therapy may prolong shedding. In animals in which oral therapy is possible, drug choices include the following: fluoroquinolones, chloramphenicol, ampicillin or amoxicillin or amoxicillin-clavulanate, trimethoprim-sulfonamide, or a cephalosporin (the activity against *Salmonella* is highest with third-generation cephalosporins).

Bacterial Septicemia Secondary to Diarrhea

When it is suspected that there may be a loss of the protective epithelial barrier, the intestinal mucosal integrity is compromised. In these cases, bacteremia and septicemia can occur because of translocation of bacteria. Signs accompanying septicemia include a severe, bloody diarrhea, fever, and leukocytosis. This may progress to signs of endotoxic shock. If septicemia is suspected, systemic antibiotics are clearly warranted.

The choice of antibiotics will vary depending on the species and the animal's age. Neonates with diarrhea will deteriorate rapidly and treatment cannot wait for culture and sensitivity results. Therefore broad spectrum antimicrobials often are used.

Recommended antibiotics include ampicillin or amoxicillin (with or without a β-lactamase inhibitor); combination of a β-lactam (penicillin, aminopenicillin, or cephalosporin) with an aminoglycoside (gentamicin or amikacin); aminoglycoside alone; cephalosporin (extended-spectrum cephalosporin); carbapenem (meropenem or imipenem); or fluoroquinolones (enrofloxacin, marbofloxacin, difloxacin, orbifloxacin). If the animal shows signs of sepsis, systemic antimicrobials should be used. Antibiotics that are poorly absorbed and confined to the gastrointestinal lumen may be of little benefit (e.g., neomycin, ampicillin).

Other Uses for Antimicrobial Drugs

Erythromycin to Increase Gastrointestinal Motility

Erythromycin, as discussed previously, is a macrolide antibiotic widely used to treat bacterial infections. It is associated with vomiting and regurgitation in small animals as an adverse consequence of treatment. This effect is caused by stomach contraction and expulsion that is most prominent at high doses. But at low doses, it can produce a beneficial stimulation of gastrointestinal motility. Not all macrolide antibiotics exhibit this property because it requires a unique chemical structure that not all drugs in this class possess (erythromycin has a 14-carbon structure, but other macrolides that are less effective—tylosin and tilmicosin—have a 16-carbon structure). In people, erythromycin has been used to promote gastric motility and increase emptying in patients with diabetic gastroparesis and in conjunction with enteral feeding in critical care patients.[26]

Erythromycin stimulates gastrointestinal motility via activation of motilin receptors, via release of endogenous motilin, or via cholinergic mechanisms in the upper GIT.[5,6,26] Motilin is a 22-amino-acid peptide released from endocrine cells of duodenal mucosa. It increases the motor contractions—housekeeper wave—during the interdigestive period. Motility is stimulated specifically in the pyloric antrum or the smooth muscle cells of the proximal intestine.[27,28] Because most of the motilin receptors are on the stomach and proximal small intestine, there is a weak response to erythromycin in the distal GIT. The effective dose in animals is 0.5 to 1 mg/kg q8h or less, much lower than the antibacterial dose.

Treatment of *Helicobacter* Gastritis

Treatment of gastritis and ulcers caused by *H. pylori* and *Helicobacter*-like organisms has gained interest in veterinary medicine. These organisms have been identified in biopsy specimens from dogs and cats, but their definitive role in gastritis and ulcers of companion animals has yet to be established.[29,30] Some studies have found no association between *Helicobacter* infection and gastritis.[31,32] However, in some animals with gastritis, treatment with ampicillin, metronidazole, and famotidine, or the combination of metronidazole, amoxicillin, and bismuth subsalicylate has helped decrease signs.[29] Triple antibiotic therapy for *Helicobacter* also decreased clinical signs in dogs with chronic vomiting.[31a] Role of *Helicobacter* as a cause of gastritis in animals has been reviewed.[32a,33] One author recommends that animals with clinical signs of gastritis and positive for *Helicobacter* or *Helicobacter*-like organisms should be treated. The oral treatment for animals that has been the most widely used is a 2-week course of the combination of metronidazole and/or clarithromycin plus amoxicillin, and a proton-pump inhibitor or H_2-receptor antagonist.

In people, *H. pylori* gastritis has been treated with the simultaneous use of metronidazole, omeprazole, and clarithromycin.[34] One regimen uses clarithromycin (Biaxin) and omeprazole (Prilosec). A product called Tritec combines ranitidine with bismuth citrate and is designed to be administered concurrently with clarithromycin (Biaxin). Some regimens also use amoxicillin or metronidazole. Some synergism is achieved with these combinations. For example, H_2-antagonists or omeprazole enhance the antibacterial activity of metronidazole and perhaps other antibiotics.

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CHAPTER 40

Antioxidant Drugs

Craig B. Webb

Definitions

Oxidative Stress

Oxidative stress is an imbalance between prooxidant compounds and antioxidant defenses.[1,2] Another term used to describe this summation of pro- and antioxidant molecules is the *redox state*.

Free Radicals

A *free radical* is any molecular species capable of independent existence and containing one or more unpaired electrons.[1,2] Examples include the hydrogen radical ($H^{\bullet}$), the superoxide free radical ($O_2^{\bullet -}$), and the hydroxyl ($OH^{\bullet}$) and peroxyl radicals ($RO_2^{\bullet}$). Metabolic processes taking place within the liver constitute a major source of free radical production. The superoxide free radical, for example, is produced by hepatic oxidative reactions and by "uncoupling" of the cytochrome P450 enzyme system. Free radicals are formed during hepatic metabolism of endogenous substances or xenobiotics such as acetaminophen.[5]

Reactive Oxygen Species

The term reactive oxygen species (ROS) is used to describe free radicals containing oxygen.[1,2] These are molecules that are formed by the reduction of oxygen and encompass both free radicals and nonfree radicals such as hydrogen peroxide (H_2O_2), hypochlorous acid (HOCl), and peroxynitrite (ONOO, which is also a reactive nitrogen species). ROS are produced under normal circumstances during normal mitochondrial respiration, and during disease processes such as inflammation, necrosis, and ischemia.

Reactive Nitrogen Species

Nitric oxide synthase (NOS) in hepatocytes and Kupffer cells produces nitric oxide ($NO^{\bullet}$), a reactive nitrogen species (RNS)[1,2] in the reaction:

L-Arginine + O_2 + NADPH → $NADP^+$ + $NO^{\bullet}$ + citrulline

where NADPH is nicotinamide adenine dinucleotide phosphate (reduced form) and $NADP^+$ is nicotinamide adenine dinucleotide phosphate.

Nitric oxide is also produced by neutrophils as part of the inflammatory process, and from the reaction of glutathione with peroxynitrite. Nitric oxide binds reversibly to free thiol groups, including reduced glutathione (GSH) through the action of glutathione-*S*-transferase. Nitric oxide is a powerful vasodilator, and acts as an antioxidant through its ability to scavenge lipid peroxyl radicals. Conversely, nitric oxide forms nitrogen-containing reactive intermediates such as nitrotyrosine, which can lead to liver necrosis, inhibit mitochondrial function, and deplete cellular pyridine nucleotides causing breaks in DNA strands. Nitric oxide can also combine with the superoxide anion free radical to form the RNS peroxynitrite. Peroxynitrite produces cell injury through lipid peroxidation, inhibition of mitochondrial respiration and Na^+/K^+-adenosine triphosphatase (ATPase) activity, and protein oxidation.

Pathophysiology[1,2]

DNA Damage

ROS cause DNA base-pair modifications, strand breaks, crosslinking, and mutations resulting in uncontrolled growth and malignant transformation. Free radicals are also implicated as initiators of apoptosis, or programmed cell death.

Lipid Peroxidation

Polyunsaturated fatty acids in cell membranes react with oxygen to produce peroxyl radicals, the primary free radical intermediate of lipid peroxidation. Change in the structure of membrane lipids will change cell membrane fluidity and significantly alter membrane functions such as ion transport, receptor recognition and signaling, and osmotic gradients. Initially a hydroxyl radical removes hydrogen from lipid molecules in the cell membrane, transforming that lipid molecule into a free radical and starting a cycle of reactions whereby a newly formed membrane lipid peroxyl radical extracts a hydrogen molecule from the next lipid molecule and the cycle is repeated.

Protein Damage

Oxidative modification of endogenous proteins causes unfolding of the tertiary and quaternary structure. Intracellular signaling pathways rely on normal protein structure and function, and ROS can oxidize amino acids within enzymes, rendering them inactive and/or antigenic.

Altered Redox State

Intracellular changes in ROS cause changes in the redox balance and second messenger signal transduction that may affect cell function, cell proliferation, and gene expression. The upregulation of matrix metalloproteinases, kinases, and transcription factors, such as nuclear factor kappa B (NF-κB), by free radicals may result in the production of mediators, such as tumor necrosis factor (TNF)-α and interleukin-1, in chronic diseases, such as inflammatory bowel disease.[2]

Drug Classifications and Mechanisms of Action

Antioxidant defenses consist of both enzymatic and nonenzymatic processes.[3] Antioxidant enzymes include superoxide dismutase, catalase, glutathione peroxidase, and glutathione reductase. These antioxidant enzymes catalyze chemical reactions that utilize ROS. The end-product of their reactions is often a much less harmful compound such as water, or a metabolite that is subject to further antioxidant reactions, such as hydrogen peroxide.

Sulfur-containing glutathione is the most important of the nonenzymatic antioxidants. Thiols exert their antioxidant action through oxidation of the sulfhydryl bond of cysteine. In this way, they scavenge free radical unpaired electrons. The inhibition of lipid peroxidation by α-tocopherol (vitamin E) is another example of a scavenging antioxidant property. These antioxidants are replaceable substrates because they can be returned to their reduced form through simple chemical reactions.

Enzymatic and nonenzymatic antioxidant defenses often work synergistically. For example, after the superoxide dismutase enzyme generates hydrogen peroxide from the superoxide anion, the glutathione peroxidase enzyme converts hydrogen peroxide to water by oxidizing GSH to the disulfide form GSSG. The glutathione reductase enzyme completes the process by returning GSSG to GSH:

$2\ O_2^{\bullet -} + 2\ H^+ \rightarrow H_2O_2 + O_2$

Superoxide dismutase enzyme

$2\ GSH + 2\ H_2O_2 \rightarrow 2\ H_2O + GSSG$

Glutathione peroxidase enzyme (selenium cofactor)

$GSSG + NADPH + H^+ \rightarrow 2\ GSH + NADP^+$

Glutathione reductase enzyme (riboflavin cofactor)

Much like glutathione, the thioredoxins are ubiquitous thiol-containing antioxidant polypeptides that are oxidized to a disulfide form while they undergo redox reactions with multiple proteins. Thioredoxins are returned to their reduced form by an NADPH-dependent reaction driven by the thioredoxin reductase enzyme, and along with GSH, are critical to cellular redox (oxidative) potential.

The Fenton reaction uses metals (copper or iron) as a cofactor during the generation of ROS: $Fe^{2+} + H_2O_2 \rightarrow OH^{\bullet} + OH^- + Fe^{3+}$

The liver serves as the major organ for iron and copper transport and storage. Hepatic copper accumulation is both cause and consequence of chronic hepatitis. Proteins that bind these metals are considered antioxidant. The liver is abundant in metallothioneins or cysteine-rich proteins that bind to various hepatic metals such as copper and zinc. Iron is bound in the hepatocyte to the protein ferritin or hemosiderin. Some of the more important of the metal-binding transport molecules are transferrin and lactoferrin, which bind iron, ceruloplasmin, and albumin, which bind copper, and the exogenous copper-chelating agent penicillamine.

Rational Use of Antioxidants in the Veterinary Patient

Therapies of oxidative stress in dogs and cats have been directed primarily at the tripeptide glutathione (γ-glutamylcysteine-glycine).

During normal hepatic metabolism, glutathione can be directly conjugated to a variety of metabolites and drugs to increase their water solubility and enhance their excretion through the kidney. This process is particularly important in the cat because hepatic glucuronidation is virtually absent in that species. Glutathione is abundant in gastrointestinal mucosa and undoubtedly serves a similar antioxidant role in that tissue.

Reduced GSH concentrations have been reported with hepatic disorders, including inflammation, cholestasis, lipidosis, copper retention, and acetaminophen toxicity.[4-6]

These studies support the role of glutathione as an antioxidant in dogs and cats and a number of glutathione precursors have been developed.

S-adenosyl-L-methionine (*S*-adenosylmethionine)

S-adenosyl-L-methionine (SAMe) is a key component of several metabolic pathways, including methylation, sulfuration, and aminopropylation reactions, but it is perhaps most important clinically as a glutathione precursor.

Oral administration of SAMe (48 mg/kg q24h) increases plasma SAMe concentrations, hepatic GSH concentration, and hepatic GSH-to-GSSG ratio in healthy cats.[7] These same doses have been shown to diminish erythrocyte peroxidation and osmotic fragility. SAMe conserves red blood cell and hepatic GSH concentrations in dogs with experimentally induced steroid hepatopathy,[8] and limit Heinz body formation and erythrocyte destruction in cats and dogs exposed to acetaminophen.[9,10] Although *N*-acetylcysteine (NAC) is traditionally considered the antioxidant of choice, comparative efficacy studies show that SAMe may be a more effective treatment of acetaminophen toxicity in mice.[9] SAMe also may be useful in the treatment of pancreatitis and gastric ulceration.[11,12]

N-acetylcysteine

NAC is the thiol donor most frequently used in emergency cases. The oral bioavailability of NAC is limited, but when given intravenously it results in a rapid increase in GSH synthesis and has direct antioxidant activity. NAC is still considered the standard of care in cases of acetaminophen toxicity, and is useful in the detoxification of hepatotoxins, as well as in cases of ischemia–reperfusion injury.

Vitamin E (α-Tocopherol)

Vitamin E inhibits lipid peroxidation, thereby stabilizing cell membranes, and preventing changes in membrane fluidity and function. Supplementation with vitamin E reduces the production of the proinflammatory mediators NF-κB and TNF-α, and decreases collagen production associated with hepatic inflammation. Vitamin E concentrations are depleted in several forms of liver injury, including hypoxia.[13] Vitamin E and cysteine supplementation ameliorates acetaminophen, but not onion powder, toxicity in cats.[14] Vitamin E plus selenium combinations also have been used for tetracycline-induced hepatotoxicity in the cat.[15] Dogs treated with vitamin E for 3 months demonstrated an increase in serum and hepatic vitamin E concentrations and an improved hepatic GSH-to-GSSG ratio.[16]

Vitamin C may help to recycle vitamin E to a useful antioxidant form, but because vitamin C can act as a prooxidant and promote hepatic iron storage, supplementation is generally not recommended.

Milk Thistle (Silymarin, Silibinin)

Silymarin is an extract of the milk thistle plant that contains a mixture of bioactive flavonolignans, the most powerful of which is silibinin. Silymarin reduces hepatic iron accumulation, collagen deposition, and fibrosis following severe hepatic injury, and has been reported to improve survival in cirrhosis,[17] but not in hepatitis C or alcohol-induced hepatitis.[18] Silibinin administered at a dosage of 50 mg/kg reduces elevations in alanine aminotransferase, alkaline phosphatase, and total bilirubin, as well as the hepatic hemorrhagic necrosis following amanita mushroom or CCl_4 poisoning in the dog.[19,20]

Table 40-1 Antioxidant Agents Used in Dogs and Cats

Drug Classification	Dose	Indications	Side Effects	Trade Names
S-adenosyl-L-methionine	20 mg/kg PO q24h	Acetaminophen toxicity, xenobiotics, hepatotoxins	Nausea, emesis	Denosyl (Nutrimax) Zentonil (Vetoquinol)
N-acetylcysteine	140 mg/kg initial dose IV, 70 mg/kg BID-QID	Acetaminophen toxicity, xenobiotics, hepatotoxins	Hypotension, allergic reactions	Mucomyst (Apothecon) Mucosil-10 (Day Labs)
Vitamin E	10 to 15 units/kg PO, BID, q24h (for liver disease)	Cholestatic liver disease, hepatitis, cirrhosis, copper-associated hepatopathy, hepatotoxins	Platelet aggregation	
Silibinin	5 to 15 mg/kg q24h, upto 30 mg/kg q24h	Amanita mushroom poisoning, other hepatotoxins, hepatitis, cirrhosis, cholestatic disorders	Suppression of cytochrome P450	Marin (Nutramax)
Ursodeoxycholate	10 to 15 mg/kg PO q24h	Cholestatic disorders, cholangitis, hepatitis, copper-associated hepatopathy	Anorexia	Actigall (Watson)

A recent study evaluated the therapeutic efficacy of combining silymarin with metronidazole for treating canine giardiasis.[21] Although the silymarin dose (3.5 mg/kg/day combined with 50 mg/kg/day of metronidazole) was quite small, a positive response was noted earlier in the silymarin-supplemented dogs.[21]

Ursodeoxycholic Acid (Ursodiol)

Ursodiol differs from other antioxidants in that it is a prescription medication and it is normally prescribed for its choleretic, not antioxidant, properties. In a rat model of alcoholic steatohepatitis, ursodeoxycholic acid (UDCA) treatment improved liver morphology; decreased aspartate aminotransferase, γ-glutamyltransferase, and liver triglyceride content; and normalized cytochrome P450 enzyme content and markers of oxidative stress.[22] UDCA administration (10 mg/kg) is safe, and is currently being used in a number of canine hepatopathies, including copper retention and chronic hepatitis.[23] Ursodiol appears to have no prokinetic effect on the biliary system.

Other Diseases

Feline intestinal ischemia–reperfusion injury is classically associated with oxygen free radical generation, and can be prevented by treatment with superoxide dismutase.[24] Canine gastric dilation-volvulus is another example of an ischemia–reperfusion injury in which the iron-chelator deferoxamine reduces the severity of injury during the period of reperfusion.[25] The free radical scavenger, fullerenol, was found to ameliorate changes in GSH in a canine experimental model of ischemic bowel syndrome.[26] None of these antioxidant strategies have become best practice standards in cases of gastrointestinal ischemia–reperfusion injury.

Combination Therapy

The first step in designing an effective antioxidant treatment plan is to define the oxidative damage that is most important in disease progression. Lipid peroxidation, DNA damage, or the signaling of inflammatory cytokines are just a few of the consequences of free radical production. A combination of these effects is likely to require a combination of antioxidants to return to homeostasis. Combination antioxidant therapy has been used to beneficial effect in racing sled dogs and in cats with renal insufficiency.[27-29]

In the meantime, logical choices for antioxidant treatments in dogs and cats can be made based on the species, the disease, evidence from studies in other animal species, the small number of veterinary studies currently available, theory, lack of toxicity, and best practice standards. Table 40-1 lists antioxidant agents used in dogs and cats.

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CHAPTER 41

Antispasmodic Agents

Robert J. Washabau

Definitions

Brain–Gut Axis

The term *brain–gut axis* refers to the bidirectional neural processing of information between the central nervous and digestive systems. The brain–gut axis plays an essential role in the regulation of gastrointestinal (GI) motility, secretion, digestion, absorption, and blood flow; in the regulation of appetite, energy balance, and metabolism; and in the modulation of mucosal immunity (see Chapter 1). In turn, the brain receives interoceptive input (i.e., endogenous stimuli) from the GI tract, integrates this information with other systems input, and transmits integrated feedback back to the end-organs of the GI tract. The brain–gut axis is designed to optimize homoeostasis during minor physiologic perturbations and to adapt GI function to the overall state of the animal.[1] In health, the great majority of interoceptive input does not reach the level of consciousness in the brain, but serves primarily as input to an autonomic reflex pathway. Brain–gut dysfunction underlies the clinical signs of the functional GI disorders such as irritable bowel syndrome, and it might mediate the development of stress-induced relapses in inflammatory bowel disease (IBD).[1]

Irritable Bowel Syndrome

Irritable bowel syndrome (IBS) is a human chronic GI tract disorder of unknown origin that is characterized by abdominal pain and altered bowel habits in the absence of detectable biochemical or structural abnormalities.[2] IBS is one of the most common functional GI disorders with an estimated prevalence of 10% to 15% in Western adult populations. Direct and indirect costs of IBS reach up to $30 billion per year in the United States alone.[2] IBS is commonly subdivided into different phenotypes, depending upon the most prevalent bowel habit: diarrhea-predominant IBS (IBS-D), constipation-predominant IBS (IBS-C), and mixed features IBS (IBS-M).[3] Symptom complex differentiation is an important strategy in the diagnosis and treatment of the disorder. Because of the inability of animal species to describe clinical signs such as abdominal pain and discomfort, IBS is not as well-defined in veterinary medicine. Nonetheless, recurring vomiting and diarrheal disorders are seen in companion animals, abdominal discomfort is readily detected on physical examination, the clinical features are unaccompanied by mucosal morphologic change, and the pathogenesis is assumed, therefore, to be of functional or physiologic origin.[4]

Antispasmodic Agents

Antispasmodic agents are drugs designed to relieve or prevent spasms of the GI tract. They are used primarily in patients with clinical signs consistent with a diagnosis of constipation-predominant IBS.

Pathophysiology of Irritable Bowel Syndrome

The pathophysiology of IBS is incompletely understood, although it is considered to have both peripheral and central mechanisms.[1]

Peripheral Mechanisms

Primary Afferent Pathways

Acute inflammation is associated with peripheral sensitization and visceral hyperalgesia. Inflammation-induced peripheral sensitization is usually transient and resolves after inflammation subsides. The role of sensitized primary sensory afferents in the symptoms of persistent or chronically recurrent abdominal pain states is not known. Evidence from mucosal biopsies of IBS patients, however, suggests neuroplastic remodeling of the epithelium. Such neuroplastic changes may affect the response properties of spinal and vagal afferent neurons.[1,5]

Infection and Microflora

A bacterial etiology of persistent abdominal pain has long been suspected (including a relationship between *Helicobacter pylori* infection of the stomach and functional dyspepsia, and the development of IBS-like symptoms following infectious gastroenteritis). Although in the great majority of patients a causal relationship between abdominal pain and acute or chronic infection cannot be established, it has been suggested that host–microbial interactions in vulnerable individuals during the early phase of the disorder may result in permanently altered immune or host cell responses, which then continue to play a role in the persistence of symptoms in the absence of the infection or inflammation. Several studies have reported the onset of IBS-like symptoms following established bacterial or viral infections of the GI tract. This so-called postinfectious IBS occurs in 10% of human patients with bacterial gastroenteritis.[1,6]

Epithelial-Immune Activation

Leukocyte infiltration and mucosal inflammatory cytokines are generally not found in the GI mucosa of the IBS patient. Instead,

enhanced release of neuropeptides from primary sensory nerve endings (such as substance P and calcitonin gene-related peptide), as well as the release of mast cell mediators (including serotonin, histamine, and proteases), has been implicated in the sensitization of primary afferent pathways. The release of nerve growth factor has also been impugned in the neuroplastic and morphologic changes of sensory and motor neurons of the colon. Such neuroplastic changes may play a role in the long-term symptoms of IBS long after the initial immune activation subsides.[1,5]

Mast Cells

Increased mast cell numbers or density, alterations in mast cell–nerve interactions, and increased release of mast cell mediators have been reported in the epithelial biopsy samples of IBS patients.[1,7] Mast cells can be activated by immunoglobulins, neuropeptides, and cytokines to secrete mediators without degranulation. They can release many signaling molecules, including histamine, serotonin, corticotropin-releasing factor (CRF), and proteases. Alterations in these signaling systems have been implicated in the pathophysiology of IBS, and mediator-specific receptor antagonists have been suggested as possible therapies. A particularly interesting aspect of mast cell regulation is the close juxtaposition of mast cells with noradrenergic, cholinergic, and peptidergic nerve endings in the villus epithelium (see Fig. 1-17). Persistent alterations in the spatial and functional relationships between mast cells and nerve endings are a plausible mechanism for recurrent abdominal pain.[1,7]

Epithelial Permeability

Increased epithelial permeability has been reported in many IBS patients, including animal species.[8] Multiple mechanisms of increased permeability have been proposed with differing underlying trigger mechanisms, including stressors and mucosal inflammation. Mast cell mediators, such as CRF and proteases, have been implicated in mediating permeability changes in the GI tract and in pain sensitization.[1,9]

Dysmotility

The concept that exaggerated and dysregulated contractile activity of the GI tract plays a role in the pathophysiology of chronic abdominal pain states has long been a central theme of IBS pathophysiology.[1] Colonic motor dysregulation has been unequivocally demonstrated in experimental canine IBD,[10] but not yet IBS.

Central Mechanisms

Enhanced Stress Responsiveness

First-symptom onset or symptom exacerbation in IBS has been linked to psychosocial stressors and enhanced visceral perception. Upregulation of central stress and arousal circuits has been postulated.[1,11] Central CRF-CRF_1 receptor signaling has been impugned in mediating some forms of acute and chronic stress-induced visceral hyperalgesia. Increased responsiveness of stress and arousal circuits is likely to contribute to the increased activity of the sympathetic nervous system observed in IBS patients, and may play a role in altered mast cell function.[7]

Central Pain Amplification

There are multiple mechanisms by which the central nervous system can modulate afferent signals from the viscera, including increased activity of endogenous pain facilitation and reduced engagement of endogenous pain inhibition. Endogenous pain modulation systems are likely to mediate the effects of affect, mood, and environmental context on pain perception.[11]

Neuroimmune Activation in the Spinal Cord

Visceral hyperalgesia is associated with activation of the glia following a psychological stressor. Activation of the glia can produce proinflammatory cytokines, such as tumor necrosis factor-α, and can result in the downregulation of the glutamate transporter on astrocytes, which, in turn, may lead to elevated synaptic glutamate. Both effects may result in an upregulation of the glutamate/*N*-methyl-D-aspartate receptor signaling system, thereby contributing to the development of central sensitization.[1,12]

Enhanced Brain Responses to Visceral Distention

In IBS patients, evidence for both increased engagement of endogenous pain facilitatory mechanisms and compromised engagement of endogenous pain inhibitory mechanisms have been reported.[1,13]

Enhanced Brain Responses to Expectation of Visceral Pain

Future-oriented worry and anxiety about abdominal symptoms play a prominent role in many human IBS patients. Alterations in prefrontal modulation of stress and arousal circuits may comprise the neurobiologic substrate underlying anxiety.[1,14]

Structural Brain Changes

Even though IBS by traditional definition excludes the presence of detectable structural changes, there is a growing body of evidence of structural (e.g., gray matter) abnormalities in patients with IBS. The mechanisms underlying such structural changes remain unclear, but excitotoxicity (related to enhanced glutamate signaling) and apoptosis (related to increased cytokine release) have been implicated.[1,15]

Clinical Manifestations of Irritable Bowel Syndrome

Humans

The main symptom of IBS is chronic or recurrent abdominal pain or discomfort associated with altered bowel habits. In general, women report IBS symptoms more often than men. Women are more likely to report IBS, bloating, constipation, chronic functional abdominal pain, sphincter of Oddi dysfunction, fecal incontinence, and pelvic floor dysfunction. Women and men report similar rates of functional esophageal symptoms and dyspepsia, while aerophagia and functional diarrhea are reported more often in men.[3] The Rome III criteria for the diagnosis of IBS were published in 2006,[16] the major categories of which are outlined in Box 41-1. The Rome III system is still largely based on symptom complexes rather than pathophysiologic parameters,[17] which has generated both enthusiasm and derision.[18,19] A general consensus has emerged around the need to validate disease-specific biomarkers as surrogate endpoints for drug development for a selective group of functional gastrointestinal disorders.[20,21]

Experimental Animal Studies[22,23]

Immobilization Stress

Restraint or immobilization procedures are the most extensively used models to study the physiologic and behavioral effects of stress exposure in laboratory animals. Immobilization procedures activate the hypothalamic–pituitary–adrenal (HPA) axis and the development of a pathophysiologic response in the brain and gut. Restraint procedures in mice and rats, for example, have been demonstrated to induce GI ulcers, altered GI motility, and altered epithelial permeability.[22,24]

Box 41-1 Rome III Classification of Functional Gastrointestinal Disorders

Functional Esophageal Disorders
Functional heartburn
Functional chest pain of presumed esophageal origin
Functional dysphagia
Globus

Functional Gastroduodenal Disorders
Functional dyspepsia
Postprandial distress syndrome
Epigastric pain syndrome
Belching disorders
Aerophagia
Unspecified excessive belching
Nausea and vomiting syndromes
Chronic idiopathic nausea
Functional vomiting
Cyclic vomiting syndrome

Functional Bowel Disorders
Irritable bowel syndrome
Functional bloating
Functional constipation
Functional diarrhea
Unspecified functional bowel disorder

Functional Abdominal Pain Syndrome
Functional gallbladder and sphincter of Oddi disorders
Functional gallbladder dysfunction
Functional biliary sphincter of Oddi disorder
Functional pancreatic sphincter of Oddi disorder

Functional Anorectal Disorders
Functional fecal incontinence
Functional anorectal pain
Chronic proctalgia
  Levator ani syndrome
  Unspecified functional anorectal pain

Functional defecation disorders
Dyssynergic defecation
Inadequate defecatory propulsion

Functional Disorders: Neonates and Toddlers
Infant regurgitation
Infant rumination syndrome
Cyclic vomiting syndrome
Infant colic
Functional diarrhea
Infant dyschezia
Functional constipation

Functional Disorders: Children and Adolescents
Vomiting and aerophagia
Adolescent rumination syndrome
Cyclic vomiting syndrome
Aerophagia
Abdominal pain–related functional gastrointestinal disorders
Functional dyspepsia
Irritable bowel syndrome
Abdominal migraine
Childhood functional abdominal pain
Constipation and incontinence
Functional constipation
Nonretentive fecal incontinence

Source: Abstracted from references 3 and 16.

Captivity

Cotton-top tamarins (*Saguinus oedipus*) develop a spontaneous ulcerative colitis that bears resemblance to the human disorder. The frequency and severity of colitis in this species is significantly higher in animals in captivity compared with animals living in their natural environment. Psychological stress because of captivity is believed to play an important role in the pathogenesis of ulcerative colitis in this species.[22,25]

Water Avoidance

Water avoidance is a model of chronic mild stress used primarily in rodents. Water avoidance procedures activate the HPA axis inducing a reduction in food intake and weight loss, as well as several GI pathophysiologic changes including increased intestinal ion secretion, increased intestinal and colonic permeability, and hyperplasia and activation of GI mucosal mast cells.[22,26]

Sleep Deprivation

Partial sleep deprivation is another model of psychological stress in rodents that has been shown to induce bacterial translocation, and to the development of gastric ulcers by decreasing mucosal blood flow.[22,27]

Neonatal Maternal Separation and Early Weaning

Neonatal maternal separation is a model of IBS in that it activates the neonatal HPA axis and increases colonic secretion and permeability leading to impaired host defense to luminal bacteria. Early life trauma increases the risk of GI dysfunction in adulthood. It predisposes adult rats to spontaneous and mild stress-induced visceral hypersensitivity and intestinal barrier dysfunction, as well as increased susceptibility to chemical-induced colitis.[22,28]

Thermal Injury

Burn injury is associated with intestinal damage, which ranges from mild transient ileus to lethal necrotizing enterocolitis. Burn injury–induced intestinal barrier dysfunction permits bacterial translocation to mesenteric lymph nodes and systemic circulation. Thermal injury also triggers activation of the HPA axis.[22,29]

Companion Animals

A large bowel diarrheal syndrome similar to IBS in humans has been reported in the dog.[4] Affected animals have clinical signs of diarrhea, excessive fecal mucous, hematochezia, and tenesmus. Abdominal pain and weight loss are occasionally reported by pet owners. Multiple diet changes and empirical medications fail to relieve clinical signs. Medical investigation is negative for bacterial and other pathogen infections, colitis-type inflammatory bowel disease, and colonic neoplasia, and the term *chronic large bowel diarrhea* has been applied to the disorder. Dogs affected with this syndrome respond to the feeding of a highly digestible diet supplemented with soluble fiber.[4]

Table 41-1 Outline of Medical Management for Irritable Bowel Syndrome in Companion Animals

Medical Principle	Clinical Sign	Classification	Examples	Dose
Antidiarrheal agents	Diarrhea	Prostaglandin synthetase inhibitor	Sulfasalazine	Cats: 10 to 20 mg/kg q12h Dogs: 10 to 40 mg/kg q8h
	Diarrhea	μ,δ-opioid agonists	Loperamide	Dogs: 0.08 to 0.2 mg/kg PO Cats: 0.08 to 0.16 mg/kg PO, q6 to 8h PRN
	Diarrhea	5-HT_3 serotonergic antagonists	Dolasetron	0.6 to 1.0 mg/kg PO, q12 to 24hr (as antiemetic)
	Diarrhea	α_2-Noradrenergic agonists	Clonidine	5 to 10 μg/kg PO, q8 to 12h PRN
Antibiotics	Diarrhea	Macrolide antibiotics	Tylosin	7 to 15 mg/kg q12 to 24h
		Nitroimidazole antibiotics	Metronidazole	Dog: 12 to 15 mg/kg PO q8 to 12h Cat: 10 to 25 mg/kg per day PO
Probiotics	Diarrhea	Lactobacillus	*Lactobacillus rhamnosus*	Many formulations, label recommendation
		Bifidobacterium	*Bifidobacterium* spp.	Many formulations, label recommendation
Laxative agents	Constipation	Bulk laxative	Psyllium	1 to 4 tsp mixed with food, q12 or 24h
		Emollient laxative	Docusate	50 mg PO, q24h
		Lubricant laxative	Petrolatum	1 to 5 mL PO, q24h
		Hyperosmotic laxative	Lactulose	1 ml per 4.5 kg PO q8h to 24h
		Stimulant laxative	Bisacodyl	5 mg PO, q24h
Prokinetic agents	Constipation	5-HT_4 serotonergic agonists	Mosapride	0.25 to 1.0 mg/kg PO, q12h
			Prucalopride	0.01-0.2 mg/kg PO q8 to 12h PRN
Antispasmodic agents	Pain, spasm	Muscarinic cholinergic antagonists	Aminopentamide	0.01 to 0.03 mg/kg PO, q8 to 12h
Antigas agents	Bloat, eructation, flatulence	Antifoam surface-acting agents	Simethicone	5 mL (liquid form) PO PRN

Medical Management

The treatment of IBS is largely dependent upon the predominating clinical sign, for example, diarrhea or constipation (Table 41-1).[2,30]

Diet

In the study of chronic idiopathic large bowel–type diarrhea in 37 dogs, most had an excellent or very good response to supplementation of soluble fiber (psyllium) in a highly digestible diet.[4] The median initial dose of psyllium was 2 tablespoons per day, with a median of 1.33 g of psyllium per kilogram of body weight per day. Fiber has multiple effects on gastrointestinal function, including increasing the fecal water content, decreasing the intestinal transit time, and increasing the frequency of defecation. Short-chain fatty acids (acetate, butyrate, propionate) derived from fiber fermentation have been shown to act as metabolic fuel for the colon, and to directly stimulate colonic motility.

Antidiarrheal Agents

Antidiarrheal agents (e.g., prostaglandin synthetase inhibitors, μ,δ-opioid agonists, 5-HT_3 serotonergic antagonists, and α_2-noradrenergic agonists; see Chapter 34) may be useful in the treatment of diarrhea-predominant IBS. Of these four drug classifications, loperamide may be the most effective in restoring smooth muscle segmentation, prolonging intestinal transit time, and improving fecal consistency.

Laxative Agents

The bulk, emollient, lubricant, hyperosmotic, and stimulant laxative agents (see Chapter 50) are generally safe, well tolerated, and effective in the treatment of constipation-predominant IBS.

Antispasmodic Agents

The antispasmodic agents include the musculotropic antispasmodics (mebeverine and pinaverine) and muscarinic cholinergic antagonists (dicyclomine and hyoscyamine). Safe and effective doses have not been established for any of these drugs in any of the companion animals. Aminopentamide, a nonselective muscarinic cholinergic antagonist, has been used in dogs at a dose of 0.01 to 0.03 mg/kg BID-TID, and may be useful as an antispasmodic agent.

5-HT_3 Serotonergic Antagonists

Alosetron and cilansetron are selective 5-HT_3 serotonergic antagonists that were developed for treatment of human diarrhea-predominant IBS. Because of severe side effects, specifically ischemic colitis and severe constipation, they are no longer available or recommended for the treatment of IBS. Ondansetron, granisetron, tropisetron, and dolasetron are members of the same classification that have been used for their antiemetic and antidiarrheal properties in companion animals.

5-HT_4 Serotonergic Agonists

Tegaserod was approved by the FDA for the treatment of constipation-predominant IBS in women. Following reports of untoward cardiac effects, it, like cisapride, was removed from most

international markets. Mosapride and prucalopride are the two most effective currently available 5-HT_4 agonists. They accelerate transit through binding of presynaptic 5-HT_4 receptors and depolarization of cholinergic neurons. Their role in reducing visceral sensation is less well understood.

Antibiotics

Small intestinal bacterial overgrowth (SIBO) has been theorized to play a role in some IBS patients. Bacterial overgrowth has long been known to disrupt epithelial absorption and secretion, but recent data also suggest that SIBO may be an important activator of mucosal-based immunity.[31] Activation of proinflammatory cytokines by bacteria may alter epithelial cellular function, enhance nociceptive pain signaling, and alter intestinal motility—all purported pathophysiologic mechanisms in IBS. Antibiotics most effective in the treatment of SIBO include tylosin, metronidazole, and tetracycline.

Probiotics

Probiotics are hypothesized to work IBS by several different mechanisms. These include a shift from a proinflammatory cytokine profile to an antiinflammatory cytokine profile, reduction of bile acid delivery to the colon, and restoration of GI motility.[2,30] Treatment with *Lactobacillus* sp. or *Bifidobacterium* spp. is associated with a reduction in abdominal pain and discomfort.[2,30]

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CHAPTER 42

Behavioral Intervention

Diane Frank

Physiologic Translation of Stress into Gastrointestinal Signs in Dogs

Moberg states that the term *stress* has been used so broadly in biology that no clear definition of stress has emerged.[1] Stress is defined as the biologic response elicited when an individual perceives a threat to its homeostasis. Threats may be real (physical) or perceived (psychological),[2] and may originate from the outside world or from within. Interoceptive stressors (e.g., gut infection, mucosal inflammation, or internal hemorrhage) may be seen as simple reflex responses, mediated at a subcortical level by the system involved in the processing of visceral information. Exteroceptive stressors (psychological), on the other hand, engage circuits in the limbic forebrain including the lateral and medial prefrontal cortex, hippocampus, and amygdala.[2] These responses are adaptive and serve to maintain the stability of the internal environment and ensure the survival of the organism. In the healthy individual, the physiologic response systems are rapidly turned on and off, synchronizing the physiologic stress response to the duration of the stressor, and limiting exposure time of the organism to potentially harmful effects of the stress response.[2] There are situations, however, in which the severity or duration of the stressor and resulting physiologic responses can cause damage, exacerbate existing disease processes, or predispose the individual to acquire new disease. These responses become maladaptive.

Researchers have relied on a variety of endocrine, behavioral, autonomic nervous system, and immunologic parameters to assess stress.[3-11] In fasted dogs, 90-dB music produces inhibition of gastric motility along with increases in heart rate and plasma cortisol,[12] and is therefore considered an example of acoustic stress. One hour of acoustic stress, associated with a fourfold increase in plasma cortisol, delays the appearance of the next gastric, but not jejunal, migrating motor complex (MMC) by 75%. Acoustic stress–induced inhibition of the gastric MMC is completely abolished with prior administration of diazepam (0.2 to 0.5 mg/kg IM) or muscimol (10 μg/kg IV) and partially abolished with lower doses of diazepam (0.1 mg/kg). Gastric MMC inhibition is unaffected by naloxone (0.1 mg/kg IM), phentolamine (0.2 mg/kg IV), or propranolol (0.1 mg/kg IV) treatment. Muscimol, a GABAergic receptor agonist, and diazepam (a benzodiazepine that interacts at the receptor level and potentiates the effects of endogenous γ-aminobutyric acid [GABA]) may act at the central or peripheral level to block the effect of noise on gastric motility. In a different study,[13] intracerebroventricular administration of ovine corticotropin-releasing factor (CRF) (100 ng/kg) in dogs also delayed the appearance of gastric MMC without affecting jejunal motility and this effect was not antagonized by previous administration of diazepam or muscimol. The effects of acoustic stress and CRF on gastric motility were both abolished after bilateral thoracic vagotomy. Consequently, the suppressive action of diazepam and muscimol on noise-induced gastric hypomotility may be related to blockade of the acoustic stress–induced CRF release.

A high prevalence of gastric lesions have been reported in racing Alaskan sled dogs.[14] Endoscopic examination of 70 dogs that participated in the 2001 Iditarod race revealed that 34 dogs (48.5%) had gastric ulceration, erosion, hemorrhage, or some combination of these findings. Gastric disease in racing sled dogs has been attributed to bacterial pathogens, ingested foreign bodies, ulcerogenic drugs (usually banned during races), exercise-induced ischemia (although mesenteric blood flow was unchanged during vigorous exercise in one study[15]), and stress. Exercise on a treadmill at low and high intensity (4.2 miles/h with a 6% or 20% incline) has been shown to increase serum cortisol concentrations in dogs.[16]

Interaction of Corticotropin-Releasing Factor and Monoaminergic Systems

CRF is the principal neuroendocrine substance regulating adrenocorticotropic hormone secretion, and is involved in inflammatory responses of the gut via vagal and peripheral pathways.[17] CRF mediates stress influences on the gastrointestinal (GI) tract either centrally (hypothalamic–pituitary–adrenal [HPA] axis) or peripherally via local CRF-based paracrine activity. CRF is also implicated in many behavioral responses. Physiologic and behavioral responses observed during stress can be induced by exogenous administration of CRF and α_1-adrenergic agonists.[18] Psychological stress triggers sympathetic activation and favors inflammatory reactions, which is associated with concurrent activation of the HPA axis. To date, it is unclear whether stress is the cause or consequence of inflammatory bowel disease development in humans.[17]

CRF immunoreactivity has been demonstrated in the raphe nuclei and the locus coeruleus, two areas of origin of the major serotonergic and noradrenergic pathways in the brain. Thus CRF may play a role in modulating these monoaminergic systems that have been implicated in the pathophysiology of depression and anxiety.[19] Dysregulation of signaling by CRF may contribute to the etiology and pathophysiology of stress-related neuropsychiatric disorders in people. Activation of serotonergic systems plays an important role in several behaviors that are influenced by CRF, including behavioral arousal, motor activity, and facilitation of anxiety-related

behaviors. In a recent study in rats,[20] intracerebroventricular injections of CRF (1 μg) increased several measures of behavioral activity, including total activity, locomotion, and spontaneous nonambulatory motor activity such as visual scanning of the environment, head movements associated with sniffing, shifts in body position, and lateral or vertical movements of the forelimbs. Treatment with fluoxetine,[20] a selective serotonin reuptake inhibitor (SSRI), prevented CRF-induced increases in spontaneous nonambulatory motor activity at all doses (0.1 mg/kg; 1 mg/kg; 10 mg/kg). These effects were most apparent during a 40- to 70-minute time period when CRF-induced behavioral activity was most pronounced. The data of this study support an interaction between CRF and serotonergic systems in the regulation of emotional behavior. These data do not exclude a role of other brainstem neuromodulatory systems such as the noradrenergic systems. Given that the behavioral consequences of CRF are similar to the behavioral consequences of anxiogenic drugs,[21] therapeutic effects of fluoxetine and other SSRIs may involve attenuation or prevention of the effects of aversive or anxiogenic stimuli on CRF-induced stress- or anxiety-related emotional states and behavior.[20]

Anecdotal Information

Marion,[22] a private practitioner, compiled retrospective data on 20 dogs with intermittent recurring bouts of vomiting and 20 control dogs without vomiting. Minimal medical workup was obtained for all vomiting dogs (serum chemistry, abdominal radiography, upper GI endoscopy and biopsies). Between episodes of vomiting, dogs were clinically normal, as is observed in people suffering from cyclic vomiting syndrome.[23] Diagnosis in all cases was assumed to be a functional GI disorder. Vomiting dogs relapsed regularly regardless of treatment, including highly digestible diets and antisecretory medication (e.g., cimetidine). The author completed a grid entitled Emotional Disorder Evaluation in Dogs (EDED)[24] for assessment of emotional disorders in all 40 dogs. Marion found that dogs in the vomiting group had significantly higher scores than the control group suggesting that these dogs were more likely to have concurrent behavioral anxiety disorders than control dogs. The EDED scale has not yet been validated in other studies. Marion also reported that she had treated some vomiting dogs with anxiolytic medications; however, she did not specify duration of treatment, drugs, or dosages.

Future Research

Stress responses may result from anxiety.[25] Anxiety is an emotional state associated with adaptive physiologic and behavioral responses and only becomes pathologic when it is exhibited in contextually inappropriate situations or in more natural ones but to a level that impairs effective adaptive responses.[21] Anxiety disorders (separation anxiety, noise phobia, generalized anxiety) have been described in companion animals.[26] Development of a validated anxiety scale would be a valuable tool to objectively score anxiety in dogs and cats. Placebo-controlled crossover studies in which a particular antianxiety medication could be given alone or concurrent with other treatments for specific GI disorders in "anxious" and "not anxious" canine patients could generate new information. Medications that could be considered would include SSRIs (fluoxetine,[20] sertraline, fluvoxamine), tricyclic antidepressants (amitriptyline,[23] clomipramine), benzodiazepines (alprazolam,[19] diazepam,[12] clonazepam), and perhaps even α_2-adrenergic agonists (clonidine[23,27]).

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CHAPTER 43

Chelating Agents

David C. Twedt

A chelating agent is a ligand (or drug) that binds to a metal ion through two or more sites to form a metal chelate that is removed from the body, usually through renal excretion. Copper (Cu) chelators are used in veterinary gastroenterology for the treatment of abnormal Cu accumulation in the canine liver.[1]

Pathophysiology of Copper

The liver is the central metabolic organ for the regulation of Cu body stores.[2] Cu enters the body through the diet and approximately 30% is absorbed by the upper small intestine with the majority of the Cu passing out through the feces. Although the exact details of intestinal Cu absorption are not completely understood, Cu is passively taken up by intestinal epithelial cells, bound to the cytosolic protein metallothionein, and actively transported into the circulation bound to either albumin or transcuprein. Cu is then transported to the liver where it is stored, mobilized to peripheral tissues, or excreted from the body.[2] Hepatic Cu is either complexed with ceruloplasmin a transport protein, incorporated in hepatic cellular pathways, or bound with metallothionein within the liver. Metallothioneins are cysteine-rich, cytosolic proteins that function to store Cu and protect the hepatocyte from Cu toxicity.[2] In health, approximately 80% of the Cu that is absorbed is eventually excreted into the bile.

Normal hepatic Cu concentrations in dogs are maintained at approximately 200 to 400 μg/g dry weight liver.[3] When Cu concentrations increase to levels exceeding hepatic metallothionein's complexing capabilities, direct hepatic damage results, primarily through formation of oxygen free radicals causing either hepatocellular necrosis or apoptosis.[4] The abnormal accumulation of hepatic Cu in the dog results from either a primary metabolic defect in hepatic Cu metabolism or secondary to cholestatic liver disease resulting in impaired biliary Cu excretion.[1] Box 43-1 lists dog breeds documented or suspected of having a hereditary defect in Cu metabolism. Thus far, only the affected Bedlington Terrier has been identified as lacking a specific gene on chromosome 10 encoding a small cytosolic protein termed COMMD1 (MURR1) that is involved in hepatic Cu transport and biliary excretion.[5] The other breeds listed in Box 43-1 do not accumulate hepatic Cu to the same extent as the affected Bedlington Terrier and most likely have a different genetic alteration in Cu metabolism. Regardless of the cause of Cu accumulation, therapy is directed at reducing hepatic Cu concentrations into the normal reference range using Cu-chelating agents. Depending on the breed, hepatic Cu concentrations, and extent of liver pathology, the choice of chelators and the dose and duration of therapy vary.

Copper Chelators

Cu-chelating agents are drugs that have a high affinity for Cu and when bound as the metal-chelator complex are excreted through the urine. When given for prolonged periods of time, chelating agents are effective in depleting hepatic Cu concentrations. Cu-chelating agents used clinically or experimentally in dogs include penicillamine, the tetramines (trientine and 2,3,2-tetramine), and tetrathiomolybdate.

Penicillamine

Penicillamine is a thiol, a compound with a sulfhydryl group, making the molecule an active metal-chelating agent with a high affinity for Cu.[6] Penicillamine was first discovered in the early 1950s when J.M. Walshe identified this unusual urinary metabolite in a human patient treated with penicillin.[7] Walshe dosed himself with penicillin and found that he also excreted penicillamine in his urine. He quickly discovered that this compound had chelation properties with the thiol group because it would bind to iron. Following a dose of penicillamine, Walshe discovered he had an increase in urinary Cu excretion. Those early studies also found that the L isomer of penicillamine was toxic to growing rats but the D isomer did not have this effect.[8] Once an adequate supply of the D-penicillamine was obtained, a patient with Wilson's disease, a hereditary disease in which Cu accumulates in the tissues, was treated and showed a positive response to therapy with increased urinary Cu excretion. Over the last 50 years D-penicillamine has been the primary Cu chelator used in the treatment of Wilson's disease.[9]

Mechanism of Action

By virtue of its sulfhydryl groups, penicillamine chelates a number of heavy metals, including Cu. It forms a stable water-soluble complex with Cu that is excreted through the kidneys. In vitro studies show 1 atom of Cu combines with 2 molecules of penicillamine, which in theory means 1 g of penicillamine would be followed by a maximum excretion of 200 mg of Cu.[9] Clinically, Cu excretion from a 1-g dose results in the loss of only several milligrams of Cu. Prolonged penicillamine therapy in Wilson's disease patients eventually results in a decline in urinary Cu excretion in spite of continued elevations in hepatic Cu concentrations. However, these patients for some reason continue to improve both clinically and in their liver histology.[10] There is now speculation that there may actually be several pools of hepatic Cu in Wilson's disease, some of which may not be removed by the drug. It is postulated that penicillamine may detoxify the remaining Cu in the liver, either by

Box 43-1 Current Breeds That Are Associated with Increased Copper Concentrations

Bedlington Terrier
Doberman Pinscher
West Highland White Terrier
Skye Terrier
Labrador Retriever
Dalmatian

Box 43-2 Some of the Reported Adverse Effects Associated with Penicillamine Therapy in Humans and Those Identified in Dogs

Dermatologic (pruritus, systemic lupus erythematosus–like syndrome)*
Gastrointestinal (vomiting, diarrhea)*
Hepatitis
Hematologic (anemia, bone marrow suppression)
Renal disease (glomerulopathy, renal failure)*
Central nervous system (tinnitus, peripheral neuropathy)

*Indicates adverse effects reported in dogs.

the formation of a hepatic chelate that is nontoxic or more likely by inducing the synthesis of hepatic metallothionein proteins that then bind and sequester Cu in the liver in a nontoxic form. Penicillamine has also been reported to have a greater affinity for Cu in tissues than in the blood.[10]

Penicillamine will also decrease cystinuria and has been used to prevent the formation of cystine calculi in dogs.[11] It combines chemically with cystine to form a stable, soluble, readily excreted complex. Penicillamine also interferes with the formation of crosslinks between procollagen molecules, thereby exerting some weak, antifibrotic activity.[10] Penicillamine may also have immunomodulatory effects and has been demonstrated to reduce immunoglobulin M rheumatoid factor and T-cell activity in human patients with rheumatoid arthritis.[10] The clinical relevance of penicillamine immunosuppression in dogs is unknown.

Dosage and Toxicity

For management of Cu-associated hepatopathies in the dog, a dose of 10 to 15 mg/kg q12h of D-penicillamine (Cuprimine [capsules] or Depen [tablets]) is given orally.[1] It should be administered on an empty stomach, at least 1 hour before meals or 2 hours after meals, and at least 1 hour apart from any other drug or food. This permits maximum absorption and reduces the likelihood of inactivation by chelating substances within the gastrointestinal tract.

Side effects from penicillamine therapy are common in humans, with an incidence estimated as high as 30% to 50% of untoward reactions, the most common being dermatologic (Box 43-2).[11] There may be some cross-sensitivity between penicillin and penicillamine in some patients. In dogs, nausea and vomiting are the most common side effects and are observed in approximately 30% of patients. These clinical signs may be minimized by reducing the dose or dividing the daily dose into three or four smaller doses. The reduced dose can usually be increased gradually over time. Alternatively, the drug can be given with a small amount of food; however, this may reduce absorption as a consequence of intestinal chelation. Very few other adverse effects have been observed or reported in dogs. The author observed skin hypersensitivity reactions (Figure 43-1 *A* and *B*) in several dogs that all have resolved with discontinuation of therapy. The author is also aware of a few anecdotal reports of renal disease following therapy. Penicillamine is reported to cause depletion of the vitamin B_6 (pyridoxine) in humans. Although this has not been observed in dogs, B-vitamin supplementation during long-term therapy may be advisable.

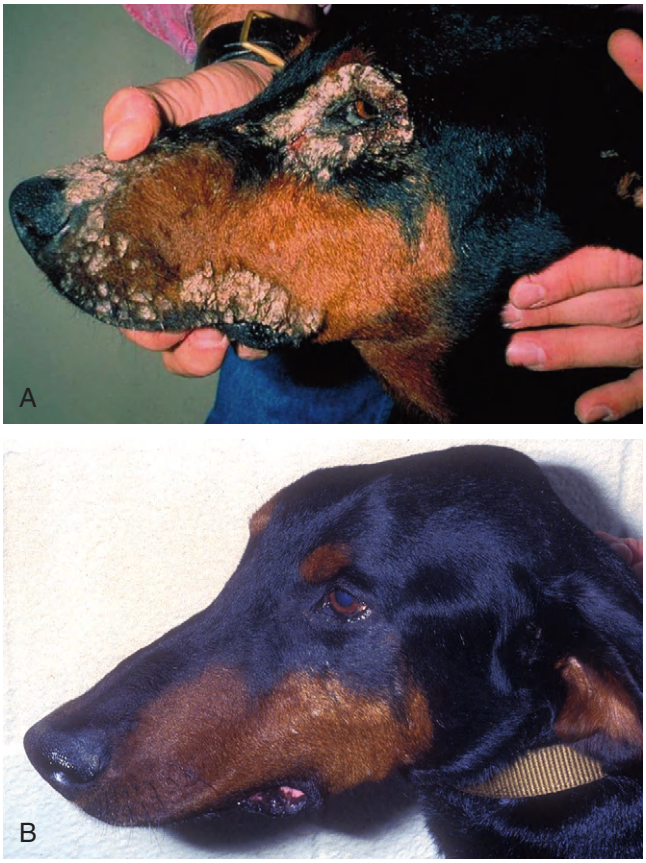

Figure 43-1 **A,** A 5-year-old female Doberman Pinscher with perioral and periocular dermatitis that developed 1 month after starting therapy with penicillamine. **B**, There is resolution of the dermatitis 2 months after discontinuation of penicillamine therapy.

Long-term Cu-chelator therapy given to a dog that is incorrectly diagnosed as having Cu hepatotoxicity can result in adverse side effects. This has been reported with trientine therapy in one dog and the author has observed similar findings in one Bedlington Terrier treated with penicillamine.[12] Anorexia, vomiting, and weight loss was observed clinically with marked elevations in serum liver enzyme activity. Both dogs had marked reductions in hepatic Cu concentrations. Discontinuation of chelation therapy resulted in clinical improvement. Consequently, it is imperative to correctly diagnose a Cu storage disease based on biopsy and hepatic Cu quantitation before starting therapy and to measure hepatic Cu concentrations during therapy.

Clinical Application

Penicillamine is the treatment of choice for Bedlington Terriers with Cu-associated hepatopathy and this therapy has been documented to be effective in removing hepatic Cu. One study of affected Bedlington Terriers treated with either placebo, penicillamine, trientine, or 2,3,2-tetramine for a 6-month period found the

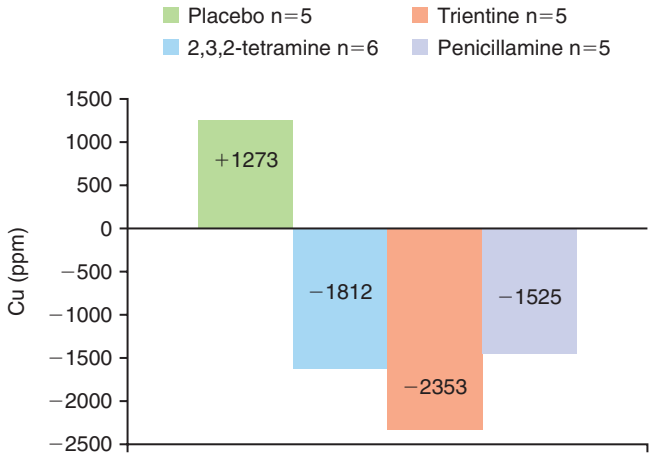

Figure 43-2 Changes in hepatic copper concentrations (µg/g dry weight) in affected Bedlington Terriers in a randomized placebo-controlled study treating with placebo, penicillamine, trientine, or 2,3,2-tetramine for 6 months. (Twedt DC: Diagnosis and management of copper associated liver disease in dogs. *Eur J Comp Gastroenterol* 2:7, 1997.)

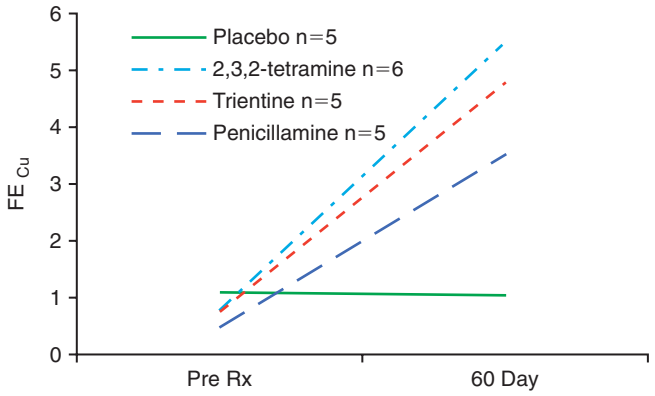

Figure 43-3 Changes in urinary fractional excretion of copper (FE_{Cu}) in affected Bedlington Terriers in a randomized placebo-controlled study treating with placebo, penicillamine, trientine, or 2,3,2-tetramine for 6 months. FE_{Cu} = urine copper/serum copper × serum creatinine/urine creatinine. (Twedt DC: Diagnosis and management of copper associated liver disease in dogs. Eur J Comp Gastroenterol 2:7, 1997.)

penicillamine treatment group had a mean decrease in hepatic Cu of 1529 µg/g dry weight liver, while the placebo group had a mean increase in hepatic Cu of 1273 µg/g dry weight liver (Fig. 43-2).[13] There was also a significant increase in urinary fractional excretion of Cu in the penicillamine group at 2 months posttreatment (Fig. 43-3).[13] A second, unpublished, long-term study was performed by the author to evaluate the effectiveness of penicillamine therapy in affected Bedlington Terrier littermates throughout their life (Fig. 43-4). Four dogs were treated with penicillamine and for two dogs the owners elected no further therapy. The treated dogs had a significantly lower hepatic Cu concentrations at death (mean: 1633 µg/g dry weight liver), whereas the two untreated dogs died having approximately four times higher hepatic Cu concentrations (mean: 6444 µg/g dry weight liver). The treated dogs died from other causes and had minimal inflammatory hepatic changes on histology. The concentrations of Cu in the treated dogs would be toxic to most other dogs. This is a similar finding in humans with Wilson's disease treated long-term with penicillamine. It appears

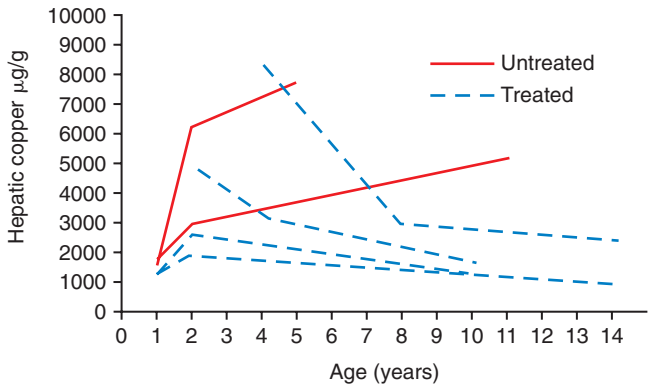

Figure 43-4 Effects of long-term penicillamine therapy in Bedlington Terrier dogs. Each line represents an individual dog.

hepatic Cu concentrations decline to a certain level after which penicillamine's "de-coppering" effect becomes diminished despite the apparent protective effect of the drug. This effect is thought to be the result of penicillamine's induction of hepatic metallothionein that sequesters the Cu. Bedlington Terriers appear to require lifetime Cu-chelation therapy to maintain that protective effect.

Penicillamine therapy has been reported in other breeds having Cu-associated hepatotoxicity. The author believes chelation therapy should be instituted in those dogs when hepatic Cu concentrations approach 750 to 1000 µg/g dry weight liver. In one 4-month study of therapy using penicillamine in five Doberman Pinschers having subclinical hepatitis and abnormal hepatic Cu concentrations (mean concentration: 1036 µg/g dry weight liver), affected animals had a significant decrease in mean hepatic Cu concentration of 407 µg/g dry weight with a significant improvement in liver pathology.[14] In another, larger, placebo-controlled study of 40 affected Labrador Retrievers with Cu-associated hepatitis, treatment resulted in a mean reduction of 863 µg/g dry weight Cu in the treated group (mean pretreatment Cu concentration was 1511 µg/g), whereas the placebo-treated group had no significant change in Cu concentrations.[15] Twenty-three percent (5/12) of the treated dogs in this study had gastrointestinal side effects, with three requiring dosage changes or administration of the drug with a small amount of food.

It appears that affected breeds other than the Bedlington Terriers do not accumulate hepatic Cu to such high concentration and consequently may not require long-term chelator therapy. Chelation for 4 to 6 months may be adequate to de-copper the liver of other breeds such as the Labrador Retriever and Doberman Pinscher, but the length of therapy should only be determined following repeated liver biopsies and Cu quantitation. Following clinical improvement, intermittent chelation therapy or oral zinc therapy to prevent further intestinal absorption of Cu may be sufficient.

Trientine

Trientine is a triethylene tetramine or 2,2,2-tetramine used as an alternative Cu chelator in humans that do not tolerate penicillamine therapy.[16]

Mechanism of Action

The exact mechanism of action of trientine is poorly understood and data on the pharmacokinetics of trientine is not available. Dosage adjustment recommendations are based upon clinical use of the drug and response to therapy. In experimentally Cu-loaded rats, trientine and penicillamine induced a similar cupruresis.[17] Trientine

appears to have a cupruretic effect similar to penicillamine in humans although trientine may mobilize a different Cu pool.[10] Trientine is thought to have a greater affinity for serum Cu, whereas penicillamine may be more effective in mobilizing Cu from tissue sites. Following trientine therapy, urinary Cu excretion increases in humans with Wilson disease.[10] It is not clear if trientine has other hepatoprotective properties beyond Cu chelation. Trientine and zinc are frequently combined in the therapy of Wilson's disease patients. Trientine has been shown to suppress of angiogenesis in animal studies and might be useful clinically as a chemopreventive agent.[18]

Dosage and Toxicity

Trientine (Syprine) is administered in dogs at a dose of 10 to 15 mg/kg q12h PO. It should be given on an empty stomach, at least 1 hour before meals or 2 hours after meals, and at least 1 hour apart from any other drugs or food. This permits maximum absorption and reduces the likelihood of inactivation by metal binding within the gastrointestinal tract. In Europe, trientine is currently available only as a designated orphan drug.

Reported side effects of trientine therapy are few and most humans and dogs seem to tolerate the drug without problems. The author has seen nausea and vomiting develop in a few dogs following therapy. The gastrointestinal signs can be alleviated by decreasing the dose with increased frequency of administration or by giving the drug with a small amount of food.

Clinical Application

Trientine is often prescribed for dogs that cannot tolerate penicillamine. When trientine was given to normal dogs at a dose of 300 mg per day for 23 days, there was a significant cupruresis without changes in serum Cu, urine zinc, or iron concentrations.[19] Trientine was also compared with penicillamine in a placebo-controlled study in affected Bedlington Terriers and showed a significant decrease in hepatic Cu concentrations and a significant increase in urinary fractional excretion of Cu with both drugs compared with placebo (see Fig. 43-2).[13] Trientine caused a mean Cu reduction of 2353 µg/g dry weight liver and no side effects were observed in seven treated Bedlington Terriers over the 6-month course of therapy.[13]

Experimental Chelators

2,3,2-Tetramine

2,3,2-Tetramine is an experimental drug having a similar structure to trientine but reported to be a more potent Cu chelator.[20] As compared with trientine therapy in normal dogs, 2,3,2-tetramine resulted in a four to nine times greater cupruresis.[21] In five treated Bedlington Terriers there was a significant (3000 µg/g) dry weight reduction in hepatic Cu over a 200-day course of therapy and a 12 times increase in 24-hour urine Cu output with no significant change in serum Cu, zinc, or iron levels.[22] These dogs showed a reduction in hepatic lysosomal Cu content based on rhodanine stain and improvement in the distribution and severity of morphologic damage. In a second study treating affected Bedlington Terriers, there was a significant mean reduction in weight liver Cu concentration of 1812 µg/g over 6 months of therapy (see Fig. 43-2).[13] There was no observed evidence of toxicity using this drug in these dogs. Because of the drug's solubility characteristics, the author treated two critical Bedlington Terriers with Cu-associated hemolysis using an intravenous formulation with good success. This compound is not commercially available.

Tetrathiomolybdate

As an experimental drug, tetrathiomolybdate appears be beneficial in the treatment of Wilson's disease patients; however, information on long-term therapy and toxicity studies are limited.[23] It is considered the drug of choice for Wilson's disease patients having Cu-associated neurologic signs. The drug acts by forming a tripartite complex with Cu and proteins. Given with food, tetrathiomolybdate binds dietary Cu and endogenously secreted Cu with food proteins and prevents absorption of the complexed Cu. Given without food, tetrathiomolybdate is absorbed into the blood where it complexes Cu to albumin making the Cu unavailable for cellular uptake. It also is believed to mobilize hepatic metallothionein-bound Cu promoting bile excretion but not urinary Cu excretion. Generally, humans with Wilson's disease are dosed by both giving the drug with meals and also between meals.[23]

There are no reported dog studies using tetrathiomolybdate. Because it is recommended for Cu-associated neurologic signs, and because dogs do not develop Cu-associated neurologic disease, it may have limited benefit. This drug may also not be beneficial in treating Bedlington Terriers or other breeds having defects in biliary Cu excretion as biliary Cu excretion is one of the drug's modes of action.

Other Chelators

Other chelators used in veterinary medicine include disodium calcium ethylenediamine tetraacetate (EDTA) used to treat lead poisoning, dimercaprol (BAL) used for arsenic and mercury toxicity, and deferoxamine used for iron toxicity and ischemia–reperfusion injury. Experimental animal studies evaluating these chelators found no appreciable increase in urinary Cu excretion.[24,25] Consequently, these drugs are not likely beneficial in the management of Cu-associated hepatotoxicity.

Iron chelators are indicated in conditions associated with hemochromatosis, a disease associated with abnormal hepatic iron concentrations. Hepatic iron overload results in inflammatory hepatic change and cirrhosis similar to the mechanisms caused by Cu. In humans, hemochromatosis is either a genetic based abnormal iron metabolism disorder or an acquired condition observed with certain types of chronic anemia in which patients require many blood transfusions. Deferoxamine is the primary drug used for iron chelation. A primary genetic hemochromatosis has not been documented in the dog; however, secondary acquired hemochromatosis has been reported associated with multiple blood transfusions, in Basenji dogs with pyruvate kinase deficiency, and from iatrogenic iron administration.[26] One dog that had been treated with chronic blood transfusions for aplastic anemia subsequently developed iron-associated liver cirrhosis and failed to respond to deferoxamine therapy.[26] It is not uncommon to identify elevations in hepatic iron concentrations in dogs with chronic inflammatory hepatic changes or portal systemic shunts.[3] In inflammatory liver disease, iron accumulation is thought to be caused by the release of iron from necrotic hepatocytes with its sequestration in macrophages. The sequestered iron is thought to be relatively inert and specific iron chelation therapy does not appear to be necessary.

Adjunct Therapy

Zinc Therapy

Zinc therapy decreases intestinal absorption of dietary Cu by inducing synthesis of an intestinal epithelial cell protein metallothionein. Cu binds more tenaciously to the increased metallothionein than does zinc and prevents its intestinal movement into the blood.[10]

Metallothionein-bound Cu is eventually lost into the feces when intestinal epithelial cells die and are sloughed into the lumen. In essence, there is a mucosal block in Cu absorption. There is also evidence that zinc therapy decreases hepatic stores of Cu and induces production of hepatic metallothionein which may be hepatoprotective.[27,28] Zinc therapy in two West Highland White Terriers and two Bedlington Terriers with Cu hepatotoxicity resulted in a significant reduction in hepatic Cu concentrations.[29] The response was slow with the process taking several years to achieve a maximal therapeutic response. Early human studies involving a combination of zinc and chelator therapy found no benefit over single therapy suggesting that chelator most likely binds the zinc in the intestinal tract. More recently, however, patients with Wilson's disease and penicillamine intolerance are sometimes treated with a combination of trientine and zinc with apparently good results.[28] The author's current recommendation is to treat affected dogs with the fast-acting Cu chelator, and when hepatic Cu concentrations approach normal levels, to switch to zinc therapy alone to prevent further Cu accumulation.

The initial report of zinc therapy described use of 100 mg of elemental zinc acetate BID for 1 to 2 months during an induction phase followed by a maintenance dose of 50 mg of elemental zinc BID thereafter.[29] Serum zinc concentrations were monitored with a goal of approximately a twofold increase in serum concentrations (<200 μg/mL). In this study, serum zinc levels remained in the suggested therapeutic range and there was no evidence of toxicity. When serum zinc concentrations become significantly increased (>750 μg/mL) hemolysis can occur. Zinc can be given either as an acetate, sulfate, gluconate, or methionine salt, but should be administered on an empty stomach to assure adequate absorption. Common problems encountered with zinc therapy include anorexia, nausea, and vomiting shortly following administration of the drug. If concurrent chelator therapy is used, the dosing should be staggered to assure adequate absorption of the chelator.

Other Therapies

Affected dogs should be placed on a low-copper diet and one should assure that dietary supplements do not contain Cu. The pathogenesis of Cu hepatotoxicity is in part related to factors associated with cellular oxidative damage and membrane lipid peroxidation.[4] Consequently, it may be prudent to also provide antioxidants to the patient as a form of liver support. Antioxidants such as vitamin E (D-α-tocopherol), *S*-adenosylmethionine (SAMe), or silibinin (milk thistle derivative) may all be helpful. Vitamin C has been shown to act as a prooxidant in the presence of increased concentrations of Cu and should not be supplemented in these animals.[30]

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CHAPTER 44

Chemotherapy

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Principles of Chemotherapy

Significant advances have been made in the chemotherapeutic management of neoplastic conditions. Unfortunately, a large proportion of cancer patients still fails to respond to therapy, or relapses following an initial response, underscoring the need for new anticancer drugs and better integration of conventional treatment modalities (e.g., surgery, radiation therapy, and chemotherapy).

Chemotherapy kills rapidly dividing cancer cells by targeting DNA, RNA, and protein synthesis. Some cell-cycle nonspecific chemotherapeutic agents damage DNA by preventing cellular replication and/or inducing apoptosis, while other cell-cycle specific agents interfere with a specific phase of the cell cycle. Cell-cycle phases include the *S-phase* (DNA synthesis); the G_1*-phase* (RNA-synthesis); the *M-phase* (mitosis); the G_2*-phase* (second period of protein and RNA synthesis); and the G_0*-phase*, characterized by resting cells that are unaffected by chemotherapy as a result of their lack of replication.

Gompertzian growth kinetics have been used to describe tumor growth.[1] In the Gompertzian model, the tumor growth fraction increases exponentially over time. Once the limit of clinical detection is reached, tumor growth progressively slows down and eventually plateaus. Response to chemotherapy highly depends on the location of the tumor on its growth curve. For example, tumor cells in the latent growth phase (i.e., prior to clinical detection) are more sensitive to chemotherapy than cells in subsequent phases because the growth fraction is greater during latency. In general, smaller tumors have higher growth fractions compared with larger tumors; consequently, they are more susceptible to chemotherapy.

Chemotherapy is indicated for patients with a measurable tumor mass known to be susceptible to a particular therapeutic modality (e.g., lymphoma) and patients likely to have micrometastatic disease. It is also used to reduce the size of an inoperable tumor to allow subsequent local therapy; as a radiosensitizer; and, as a palliative treatment modality to alleviate clinical signs associated with metastatic or bulky disease.

Several factors influence the ability of chemotherapeutic agents to kill cancer cells. These include (a) intrinsic or acquired resistance to a chemotherapeutic agent; (b) impaired drug delivery across cell membranes; (c) duration of exposure to an effective concentration of the drug; (d) upregulation of glutathione, glutathione-*S*-transferases, or other detoxification pathways; (e) dysregulation of apoptotic (cellular death) pathways; or (f) activation of survival pathways by growth factors, such as epidermal growth factor. Acquired resistance to chemotherapy is often associated with overexpression of P-glycoprotein, a transmembrane pump encoded by the multiple-drug resistance gene.[2]

The P-glycoprotein extrudes xenobiotics from the cell cytoplasm. Overexpression of P-glycoprotein leads to a resistance to various drugs, including anthracyclines, vinca alkaloids, and taxanes. Dogs with a defective multiple-drug resistance gene have greater susceptibility to drugs affected by the P-glycoprotein and are more likely to experience toxicity following administration of these drugs.

It is unclear as to whether any tumor cell or only stem cells develop resistance. Tumors develop intrinsically resistant cell lines (or clones) because of genetic instability that cause a susceptible tumor to become subsequently unresponsive to chemotherapy and to relapse.[3] Based on this theory, induction chemotherapy should consist of a combination of drugs rather than a single agent.[4]

Resistance can also be explained by the "tumor stem cell theory," according to which committed cancer cells are killed by induction chemotherapy whereas stem cells survive and repopulate the tumor.[5]

Chemotherapeutic agents are generally administered at the maximum tolerated dose and at the highest dose intensity (i.e., shortest dosing interval). In addition, they are commonly dosed based on the estimated body surface area. As a result of the increased toxicity observed with this dosing scheme in cats and small dogs receiving drugs such as doxorubicin and carboplatin, it is currently recommended, that the dose of specific chemotherapeutic agents be calculated on an mg/kg basis for animals weighing less than 10 kg rather than on the estimated body surface area.[6] The author applies the mg/kg dosing scheme to dogs weighing less than 15 kg.

Classes of Chemotherapeutic Agents

Alkylating Agents

The first nonhormonal chemical found to have antitumor properties was a nitrogen mustard alkylating agent (sulfur mustard gas). When used as a weapon during World War II for its vesicant effects, the gas resulted in bone marrow suppression among the victims. This led to the development of a nitrogen mustard compound (mechlorethamine or Mustargen) and to its clinical application for the treatment of various cancers, primarily lymphomas.[7] Alkylating agents react with DNA strands by inserting an alkyl group (thus the term *alkylating*), and changing the DNA structure. Some agents are monofunctional (i.e., they react with only one strand of DNA), some are bifunctional (i.e., they react with both DNA strands to produce a "crosslink"), and they are cell-cycle nonspecific. The most commonly utilized alkylating agents in veterinary oncology are chlorambucil (Leukeran), cyclophosphamide (Cytoxan),

Table 44-1 Classification of Chemotherapy Drugs for Treatment of Gastrointestinal Disease

Drug	Indications	Toxicity	Dosage and Route of Administration
Alkylating Agents			
Cyclophosphamide	Lymphoma, sarcoma, carcinoma	Sterile hemorrhagic cystitis, BM, GI	Typically 200-250 mg/m^2 IV or PO
Chlorambucil	Lymphoma (lymphocytic) CLL, MCT, to replace cyclophosphamide if sterile hemorrhagic cystitis occurs	Bone marrow (mild)	Variable, PO
CCNU (Lomustine)	Lymphoma, MCT	Bone marrow, liver	Dogs: 60-90 mg/m^2 PO q3wk Cats: 50 to 60 mg/m^2 PO or 10 mg/cat PO q3 to 4wk
Melphalan	MM, plasma cell tumors	Bone marrow	0.1 mg/kg/day PO × 10 days, then 0.05 mg/kg QOD; pulse dose at 7 mg/m^2 daily for 5 days q3wk
Anthracyclines			
Doxorubicin	Lymphoma, sarcoma, carcinoma	Bone marrow, GI, hypersensitivity reaction, perivascular damage with extravasation, cumulative myocardial toxicity (dogs), nephrotoxicity (cats)	Dogs: ≥15 kg: 30 mg/m^2 IV q2 to 3wk Dogs: <15 kg: 1 mg/kg IV q2 to 3wk Cats: 1 mg/kg or 25 mg/m^2 q3wk
Mitoxantrone	Lymphoma, carcinoma	Bone marrow, GI, perivascular damage with extravasation	Dogs: 5 to 6 mg/m^2 IV q3wk Cats: 6 to 6.5 mg/m^2 IV q3wk
Platinum Drugs			
Carboplatin	Sarcoma, carcinoma	Bone marrow, GI	Dogs: 300 mg/m^2 IV q3wk Cats: 240 to 260 mg/m^2 IV q3 to 4wk
Cisplatin	Sarcoma, carcinoma	Bone marrow, nephrotoxicity, emesis, diuresis). Fatal pulmonary edema (cats)	Dogs: 70 mg/m^2 IV q3wk (saline Do not use in cats
Antimetabolites			
Methotrexate	Lymphoma	Bone marrow (mild), GI	0.8 mg/kg IV once weekly
Cytosine arabinoside	Lymphoma	Bone marrow (mild), GI	Variable; SQ, IM, IV
Gemcitabine	Lymphoma, MM, carcinoma, feline SCC	Bone marrow	Limited studies Dogs: 100 to 1000 mg/m^2 IV; 50 mg/m^2 twice/wk with RT Cats: 25 mg/m^2 twice/wk with RT
5-FU	Sarcoma, carcinoma	Bone marrow, GI, neurotoxicity, fatal neurotoxicity in cats	Dogs: 150 mg/m^2 once/wk IV, topically Do not use in cats
Antimicrotubule Agents			
Vincristine	Lymphoproliferative cancer, sarcoma	Bone marrow, GI, constipation (ileus), peripheral neuropathy, perivascular tissue reaction	0.5 to 0.75 mg/m^2 IV weekly or every other week
Vinblastine	Lymphoma, MCT	Bone marrow, GI, perivascular tissue reaction	2 to 2.2 mg/m^2 IV weekly
Miscellaneous			
L-Asparaginase	Lymphoma	Hypersensitivity reaction	400 IU/kg or 10,000 IU/m^2 SQ or IM (10,000 IU maximum) weekly
Procarbazine	Lymphoma	GI, bone marrow	Variable; dogs: 50 mg/m^2/day

BM, bone marrow; CLL, chronic lymphocytic leukemia; GI, gastrointestinal; MCT, mast cell tumor; MM, multiple myeloma; RT, radiation therapy; SCC, squamous cell carcinoma.

mechlorethamine (Mustargen), melphalan, and lomustine (Table 44-1). A unique toxicity to cyclophosphamide is the possible development of sterile hemorrhagic cystitis, an irritation of the urinary bladder caused by the inactive metabolite acrolein.

Anthracyclines

Anthracycline antibiotics are derived from the bacteria *Streptomyces peucetius*. Doxorubicin, a hydroxylated daunorubicin derivative, is widely utilized in human and animal patients for a variety of malignancies, including lymphoma, sarcomas, and carcinomas. It is cell-cycle nonspecific and exerts its cytotoxic effect through different mechanisms, including free radical formation, DNA intercalation, and inhibition of protein synthesis. It also inhibits topoisomerase, leading to the formation of cleavable complexes, DNA damage, and cellular death. It is metabolized by the liver and eliminated primarily in the feces. Doxorubicin can promote oxidative reactions, forming

highly reactive oxidative species, including superoxide anions, hydrogen peroxide, and hydroxyl free radicals that can damage lipid membranes. Cellular defenses against free radical formation (e.g., catalase, glutathione) become saturated and because catalase levels are low in cardiac muscle of humans and dogs, cardiotoxicity is a potential side effect of this drug. Nephrotoxicity has been observed in cats treated with doxorubicin, but the pathogenesis is unclear.[8]

Mitoxantrone is a synthetic antitumor antibiotic that was originally developed as a noncardiotoxic alternative to anthracycline compounds. It inhibits topoisomerase IIα by stabilizing topoisomerase IIα–cleavable complexes. Unlike doxorubicin, mitoxantrone does not result in free radical formation, which may account for its reduced cardiotoxic potential. Mitoxantrone is metabolized in the liver and is eliminated via feces and urine. In humans, it is used for the treatment of non-Hodgkin lymphoma and acute leukemias, as well as for the treatment of breast cancer and hormone-refractory prostate cancer (see Table 44-1).[9]

Platinum Drugs

The antitumor activity of platinum coordination complexes was first recognized by Rosenberg and colleagues in 1961. They observed that cisplatin induced filamentous growth in bacteria without affecting RNA or protein synthesis (suggesting DNA as the primary target of the drug).[10] Platinum drugs act preferentially at the N7 position of guanine and adenine residues, forming mono- and bifunctional adducts. Initially, monofunctional adducts form and these may subsequently form intra- or interstrand crosslinks. The toxicity profile of cisplatin, as observed in early clinical trials, led to the development of platinum analogues (carboplatin, oxaliplatin) with less toxicity and potentially greater efficacy against various tumor types. They are cell-cycle nonspecific, and elimination occurs through the kidneys (see Table 44-1).

Antimetabolites

Methotrexate

Methotrexate (MTX) is a commonly used antifolate agent that has activity against hematopoietic malignancies and various solid tumors in people. In dogs, this agent has been incorporated primarily in combination chemotherapy protocols for the treatment of lymphoma. MTX is an inhibitor of dihydrofolate reductase, an enzyme responsible for maintaining the intracellular folate pool of the reduced form of tetrahydrofolates that is critical for the synthesis of certain amino acids and purine nucleotides. It is primarily eliminated via renal excretion.

Cytarabine

Cytarabine (Ara-C, Cytosar) is a cell-cycle phase-specific pyrimidine analogue that targets cells undergoing DNA synthesis in S-phase. Maximum cytotoxicity is observed during periods of rapid DNA synthesis. The duration of cytarabine exposure is an important determinant of the degree of cytotoxicity (a higher proportion of cells enters the S-phase with prolonged exposure of the drug). Intracellular activation of the drug is necessary for cytotoxicity to occur. It is primarily used for the treatment of hematologic malignancies. The drug is eliminated in the urine.

Gemcitabine

Gemcitabine is a deoxycytidine analogue that requires the nucleoside transporter system for entry into cells. Similarly to cytarabine, it requires intracellular activation to exert its cytotoxic effect. Gemcitabine has a broader spectrum of activity compared with cytarabine with recognized activity against human solid tumors, including pancreatic cancer.

5-Fluorouracil

5-Flourouracil (5-FU) is a fluoropyrimidine that requires intracellular activation to exert cytotoxicity. It enters the cells through a facilitated uracil transport mechanism and is subsequently converted into the active metabolite 5-fluoro-2′-deoxyuridine monophosphate (FdUMP), which interferes with DNA synthesis and repair. Elimination occurs through the lungs and the kidneys (see Table 44-1).

Antimicrotubule Agents

Microtubules are cellular organelles that can be targeted by a variety of natural anticancer drugs, primarily vinca alkaloids (vincristine, vinblastine) and taxanes (paclitaxel). These agents interfere with the microtubules that form the mitotic spindle, inhibiting cellular division and proliferation. Microtubules are also involved in chemotaxis, membrane transport, secretion, adhesion, and signaling.

While the vinca alkaloids bind to microtubular proteins involved in the mitotic spindle during metaphase (thus preventing cell division), the taxanes decrease the availability of tubulin to be used for microtubule formation.

The vinca alkaloids and paclitaxel are metabolized by the liver and excreted in the feces (see Table 44-1).[11]

Miscellaneous Agents

L-Asparaginase is a bacterial-derived enzyme that depletes the circulating pool of L-asparagine. Although normal cells are able to synthesize L-asparagine from aspartic acid through asparagine synthase, cancer cells lack this enzyme and their survival depends on exogenous sources of this amino acid. Elimination occurs in the urine and feces.

Hydroxyurea interferes with the activity of the ribonucleoside diphosphate reductase enzyme and prevents the conversion of ribonucleotides to deoxyribonucleotides in an S-phase specific manner. Hydroxyurea is metabolized by the liver and eliminated in the urine.

The mechanism of action of procarbazine is unclear, although inhibition of DNA, RNA, and protein synthesis has been described, and the drug has possible activity through DNA alkylation and methylation. Procarbazine is metabolized by the liver and eliminated in the urine.

Imatinib mesylate (Gleevec) is a tyrosine-kinase inhibitor that occupies the adenosine triphosphate (ATP) binding site of the Bcr-Abl tyrosine kinase and of other tyrosine kinases, platelet-derived growth factor, c-kit, and stem cell factor. In humans, imatinib is considered the first-line therapy for chronic myeloid leukemia and for gastrointestinal stromal tumors (GISTs) expressing the c-kit tyrosine kinase (see Table 44-1).[12]

Corticosteroids

Prednisone is a catabolic steroid frequently incorporated in chemotherapy protocols used for lymphoproliferative disorders, mast cell tumors, and plasma cell tumors. It binds to cytoplasmic receptors, thereby inhibiting DNA synthesis. Prednisone is converted in the liver into its active form (prednisolone).

Metronomic Chemotherapy

Blood vessel formation plays a pivotal role in the process of tumor growth and metastasis. Some of the antitumor effects of standard

chemotherapeutic agents resides in their ability to target the vascular endothelium. The observation that the functional impairment of a single capillary negatively impacts a high number of cancer cells, and the fact that endothelial cells, unlike cancer cells, are "genetically stable" and thus less likely to develop resistance, makes the endothelium a desirable target for cancer therapy.[13,14] Metronomic (antiangiogenic) chemotherapy strategies are being developed and include small, continuous, daily dosing of chemotherapy that results in targeting and inhibition of vascular endothelial cells, with decreased potential for systemic toxicity, reduced risk for resistance, and longer-lasting effects compared with standard chemotherapy regimens.[15]

This approach, although promising in rodent tumor models, has not yet been validated through clinical trials in animal or human cancer patients.

Chemotherapy in the Treatment of Gastrointestinal Cancer

Adjuvant therapy for gastrointestinal cancer, particularly gastric, pancreatic, and colorectal cancer, has been explored extensively in human oncology for the past 30 years. To date, the only treatment option potentially able to cure gastrointestinal neoplasia is surgery, but the vast majority of patients have unresectable or metastatic tumors that cannot be cured by means of surgery alone. Furthermore, even patients whose tumors are completely excised often develop metastatic disease following surgery. Although chemotherapy is generally unsuccessful in providing long-term tumor control in these cases, it is often indicated as an adjunctive treatment to surgery to prevent or delay the onset of metastatic disease and local tumor recurrence, often resulting in amelioration of quality of life and extended survival times.[16]

Oral Cancer

Although surgery and radiation therapy are used to achieve local and regional tumor control, chemotherapy is often indicated as an adjunct to standard local treatment modalities for highly metastatic tumors, including oral melanoma and tonsillary or lingual squamous cell carcinoma.

Oral melanoma has historically been described as a chemoresistant malignancy, but measurable responses have been reported for dogs treated with melphalan,[17] carboplatin,[18] and intralesional cisplatin chemotherapy.[19] Because melanoma is a highly immunogenic tumor, biologic response modifiers[20] and immunotherapy approaches, including the recently developed canine melanoma vaccine,[21] have emerged as promising strategies for the treatment of this disease.

The use of nonsteroidal antiinflammatory medications, such as piroxicam, has not been consistently beneficial in the management of feline oral squamous cell carcinoma (SCC), despite the overexpression of cyclooxygenase-2 in this malignancy.[22,23] However, piroxicam appears to have potential efficacy against canine oral SCC. In fact, increased response rates were noted when piroxicam was combined with cisplatin or carboplatin chemotherapy.[24] However, because of the high incidence of renal toxicity, the combination of piroxicam with cisplatin is not recommended.[25,26] In cats, mitoxantrone chemotherapy has yielded encouraging results when combined with radiation therapy.[27]

Some chemotherapeutic drugs also play a role as radiosensitizing agents. For example, platinum drugs have been used in dogs with oral melanoma while gemcitabine has been combined with radiation therapy for the treatment of feline oral SCC.[28,29]

Gastric Cancer

Gastric cancer accounts for only 1% of all malignancies in dogs and 70% to 80% of these tumors are adenocarcinomas.[30] In cats, lymphoma is the most common gastric malignancy whereas adenocarcinomas are rarely reported.[31]

With the exception of disseminated lymphoma, for which chemotherapy remains the treatment of choice, surgery is the first-line therapeutic modality recommended for most gastric cancers. There is currently no effective chemotherapy for the treatment of adenocarcinomas and, in general, the effectiveness of chemotherapy as an adjuvant to surgery for the treatment of gastric cancer is unknown.

In humans, c-*kit* inhibitors have shown efficacy in the treatment of GISTs, with approximately 80% of these responding to the small molecule imatinib.[32] Because approximately 75% of canine GISTs are characterized by c-*kit* mutations, it is conceivable that c-*kit* inhibitors may have efficacy in the treatment of canine GISTs, but this hypothesis has yet to be fully evaluated. London et al. reported on the use of toceranib phosphate (Palladia, SU11654), a small-molecule tyrosine kinase inhibitor recently approved by the FDA for the treatment of pet dogs with cutaneous mast cell tumors, which, similarly to GIST, often have an activating mutation of c-*kit*. Toceranib phosphate has antitumor and antiangiogenic properties through the inhibition of c-*kit*, platelet-derived growth factor receptor-β, and vascular endothelial receptor factor 2.[33]

Salivary Gland, Esophageal, and Pancreatic Cancer

Primary neoplastic conditions of the salivary gland, the esophagus, and exocrine pancreas of dogs and cats are rare.

Adenocarcinomas are the most common cancers affecting the salivary gland of dogs and cats; other reported tumor types include malignant fibrous histiocytoma, osteosarcoma, mast cell tumor in dogs, and sebaceous carcinoma in cats.[34] Surgical excision should be performed whenever possible and radiation therapy considered in cases of incomplete resection or inoperable masses. Chemotherapy is not reported widely in veterinary oncology because of the lack of effective chemotherapeutics and the local disease control afforded by surgery and radiation therapy.

The most common esophageal tumors include carcinomas (primarily SCC), but sarcomas including leiomyosarcoma, osteosarcoma, and fibrosarcoma also have been reported. *Spirocerca lupi* infestation has been implicated in the pathogenesis of esophageal sarcomas.[35,36] With the exception of lymphoma, chemotherapy has rarely been utilized for the treatment of esophageal cancer. Surgery is considered the treatment of choice, but often times it is not feasible because of location and advanced stage of disease (intrathoracic resections are particularly difficult). Likewise, radiation therapy can result in unacceptable toxicity to the surrounding normal tissues when directed to intrathoracic lesions, but it can be applied to cervical locations.[36]

The vast majority of cancers affecting the exocrine pancreas are adenocarcinomas of ductal origin, which are characterized by a high metastatic potential. Surgery (total pancreatectomy or pancreaticoduodenectomy, also called Whipple's procedure) has been reported in humans and dogs, but cure rates are low while morbidity and mortality are high.[37] Charney and colleagues reported the use of intracavitary carboplatin and/or mitoxantrone chemotherapy in 12 dogs with carcinomatosis, sarcomatosis, and mesothelioma. The median survival time of treated dogs was 332 days, compared with only 25 days for seven untreated dogs included in the retrospective evaluation.[38] In humans, amelioration has been achieved with chemotherapy alone (gemcitabine, paclitaxel, docetaxel) or in combination with local treatment modalities, but survival times are still woefully short.

Hepatobiliary Cancer

Hepatic tumors are rare in pet animals. In dogs, the liver is more commonly a secondary (i.e., metastatic) site from nonhepatic neoplasias whereas in cats primary hepatobiliary tumors occur more commonly than metastatic disease.

Liver lobectomy is the recommended approach for all canine and feline resectable liver masses, including localized hepatocellular carcinoma (HCC). Surgical excision is, however, not possible in the diffuse and nodular forms of HCC, and the role of chemotherapy in the treatment of liver neoplasia has not been investigated.

In humans, HCC is considered a chemoresistant tumor with response rates no greater than 25% with single-agent therapy or combination of various chemotherapeutics, including 5-fluorouracil, interferon, cisplatin, and doxorubicin. Chemoresistance may be caused by P-glycoprotein expression and by the detoxification biochemistry of hepatocytes. Aside from the disappointing results provided by the use of systemic chemotherapy for the treatment of HCC, encouraging reports have emerged regarding various regional chemotherapies for the treatment of nonmetastatic HCC.[39]

Liver lobectomy can be performed in case of hepatic sarcomas. However, the prognosis associated with these tumors is poor because of the presence of metastatic disease at the time of diagnosis. Doxorubicin-based protocols have yielded promising results when applied to the treatment of canine and feline sarcomas located elsewhere in the body, but they have not yet been investigated for primary hepatic sarcomas in these species.

Intestinal Cancer

In a retrospective study evaluating 46 cats with malignant colonic neoplasia, a significant survival advantage was found for cats treated with surgery and adjuvant doxorubicin compared with cats treated with surgery alone (280 days vs. 56 days, respectively).[40]

In another study evaluating 14 dogs with gastrointestinal leiomyosarcoma, two dogs received adjuvant doxorubicin chemotherapy following surgery; one developed metastatic disease 4 months following completion of the chemotherapy regimen, whereas the other dog was lost to follow up 2 years later.[41]

Doxorubicin was also used following surgical resection in two dogs with intestinal adenocarcinoma and survival times greater than 17 months were reported.[42]

Although the addition of chemotherapy could provide a potential survival advantage, the usefulness of adjuvant chemotherapy in the treatment of intestinal nonlymphoid malignancies is unclear and further research and prospective clinical trials are greatly needed.

Less controversial is the role of chemotherapy in the treatment of intestinal lymphoid malignancies. In a recent prospective clinical trial, dogs with gastrointestinal lymphoma were treated with a 20-week combination chemotherapy protocol consisting of induction and consolidation phases. Thirteen of the dogs studied had primary gastrointestinal lymphoma and five had multicentric lymphoma with gastrointestinal involvement. The overall remission rate was 56% with nine dogs achieving a complete remission for a median of 86 days (range: 22 to 420 days) and one dog achieving a partial remission for 26 days. The overall median survival time was 77 days (range: 6 to 700 days). Although long-term survival times were noted in this study, results suggest that dogs with gastrointestinal lymphoma treated with multiagent chemotherapy have poor response rates and survival times compared to dogs without gastrointestinal involvement treated with similar cyclophosphamide, hydroxydaunorubicin, methotrexate, prednisone (CHOP)-based protocols. Significantly shorter survival times were found in dogs that failed to achieve a remission or had diarrhea at the time of the initial presentation.[43]

In cats with intestinal lymphoma, median survival times ranging from 6 to 9 months have been reported, with some cats living 2 years or longer. Long-term survivors are typically cats with inflammatory bowel disease or low-grade lymphocytic lymphoma (often indistinguishable histopathologically, see Chapter 57) whose median survival time is significantly longer than that of cats with the lymphoblastic form of the disease (22.8 months vs. 2.7 months).[44] In a study by Zwahlen and colleagues, the addition of surgery to chemotherapy did not provide any survival advantage over chemotherapy alone.[45] It must be noted, however, that the number of cases included was small and it was not a randomized, prospective clinical trial. In the author's opinion, surgery may be a beneficial addition to chemotherapy in cats and dogs affected by lymphoma, manifesting as a solitary intestinal lesion.

Interestingly, the nonsteroidal antiinflammatory piroxicam resulted in considerable amelioration of clinical signs when used in dogs with rectal tubulopapillary polyps. Furthermore, its use has been postulated for the adjunctive treatment of surgically excised colonic tumors, but randomized, prospective studies evaluating the role of piroxicam or adjuvant chemotherapy following surgical resection for the treatment of intestinal tumors in dogs, cats, and humans are lacking.

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CHAPTER 45

Gastric Cytoprotective Agents

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Introduction

Gastric cytoprotective agents are used when normal gastric defense mechanisms are disrupted, thereby exposing submucosal layers to damage from gastric acid, or when there is another need for reducing gastric acidity, such as esophageal disease. Signs of significant gastric ulceration are hematemesis and melena. Hematemesis refers to the vomiting of blood, which, when digested, may have the appearance of coffee grounds. Gross melena (digested blood in the feces) only occurs after significant volumes of blood have been lost into the intestinal lumen.

The gastric mucosa has several intrinsic properties that protect it from autodigestion, including intact apical cell membranes, tight junctions, bicarbonate secretion, mucus production, rich blood supply, active cell renewal, surface active phospholipids, and endogenous prostaglandins. Gastric ulceration is believed to have its origins in the disruption of the mucosal barrier, or as a result of excessive acid secretion (Box 45-1), and is more commonly reported in dogs than in cats.[1-4] History and physical examination, as well as full metabolic assessment, will help to rule out systemic disease and drug administration as the underlying cause. Strenuous exercise, particularly in sled dogs, is associated with increased intestinal permeability and gastrointestinal ulceration.[5,6] The use of corticosteroids in dogs with intervertebral disk disease has been associated with severe gastrointestinal ulceration.[7] If no underlying cause is identified abdominal ultrasound combined with further testing, such as endoscopy or gastric biopsy, may be required.

For many of the conditions listed in Box 45-1 the true incidence of ulceration is unknown, especially with regards to nonsteroidal antiinflammatory drug (NSAID) toxicity. NSAIDs (particularly aspirin) are reported to exert their adverse effects by direct toxicity to the gastric mucosa as well as by inhibition of the cyclooxygenase pathways, thereby reducing endogenous prostaglandin and mucus production.[8] It may well be that the superficial gastric erosions reported and identified in animals given NSAIDs are not clinically significant.

In addition to the conditions detailed in Box 45-1, gastric cytoprotective agents have been used in the treatment of gastroesophageal reflux disease. Gastroesophageal reflux may occur secondary to general anesthesia (especially when the animal has not been fasted),[7] protracted vomiting disorders, or physical defects such as hiatal hernias.[9] Ingestion of caustic substances such as clindamycin or generic doxycycline capsules in cats may cause severe esophagitis requiring gastric antisecretory therapy.[10,11]

It is important to bear in mind that ideal treatment goals for specific gastric conditions have not been established in veterinary medicine. In human medicine it is recommended that the gastric pH should be increased to more than 4 for approximately 16 to 22 hours per day in the treatment of gastroesophageal disease, as well as in critically ill patients, whereas for conditions of gastrointestinal hemorrhage the pH should be as high as 6 to promote hemostasis.[12] Similar standards have not yet been developed for most companion animal disease conditions.

Classification

Drugs used for gastric protection are classified according to their mechanism of action and are discussed under the following sections:

- Oral Antacids
- Chemical Diffusion Barriers
- Prostaglandin Analogue(s)
- Histamine H_2-Receptor Antagonists
- $H,^{+}K^{+}$-ATPase (Proton Pump) Inhibitors

Oral Antacids

Mechanism of Action

Antacids react chemically with gastric acid to reduce the overall acidity of the stomach. Antacids do not directly decrease acid secretion. The most commonly used antacids are aluminum hydroxide ($Al[OH]_3$), magnesium hydroxide ($Mg[OH]_2$), and calcium carbonate ($CaCO_3$). Many of these are available as over-the-counter formulations for the symptomatic relief of gastroesophageal reflux and dyspepsia, and are often formulated with other drugs (see Box 45-1). They are given orally as tablets or liquids and are often flavored for palatability. There is little absorption from the gastrointestinal tract so the risk for adverse systemic effects is minimal.

The use of antacids for stomach ulceration is based on the premise that buffering or decreasing gastric acid will permit ulcer healing.[13] However, ulcer healing seen with aluminum hydroxide may not be related to gastric acidity,[14] as it may also release prostaglandin (PG) E_2 into the gastric lumen and submucosa.[15] The significance of this finding requires further investigation. There is very little scientific literature assessing the efficacy of local antacids for dog and cat gastric ulceration.

Box 45-1 Differential Diagnoses of Gastric Ulceration

Primary Gastrointestinal Disease
Helicobacter-like organisms*
Inflammatory bowel disease†
Gastric neoplasia (especially gastric carcinoma, lymphoma)†
Pyloric outflow obstruction
Gastric dilation-volvulus

Drugs
Nonsteroidal antiinflammatory drugs and corticosteroids†

Gastric Hyperacidity
Gastrinomas
Mast cell tumors*

Systemic Disease
Pancreatitis
Disseminated intravascular coagulation†
Renal failure
Hypoadrenocorticism
Shock
Liver disease†

Miscellaneous
Parasitic disease
Hypereosinophilic syndrome

*The most common potential underlying causes of gastric ulceration in dogs.[1]
†The most common potential underlying causes of gastric ulceration in cats.[4]

Dose

The onset and duration of antacid effect in humans is rapid and extends from 20 minutes to 3 hours, depending on the preparation that has been used.[16] Antacids act locally so the presence of food will delay gastric emptying, thereby prolonging the effect of these drugs.[17] This short duration of action, which presumably also occurs in dogs and cats, necessitates that these drugs be taken often. Dose recommendations are estimations only and have not been scientifically determined for dogs or cats (Table 45-1).

Rational Use

These drugs are an unattractive option for the management of stomach ulceration and more appropriate alternatives usually should be used. They are likely more appropriate for mild to moderate gastric disease.

Contraindications and Side Effects

The cations in antacids are capable of binding to fluoroquinolones and tetracyclines and may decrease the systemic absorption of this drug class. Ketoconazole and itraconazole, which depend on gastric acidity for oral absorption, will show decreased systemic absorption when given concurrently with any drug capable of reducing gastric acidity. Recommendations to prevent decreased bioavailability of these drugs that are based on controlled animal studies do not exist, but human recommendations are that these drugs be given parenterally (if appropriate) or orally a few hours before or after administration of the antacid.[16] In dogs, the bioavailability of oral propranolol in the presence of aluminum hydroxide or magnesium hydroxide is reduced.[18]

Table 45-1 Commonly Used Gastric Cytoprotective Agents in the Dog and Cat

Generic Name	Trade Name	Dose (dog)	Dose (cat)	Comments
Aluminum hydroxide-magnesium hydroxide combination	Mylanta	5 to 10 mL PO q4h	5 to 10 mL PO q4h	Give with food.
Calcium carbonate	TUMS	5 to 10 mL PO q4h	5 to 10 mL PO q4h	Give with food.
Bismuth		1 to 3 mL/kg PO q24h	1-3 mL/kg PO q24h	May cause black feces
Sucralfate	Carafate	0.5 to 1 g PO q8 to 12h	0.25 to 0.5 g PO q8 to 12h	
Misoprostol	Cytotec	2 to 5 µg/kg PO q8 to 12h†	3 to 5 µg/kg PO q8h*	
Cimetidine	Tagamet, Zitac	5 to 10 mg /kg PO, SC, IV q6 to 8h	5 to 10 mg /kg PO, SC, IV q6 to 8h	Reduce dose by 50% in animals with renal impairment. Use with care with concurrent administration of drugs with extensive hepatic metabolism.
Ranitidine	Zantac	1 to 2 mg/kg PO, SC, IV q12h	2.5 to 3.5 mg/kg PO, SC, IV q12h	Reduce dose by 50% in animals with renal impairment.
Famotidine	Pepcid	0.1 to 0.2 mg/kg PO, IV q12 to 24h	0.1 to 0.2 mg/kg PO, IV q12 to 24h	Reduce dose by 50% in animals with renal impairment.
Nizatidine	Axid	2.5 to 5 mg/kg PO, q12 to 24h	2.5 to 5 mg/kg PO, IV q12 to 14h	Reduce dose by 50% in animals with renal impairment.
Omeprazole	Losec (USA: Prilosec)	0.7 to 1 mg/kg PO q24h	0.7 to 1 mg/kg PO q24h	Do not crush enteric-coated granules inside tablets or capsules. Increased benefit may be seen with 1 mg/kg q12h dosing.
Pantoprazole	Somac (USA: Protonix)	0.5 to 1 mg/kg PO, IV q24h	0.5 to 1 mg/kg PO, IV q24h	Intravenous doses should be given over at least 15 minutes or given as an infusion spread over 24 hours.

*This drug has not been assessed for safety, efficacy, or pharmacokinetics in cats.
†Efficacy in dogs has only been shown against aspirin-induced damage to gastrointestinal mucosa.

Magnesium hydroxide has mild laxative effect whereas aluminum hydroxide has a mild constipating effect. These two salts are often given together in the same formulation such that changes in fecal consistency are uncommon. It has been suggested that magnesium-containing antacids should be avoided in patients with renal failure to avoid hypermagnesemia that may lead to central nervous system toxicity.[19] Calcium carbonate reacts with stomach acid to liberate carbon dioxide, and belching may be noted.[19] Aluminum hydroxide is capable of binding to phosphates and is sometimes used for cases of hyperphosphatemia.[20] Aluminum toxicity to with aluminum hydroxide antacids has been reported.[21]

Antacids have sometimes been singled out as drugs that produce significant rebound gastric acid hypersecretion once therapy has stopped, however, this hypersecretion may simply be a function of gastric hypoacidity caused by many of the gastric acid-lowering drugs.[22]

Prostaglandin Analogues

Mechanism of Action

Gastric prostaglandins play an important role in gastric mucosal defense in that they increase mucosal blood flow, mucus production, and bicarbonate secretion.[23,24] The most commonly studied and used prostaglandin analogue in veterinary medicine is misoprostol, an analogue of prostaglandin E_1.[25-28]

Dose

Beneficial effects have been reported at a dose of 3 µg/kg body weight every 8 to 12 hours in dogs,[8] with a half-life of approximately 30 minutes, and a duration of action of 3 to 6 hours.[29] Only oral formulations for this purpose are available. No known pharmacokinetic or safety studies have been performed in cats, but the anecdotal dose is recommended to be 2 to 5 µg/kg body weight every 12 hours.[8]

Rational Use

The veterinary application of this drug originated from its use in people to prevent NSAID-induced gastric injury, although it is not clear how superior it is to other gastric cytoprotective agents.[30,31] NSAIDs are frequently used in older animals and may inhibit tissue cyclooxygenase pathways.[2,32] In most in vivo veterinary assessments of this drug, misoprostol was given along with a nonsteroidal drug, usually aspirin, and compared with placebo. Despite slight variation in study design, it has been shown that there was significantly less gastroduodenal hemorrhage and vomiting in the misoprostol group over 14-day[25] to 30-day[26] periods. The benefit of misoprostol is less convincing in studies of dogs given corticosteroids because of intervertebral disk disease.[7,33] This may be due to differences in the pathogenesis of glucocorticoid-induced gastric ulceration or additional neurogenic factors. Based on these studies, it would seem prudent to only recommend the prophylactic use of misoprostol in dogs receiving NSAID therapy that are at high risk of developing gastric ulceration. However, its use is not generally supported in healthy animals receiving cyclooxygenase-2–specific antagonists or animals receiving glucocorticoids alone.

Contraindications and Side Effects

The use of this drug is contraindicated in dogs receiving gentamicin or other nephrotoxic drugs, as it has been shown to potentiate nephrotoxic effects.[27] Side effects that have been reported include intestinal cramping and diarrhea, caused by the stimulation of migrating motor complexes. The incidence of diarrhea is dose dependent, especially when the recommended dosage is exceeded.[28] Because of the potential to induce abortion, the drug should not be handled by women who are pregnant or trying to conceive.

Chemical Diffusion Barriers

Mechanism of Action

This class of drugs provides physicochemical barriers between the gastric epithelium and the acidic content of the gastric lumen. These drugs are seen as a replacement or support for the mucus layer of the gastric epithelium. The two drugs most commonly used in small animal medicine from this class are bismuth and sucralfate. US formulation is bismuth subsalicyclate, and its use is cautioned against in cats due to potential for salicylate absorption and toxicity.

Bismuth is capable of binding to an ulcer bed, providing a protective coating. In addition, it can enhance bicarbonate secretion and local prostaglandin synthesis, and adsorb the proteolytic enzyme pepsin.[34]

Sucralfate is a complex of sucrose octasulfate and aluminum hydroxide that in the presence of acid dissociates into these two components. Sucrose octasulfate will polymerize into a sticky, viscous, yellow-white gel that is strongly anionic and electrostatically binds to cationic tissue proteins of ulcerated mucosa. The ulcerated site covered by this "liquid band aid" is protected from backward diffusion of hydrogen ions. It seems likely that both the sucrose octasulfate and aluminum hydroxide components contribute to cytoprotection.[35] Sucralfate has additional cytoprotective roles that may involve mucosal synthesis of protective prostaglandins, secretion of mucus and bicarbonate, and increases in epidermal growth factor. It has little effect on stomach acidity.

Dose

In humans, approximately 30% of the polymerized viscous paste of sucralfate remains in the stomach 3 hours after administration. In one study in dogs, radiolabeled sucralfate could still be detected bound to acetic acid–induced gastric ulcers 8 hours after oral administration.[36] Anecdotal reports suggest 8- to 12-hour dosing at 0.5 to 1 g for dogs and 0.25 to 0.5 g for cats.

Rational Use

Bismuth has shown efficacy as an antiulcer medication in rats,[37] but is largely ineffective against NSAID-induced ulceration in people.[38] Most of the attention given to bismuth as an antiulcer drug has been in humans for its use in cases of *Helicobacter pylori*-gastritis. The interaction between bismuth, stomach ulcers, and *Helicobacter*-like organisms in small animal medicine requires further investigation. Because of the limited information concerning the efficacy of bismuth as an antiulcer medication in dogs or cats, its use in these species for this indication cannot be recommended at this time.

Despite the widespread use of sucralfate in dogs and cats for stomach ulceration and esophagitis, there are few data demonstrating efficacy for these indications. The use of sucralfate to prevent NSAID-induced ulceration in people appears to be poor.[39] It has been shown that sucralfate does not provide any benefit when used prophylactically to prevent methylprednisolone-induced gastrointestinal tract bleeding in dogs.[33] Liquid sucralfate is able to prevent acid-induced esophagitis in cats and, in this role, outperformed a PGE_1 analogue[40] and cimetidine.[41]

Contraindications and Side Effects

Similar to the cationic antacids, sucralfate is capable of binding to fluoroquinolones and tetracyclines, and will likely decrease their systemic absorption when given orally. Also, the absorption of digoxin, theophylline, and phenytoin is decreased when given concurrently with sucralfate. All these drugs should be given orally at least 2 hours prior to sucralfate. It would seem logical that concurrent use of antacids or H_2-histamine antagonists would neutralize stomach acid and therefore decrease the efficacy of sucralfate, but one study in dogs showed the concurrent administration of these drugs did not affect sucralfate's ability to bind to gastric ulcers.[36] Bismuth will create blackened stools that do not represent melena; the owner should be made aware of this.

H_2-Histamine Antagonists

Mechanism of Action

These drugs competitively inhibit H_2-histamine receptors in the gastric parietal cells and cause approximately 70% to 90% reduction in gastric acid and pepsin secretion. H_2-histamine antagonists have significant popularity in human medicine, and in many countries are sold over the counter. Despite differences in the degree of gastric acid inhibition between the different drugs of this group, no study shows one to be superior to the other in a clinical setting.

In a recent study of healthy Beagles, intragastric pH was measured before and after feeding during 7 days of treatment with ranitidine, famotidine, pantoprazole, omeprazole, or saline at therapeutic doses.[12] Generally, pH was higher for longer periods after treatment with famotidine, pantoprazole, or omeprazole. Only twice-daily administration of omeprazole reached the therapeutic criteria as established in people.

Rational Use

Potential reasons for using an H_2-antagonist include treatment of gastric ulceration, prevention of gastrointestinal ulceration in critically ill animals, and treatment of gastroesophageal reflux. There is insufficient evidence to support their use for prevention of NSAID-induced gastric damage,[42,43] although in one pharmacokinetic study cimetidine reduced the half-life of piroxicam in healthy cats,[44] and famotidine increased gastric blood flow in healthy dogs administered diclofenac sodium.[45]

Each drug may have additional effects and contraindications, and is discussed separately.

Of the H_2-histamine receptor antagonists, historically cimetidine was commonly used, but is reported to be least effective in reducing gastric pH. It is also without effect on gastrointestinal motility. Cimetidine has important effects on drug metabolism by inhibiting hepatic microsomal enzymes and decreasing hepatic blood flow.[46] Other effects of cimetidine relate to immunomodulatory benefits, mainly by dampening cell-mediated immunity.

Dose

A dose of 5 to 10 mg/kg either intravenously or orally every 6 to 8 hours is recommended in both dogs and cats. If given orally with food there is a delay in drug absorption, and there should be at least 2 hours between administration of cimetidine, ketoconazole, antacids, or digoxin.

Contraindications and Side Effects

Care should be used if giving this drug intravenously in animals with impaired renal function. Most of the drug is excreted through the kidneys and the dose should be reduced by 50%. Care should also be used in giving this drug to animals receiving drugs that require extensive hepatic metabolism (e.g., phenobarbital, metronidazole, theophylline, calcium channel blockers, and benzodiazepines). Other drugs in this class have less of an effect on hepatic microsomal enzymes and should be used preferentially in animals receiving concurrent medications such as these.

Ranitidine

Ranitidine has less of an inhibitory effect on the hepatic microsomal enzyme system. It has a prokinetic property through an anticholinesterase effect that has been shown to stimulate gastrointestinal motility.[47] This motility effect has been shown to occur in the gastroesophageal sphincter and the gastrointestinal tract in dogs and cats, and is one drug recommended for therapy in feline megacolon.[48] Despite its safety, little is known regarding its efficacy and, as mentioned earlier, in one recent study of healthy dogs it was shown to be significantly less effective than famotidine, omeprazole, or pantoprazole at increasing intragastric pH.[12]

Dose

The dose is 1 to 2 mg/kg (dogs) and 2.5 to 3.5 mg/kg (cats) orally, subcutaneously, or intravenously every 12 hours in both dogs and cats. Absorption is not affected by feeding.

Contraindications and Side Effects

As for all H_2-antagonists, the dose should be reduced by 50% in animals with renal impairment.

Famotidine

Famotidine is more effective at reducing gastric acid secretion than ranitidine.[49] It is preferred to omeprazole in the treatment of *H. pylori*–associated gastroesophageal reflux in people.[50] Like cimetidine, it has no effect on gastrointestinal motility or gastroesophageal sphincter tone.

Dose

Famotidine has minimal hepatic first-pass metabolism and limited oral bioavailability. Absorption is not affected by feeding or fasting, a fact that has made this drug preferable to omeprazole in endurance dogs during racing.[51] The dosage in dogs and cats is 0.1 to 0.2 mg/kg orally or intravenously every 12 to 24 hours.

Contraindications and Side Effects

Famotidine should be reduced by 50% in animals with impaired renal function. It may exacerbate cytopenias if given in conjunction with other myelosuppressive agents. Anecdotal cases of hemolytic anemia in cats have been reported.[52]

Nizatidine

Nizatidine is the least-studied drug in animals from this group. It has similar effects on gastrointestinal motility to those of ranitidine, also at antiulcer therapeutic doses.[48]

Dose

Food improves oral bioavailability, but this is not thought to be clinically important. There is minimal hepatic first-pass metabolism and rapid and virtually complete oral absorption.[53] Administration of 2.5 to 5 mg/kg orally or intravenously every 12 to 24 hours is recommended for both prokinetic and H_2-antagonistic effects.

Contraindications and Side Effects

Dosage should be reduced by 50% in animals with significant renal impairment.

Theoretically, the use of any H_2-antagonist may induce cardiac side effects because of the presence of type 2 histamine receptors on cardiac myocytes, but only transient arrhythmias seem to occur. Long-term usage has resulted in bacterial overgrowth in humans because of acid hyposecretion, but clinical cases in dogs and cats have not been reported.

H^+,K^+-ATPase (Proton Pump) Inhibitors

Mechanism of Action

Proton pump inhibitors covalently bind and irreversibly inhibit the proton pump (H^+,K^+-adenosine triphosphatase [ATPase]) on the luminal surface of the parietal cell. New synthesis of H^+,K^+-ATPase enzyme is continuous, so the pharmacologic effect of a proton pump inhibitor is not permanent. All afferent pathways that culminate in the basal or stimulated secretion of hydrogen ions from the parietal cell (gastrin, histamine, and acetylcholine) are inhibited. The two drugs from this class most commonly utilized in small animal medicine are omeprazole and pantoprazole.

Dose

These drugs should be given on an empty stomach as the presence of ingesta will decrease oral bioavailability. Proton pump inhibitors are absorbed in the small intestine and arrive at the parietal cell through the vascular system and resecretion. They are weakly alkaline and therefore will concentrate and persist in the acidic parietal cell, prolonging their duration of action. The inhibition of acid secretion from a single dose may extend for longer than 24 hours in the dog.[54] However, their onset of activity is slower than drugs that act locally. In humans, the antisecretory effect is first seen within 1 hour of oral administration and maximal effects usually occur within 4 days of therapy. The antisecretory effect continues after therapy is discontinued (3 to 4 days) as acid secretion is dependent on the synthesis of new protein. Dogs and cats are often treated with oral omeprazole at a dose of 0.7 to 1 mg/kg daily.

Human preparations of omeprazole are formulated as tablets or capsules containing enteric coated granules of the drug. Omeprazole is labile to protonation in the acidic environment of the stomach, which will decrease gastrointestinal absorption. Disrupting the enteric coating by crushing the granules should therefore be avoided. It has been suggested[54] that once acid secretion has decreased, subsequent doses will not be affected. Enteric-coated omeprazole paste preparations registered for use in horses (e.g., Gastrozol) have not been assessed for use in dogs and cats. The recruitment of compounding pharmacies to produce compounded omeprazole should be treated cautiously as pharmaceutically equivalent preparations may not be bioequivalent to their commercial counterparts.[55]

Rational Use

Metaanalysis in people reveals that omeprazole is the "gold standard" for treatment of acute gastric ulceration.[56] Omeprazole outperformed placebo in the prevention of exercise-induced gastritis in sled dogs[57] and, as mentioned previously, was the only drug capable of increasing gastric pH in healthy dogs to levels that are considered optimal for the treatment of gastroesophageal reflux disease and duodenal ulcers in people.[12] In another study, however, omeprazole did not demonstrate any statistically significant benefit compared with a negative control in the prevention of gastric mucosal lesions in glucocorticoid-treated dogs with intervertebral disk disease.[7]

Proton pump inhibitors may provide support in the prevention of rebleeding from sites of gastric ulceration. It has been suggested that clot formation is impaired in acidic environments (pH <6).[12] To elevate gastric pH to greater than 6 requires an almost complete inhibition of acid secretion. In dogs and cats, studies to determine the dose necessary to achieve these levels are nonexistent.

Contraindications for Use and Side Effects

Proton pump inhibitors are capable of causing complete cessation of gastric acid secretion. There is no direct evidence in dogs and cats that achlorhydria is harmful, but long-term data are lacking. Currently, there is no evidence that bacterial overgrowth occurs in either dogs or cats with long-term therapy. Long-term use of proton pump inhibitors (>8 weeks) may lead to increased levels of gastrin following inhibition of negative feedback pathways. Posttherapy rebound hypersecretion of gastric acid has been seen with proton pump inhibitors in humans,[22] but rebound hypersecretion was not reported in one dog study.[58] Overall, side effects from proton pump inhibitors are considered uncommon.

As with all drugs capable of decreasing gastric acidity, concurrent administration of ketoconazole or itraconazole with proton pump inhibitors may result in decreased bioavailability of these two antifungal azoles. Proton pump inhibitors have the ability to mask some of the symptoms associated with gastric cancer.

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CHAPTER 46

Hepatobiliary Cytoprotective Agents

Cynthia R. L. Webster

Natural Hepatobiliary Defense Mechanisms

The liver is uniquely susceptible to damage as a consequence of its role in the metabolism of endogenous metabolites and xenobiotics, and its position as a filter for portal blood. These processes expose the liver to high levels of oxidative stress from free radicals generated not only in hepatobiliary cells but also in activated Kupffer cells (resident macrophages in the liver) and infiltrating neutrophils. The liver has developed strong cyto- and hepatoprotective mechanisms, including enzymatic (catalase, superoxide dismutase, glutathione peroxidase, glutathione transferase) and nonenzymatic (glutathione, vitamin E, beta-carotene, bilirubin) antioxidant systems. Glutathione (GSH), a tripeptide of cysteine, glycine, and glutamine, is a major free radical scavenger in the liver. It is synthesized in the cytosol and transported into intracellular organelles. The rate-limiting step in GSH formation is the intracellular availability of cysteine.

Hepatobiliary cells also respond to toxic signals by initiating intracellular prosurvival biochemical pathways. These pathways, which protect against necrotic and apoptotic cell death, are controlled by hormones, such as glucagon, and growth factors, such as hepatocyte growth factor, and work through the modulation of survival kinases, including phosphoinositol-3-kinase (PI3K) and Akt.[1]

Hepatoprotective Agents

A summary of the hepatoprotective agents discussed in the following section can be found in Table 46-1.

Ursodeoxycholate

Chinese black bear bile has been used for its hepatobiliary healing power for centuries. The major bile acid in this bear is ursodeoxycholate (UDCA). Bile acids, a family of molecules synthesized exclusively in the liver, are formed when a hydroxyl group (OH) is added to cholesterol's steroid nucleus. The simplest bile acids are thus the di-OH bile acids, chenodeoxycholate and UDCA. Additional hydroxylation creates the tri-OH bile acids in the cholate group. Bile acids are conjugated to either taurine or glycine in the liver. In cats and dogs, the tri-OH bile acid, taurocholate, is the major circulating bile acid. Some bile acids, unlike UDCA, are hepatotoxic.[2] The structural basis for the differential cytotoxicity of bile acids is not fully understood but is roughly correlated with their degree of hydrophobicity. Toxic bile acids damage hepatocytes by disrupting biologic membranes and stimulating apoptosis.[2]

UDCA's cytoprotective effect is associated with several factors.[3] First, UDCA can replace more hydrophobic hepatotoxic bile acids from the circulating bile acid pool. This effect is of limited value in dogs and cats in which the major circulating bile acid is the relatively nontoxic, taurocholate. A major cytoprotective action of UDCA lies in is its ability to inhibit apoptosis. Mitochondria are key regulators of apoptotic pathways and UDCA can stabilize mitochondrial membrane function, increase mitochondrial stores of glutathione, and prevent the mitochondrial-mediated generation of free radicals, all of which contribute to mitochondrial instability and the initiation of apoptosis. UDCA's antiapoptotic action also involves stimulation of cellular survival signaling through activation of protein (Akt, mitogen-activated kinases) and lipid kinases (PI3K). UDCA is a choleretic agent and this action promotes the excretion of potentially toxic endogenous metabolites retained during cholestasis. UDCA induces choleresis by (a) direct stimulation of a bicarbonate-rich bile flow in the bile ducts (followed by the osmotic movement of water) and (b) increasing the membrane expression of transport proteins necessary to generate bile flow. Emerging evidence suggests that UDCA also works as a biologic response modifier of the glucocorticoid receptor. UDCA can activate the glucocorticoid receptor by interacting with a distinct region of the receptor (not the same binding site as cortisol), inducing nuclear translocation of the glucocorticoid receptor, and suppressing transcription of inflammatory mediators.

Following oral administration, UDCA is absorbed primarily in the small intestine. Absorption is enhanced in the presence of food. UDCA has high hepatic first-pass metabolism (70%). In the liver, UDCA is conjugated to taurine or glycine and then undergoes enterohepatic circulation. UDCA that escapes enterohepatic circulation is metabolized to lithocholate in the colon and eliminated in the feces or urine. The bioavailability of UDCA may decrease with advanced cholestasis because of decreased hepatic extraction and increased renal elimination. Thus in severe cholestasis, twice daily administration of UDCA may be beneficial.

There is little information in the literature on the use or efficacy of UDCA in small animals. The recommended dose (10 to 15 mg/kg/day PO), has been extrapolated from human medicine. One study each in the cat and the dog shows that oral administration of this dose results in the appearance of UDCA in the serum.[4,5] In the dog case report, this dose was associated with biochemical and clinical improvement of chronic hepatitis.

UDCA is well tolerated. Diarrhea and vomiting may occur rarely. Extensive toxicologic studies performed in healthy dogs did not

Table 46-1 Hepatoprotective Agents

Drug	Mechanism of Action	Dose	Indication	Side Effects
Ursodeoxycholic acid	Choleretic Upregulates survival pathways Replaces hepatotoxic bile acids Immunomodulatory	10 to 15 mg/kg/day PO Absorption enhanced in the presence of food	Cholestatic, inflammatory, and metabolic hepatopathies	Rarely vomiting May increase the bioavailability of vitamin E and cyclosporine
S-adenosylmethionine	Transmethylation reactions Increase glutathione levels Increases polyamine synthesis	20 mg/kg/day PO Do not give with food	Cholestatic, inflammatory, and metabolic hepatopathies	None
Silymarin (milk thistle)	Antioxidant Antifibrotic Choleretic	Silymarin: 5 to 15 mg/kg/day PO Siliphos: 3 to 6 mg/kg/day PO	Inflammatory, cholestatic, and metabolic hepatopathies	None Inhibits drug-metabolizing enzymes
Vitamin E	Antioxidant Antiinflammatory	10 to 15 IU/kg/day PO of α-tocopherol acetate	Inflammatory, cholestatic, and metabolic hepatopathies	None
N-acetylcysteine	Antioxidant Restoration of capillary dynamics in acute liver failure	140 mg/kg IV once then 70 mg/kg q6h	Acetaminophen toxicity Acute liver failure Feline hepatic lipidosis syndrome	Vomiting with oral preparations
Carnitine	Necessary for transport of fatty acids into mitochondria Detoxifies toxic intermediates that accumulate in disorders of β-oxidation May retard lipid accumulation	250 mg/cat/day PO	Feline hepatic lipidosis syndrome	None
Zinc	Inhibits intestinal absorption of copper Antifibrotic Antioxidant	100 mg/kg elemental zinc/day q12h	Copper-associated hepatopathies Inflammatory hepatopathies	Vomiting Iron deficiency Hemolytic anemia Monitors serum values, goal is 200 to 500/mg/dL
Colchicine	Inhibits microtubule function and thus secretion of collagen into extracellular matrix	0.01 to 0.3 mg/kg/day PO	Noninflammatory fibrotic hepatopathies	Diarrhea

reveal any serious side effects. No adverse effects were noted in normal cats treated with 10 mg/kg/day PO for 3 months or with 15 mg/kg/day PO for 8 weeks.[4,6] UDCA can increase the bioavailability of cyclosporine and vitamin E.

Currently, this author uses UDCA as ancillary therapy in a variety of acute and chronic hepatopathies in the dog and cat. In some chronic inflammatory hepatopathies in dogs, particularly where corticosteroids are contraindicated, UDCA is used a sole therapy. UDCA is also used to promote bile flow in acute and chronic cholestatic disorders in the absence of bile duct obstruction.

The effect of UDCA on serum total bile acid concentrations has been investigated in normal dogs and cats. In cats given 15 mg/kg/day, pre- and postprandial serum bile acid concentrations increase but are not out of the normal range.[4] In normal dogs, one study showed that 15 mg/kg/day UDCA increased postprandial serum bile acids in only one of 16 dogs whereas another study using the same dose showed that six of 14 dogs developed increased serum total bile acids 1 to 6 hours after oral dosing.[7,8] The effect of UDCA administration on serum bile acid profiles in animals with hepatic disease has not been reported.

S-Adenosylmethionine

The liver is the major site of *S*-adenosylmethionine (SAMe) synthesis and degradation. Methionine is actively transported into the liver and converted to SAMe by the enzyme, methionine adenosyltransferase. The activity of methionine adenosyltransferase is impaired in experimental models of liver injury in laboratory rodent and in human patients with alcoholic cirrhosis. Thus, in the setting of severe liver disease, SAMe becomes a conditionally essential nutrient.[9,10]

In the liver there are three metabolic pathways for SAMe metabolism: (a) transmethylation, (b) transsulfuration, and (c) aminopropylation, and all three are implicated in the compound's hepatoprotective effects.[9,10] In transmethylation reactions, SAMe donates a methyl group to a large number of molecules, including proteins, DNA, and membrane phospholipids. Through methylation of the latter two, SAMe can decrease the expression of

inflammatory cytokines and stabilize mitochondrial membranes. Once SAMe has donated its methyl group, it is converted to *S*-adenosylhomocysteine. In the transsulfuration pathway, *S*-adenosylhomocysteine can be converted by a series of enzymatic steps to cysteine. Because the availability of cysteine is the rate-limiting step in the synthesis of glutathione, SAMe administration can increase hepatic glutathione levels in normal dogs and cats.[11,12] It also ameliorates acetaminophen-induced red blood cell and hepatic damage in cats and dogs, respectively.[13,14] In the third major pathway, SAMe can be decarboxylated to polyamines that can stimulate protein synthesis. Methyladenosine, an intermediate in this pathway, is antiapoptotic in hepatocytes.

Two stable salts of SAMe are available for oral administration.[15] The 1,4-butanedisulfonate salt is marketed for veterinary use as Denosyl-SD4 (Nutramax Laboratories, Inc.) and the tosylate salt is marketed as Zentonil (EVSCO Pharmaceutical). The dose is 20 mg/kg/day. SAMe tablets must be enteric coated and stored in a blister pack. The tablets should not be split or crushed. Because food interferes with absorption, SAMe should be given in the fasting state. SAMe has low oral bioavailability (approximately 3%) because of a significant hepatic first pass effect and rapid metabolism within the liver. SAMe crosses the blood–brain barrier[16] and there is a significant body of literature to support an antidepressant effect in humans.[17] SAMe is rapidly metabolized intracellularly, but that portion not metabolized undergoes renal and fecal excretion. Limited pharmacokinetic studies in dogs show that peak plasma concentrations occur within 1 to 4 hours.[12] No side effects have been reported in human trials and the LD_{50} (median lethal dose for 50% of test subjects) in laboratory rats is greater than 4650 mg/kg/day. Cats given four times the recommended dose for 3 months had no adverse effects.[11]

In a study of prednisone-treated dogs, SAMe did not prevent the development of hepatic vacuolar changes or the induction of serum hepatic enzyme activity.[12] In this study, concurrent prednisone use did not adversely affect the pharmacokinetics or pharmacodynamics of SAMe administration.

In human clinical trials, SAMe has shown beneficial effects in alcoholic and cholestatic liver disorders.[18,19] The therapeutic potential of SAMe in veterinary medicine is unknown as limited clinical studies have been published. Because glutathione levels are decreased in some animals with hepatic disease,[20,21] particularly cats with hepatic lipidosis, SAMe supplementation may be beneficial. SAMe may also be useful as adjunctive therapy in dogs and cats with inflammatory liver disease. This author often uses SAMe in combination with corticosteroids and/or ursodeoxycholate. There is some evidence that the concurrent use of SAMe and ursodeoxycholate may be synergistic.[19] Typically, animals are given a 3-month trial of SAMe to evaluate whether addition to the therapeutic protocol provides symptomatic or biochemical improvement. Because SAMe crosses the blood–brain barrier and there is a considerable body of evidence to suggest that SAMe is effective in the treatment of depression in humans, the possibility of "mood elevating" effects in symptomatic control of hepatopathies cannot be overlooked. SAMe therapy may be useful in the recovery phase of hepatotoxic drug reactions.[22]

Silymarin

The active ingredient in milk thistle, silymarin, is a mixture of flavonoids (silibinin, silidianin, and silichristin), all of which have antioxidant properties.[9,23] Their antioxidant effects are a result of inhibition of lipid peroxidation and inactivation of inflammatory transcription factors and cytokines. Silymarin also promotes protein and DNA synthesis, inhibits collagen synthesis, and restores normal glutathione stores. Because silymarin inhibits the uptake of *Amanita* toxin in dogs, it can be used as an antidote for mushroom hepatotoxicity.[24] Silymarin also promotes choleresis by increasing the insertion of transporters into the apical membrane of hepatocytes.[25] Silymarin inhibits drug-metabolizing enzymes including P-glycoprotein, glucuronyltransferases, and cytochrome P450, so coadministration with other drugs metabolized by these systems should be closely monitored.

Silymarin's bioavailability is low as a result of erratic absorption from the gastrointestinal tract. It has a short plasma half-life in humans (6 hours), but is preferentially accumulated in the liver. It is excreted in the biliary tract as a glucuronide and sulfoglucuronide conjugate, and undergoes some enterohepatic circulation. Bile concentrations are 100 times those in serum. Silymarin appears to be safe and well tolerated. It has been difficult to show clinical benefit of silymarin in randomized control trials in human liver disease.[26] Metaanalyses show that available studies suffer from poor study designs, including a heterogeneous cohort of patients with differing etiology and/or extent of liver disease, small sample sizes, and variation in formulation, dosing, and duration of silymarin therapy. Extrapolation of dose from these studies is difficult, but suggests that 5 to 15 mg/kg/day divided into two to three daily doses might be in the therapeutic range. Typical formulations of milk thistle should contain 70% to 80% silymarin. Siliphos, a formulation of silymarin complexed with phosphatidylcholine, is four to five times more bioavailable than silymarin itself in dogs.[27,28] It is currently marked as a combination product with vitamin E and zinc (Marin, Nutramax, USA) or SAMe (Denamarin, Nutramax, USA).

Vitamin E

The term *vitamin E* refers to a family of eight related, lipid-soluble, antioxidant compounds that are widely distributed in plants.[29,30] α-Tocopherol is the most active form of vitamin E. Vitamin E is important in protecting membrane phospholipids from oxidative damage. In addition to its membrane-protective effects, vitamin E also modulates signal transduction and gene expression. Vitamin E analogues can modulate the activity of lipooxygenases, cyclooxygenases, and protein kinase C, and inhibit activation of the proinflammatory transcription factor, nuclear factor-kappa B. In some instances different synthetic derivatives of vitamin E are more effective than others; for example, the α-tocopherol succinate ester is better at nuclear factor-kappa B inhibition than α-tocopherol acetate. The former analogue also has the unique ability among the vitamin E family members to stimulate selective apoptosis of cancer cells.

There is considerable experimental evidence of the therapeutic benefit of oral administration of vitamin E in chronic hepatic disease in humans and experimental models.[30] A small pilot study in 20 dogs with chronic hepatitis treated with a vitamin E supplemented diet for 3 months showed an increase in serum and liver vitamin E levels and some indication of increased antioxidant protection.[31] The diet provided a low daily dose of vitamin E (0.58 IU α-tocopherol acetate/kg body weight/day) so it is not surprising that no effect was seen on biochemical indicators of hepatic disease. The recommended oral formulation of vitamin E is the acetate form of α-tocopherol. It is used at a dose of 10 to 15 IU/kg PO once a day. Because cholestasis can interfere with the intestinal absorption of this fat-soluble vitamin, an emulsified formulation of vitamin E for parenteral administration has been developed. In a recent study, administration of this emulsified vitamin E ameliorated acute hepatobiliary injury that was induced by administration of hydrophobic

bile acids.[32] This formulation may prove to be useful in the management of acute cholestatic hepatopathies such as idiopathic hepatic lipidosis in cats.

N-acetylcysteine

N-acetylcysteine (NAC) is a stable formulation of the amino acid L-cysteine that can be given parenterally to replenish intracellular cysteine, and thus glutathione, levels.[33] It is a well-recognized antidote for acetaminophen-induced red blood cell and hepatocyte toxicity. NAC restores intracellular GSH levels that result in the detoxification of the reactive intermediate generated by cytochrome P450 metabolism of acetaminophen. The dose is 140 mg/kg IV initially, then 70 mg/kg q6h for seven treatments. NAC has additional beneficial effects, particularly in acute liver failure, where it is cytoprotective to endothelial cells and can improve blood flow and oxygen extraction in microcapillary beds. A high incidence of gastric irritation and vomiting limits the use of oral formulations of NAC.

Colchicine

Colchicine is a microtubular inhibitor that is used in hepatobiliary disease primarily for its antifibrotic effects. Colchicine's main mechanism of action is to inhibit collagen secretion, but it can also suppress inflammation by inhibiting neutrophil migration and degranulation and promote collagen degradation by stimulating collagenase activity. In isolated case reports, colchicine has shown variable efficacy in canine chronic hepatitis when used at 0.01 to 0.3 mg/kg/day PO.[34,35] In human medicine, metaanalysis of several large, randomized clinical trials of patients with chronic hepatitis/cirrhosis have not shown a beneficial effect of colchicines, and some studies actually have shown increased morbidity/mortality in the colchicine-treated patients.[36] Colchicine use should be limited to those canine patients with noninflammatory fibrotic hepatopathies. The major side effect is hemorrhagic diarrhea, although bone marrow suppression and peripheral neuropathies have been reported in humans. The use of colchicine has not been reported in cats.

Zinc

Zinc, a trace mineral that is an essential cofactor for a number of enzymes, has antifibrotic, antiinflammatory, and antiapoptotic effects in the liver.[37] Zinc is also used to treat copper-associated liver disease.[38] Zinc deficiency accompanies some chronic hepatopathies in humans, and there are anecdotal reports of low hepatic zinc levels in canine chronic hepatitis. Zinc is available as zinc acetate, sulfate, and gluconate salt. The suggested dose is 100 mg/kg of elemental zinc per dog q12h. The percentage of elemental zinc in the various salts is: Zn acetate, 30%; Zn gluconate, 14%; and Zn sulfate, 23%. Zinc should be administered on an empty stomach. Side effects include anorexia, vomiting, and hemolytic anemia. Plasma zinc levels should be monitored and kept below 800 µg/dL.

Carnitine

Carnitine is a cofactor in the transport of long-chain fatty acids across the inner mitochondrial membrane into the mitochondrial matrix where they can be utilized for energy production. Carnitine is also important in removing excess mitochondrial acetylcoenzyme A, the accumulation of which can impair β oxidation. Carnitine is derived from dietary sources (meat and dairy sources) or synthesized by the liver. Studies suggest that carnitine supplementation in obese cats undergoing weight loss increases the β-oxidation of fatty acids and decreases hepatic lipid accumulation.[39] Thus carnitine supplementation (250 mg/cat/day) has been advocated in the management of cats with liver failure as a consequence of hepatic lipidosis. This is despite the fact that cats with this syndrome have liver and skeletal muscle carnitine levels that are greater than those seen in control cats.[40] Carnitine supplementation can also improve neurologic status in human cirrhotic patients with hepatic encephalopathy.

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CHAPTER 47

Enzyme Supplementation

Elias Westermarck

The exocrine pancreas has great reserve capacity; consequently, the clearly recognizable signs of failure emerge only when up to 90% of the exocrine gland tissue has been compromised. Replacement therapy with enzyme supplementation is then needed to compensate for the lack of endogenous enzyme production.[1]

Pancreatic enzyme replacement therapy was first attempted in human medicine at the turn of the twentieth century and it was shown that nutritional status could be significantly improved with such therapies. One challenge to this therapy is the sensitivity of pancreatic enzymes to gastric acid. Amylase and lipase are the most susceptible and are destroyed at a pH below 4.5. Trypsin can withstand a pH of 3.5, thus remaining unaffected by most pH conditions in the stomach. In humans, only 17% of ingested lipase can be recovered intact from the duodenum.[2] To improve passage of pancreatic enzymes through the acidic environment of the stomach, pharmaceutical companies have developed porcine, enteric-coated pancreatic enzyme preparations. The manufacturing process must be gentle to ensure that enzymes are not destroyed. Although much is already known about pancreatic enzyme supplementation, modern replacement therapy has significant room for improvement. Despite adequate enzyme supplementation, digestion capacity does not return to normal in humans or dogs with exocrine pancreatic insufficiency (EPI). Only a small portion of the orally administered enzyme is delivered intact and functional to the small intestine.[1] For maximum digestive efficiency, pancreatic enzyme preparations should be formulated to (a) protect acid-labile enzyme from gastric inactivation, (b) provide concomitant gastric emptying of the enzyme with the ingested meal, and (c) deliver maximal enzyme activity to the proximal duodenum. To fulfill these criteria, formulation of a sustained-release preparation of pancreatic extract that releases enzymes over a prolonged period of time to a site favorable for their function would be highly desirable. Unfortunately, this preparation is not yet commercially available.[3]

The gastric-emptying rates of nondisintegrating forms of enzyme have been reported in several studies. Early studies reported that particles reduced to a size of 2 mm or less are emptied rapidly from the canine stomach.[4] More recently, however, in normal dogs and in one dog with EPI, the majority of multiunit preparations (diameter, 1 to 1.7 mm) have been shown to remain in the canine stomach for up to 8 hours before being emptied into the duodenum by the interdigestive migrating motility complex.[5] The majority of pancreatic enzymes prepared in granule form obviously would never be emptied from the stomach simultaneously with food. Even a reduction of granule size to 0.3 mm had no clear effect on the gastric-emptying time of these preparations. It can be concluded, therefore, that smaller granules (<0.3 mm) will be needed to optimize gastric emptying of multiple-unit preparations in pancreatic replacement enzyme therapy. It should be recognized, however, that this could aggravate existing problems in manufacturing associated with granulation and particle coating.[3] In humans with chronic pancreatitis or cystic fibrosis, encapsulated enteric-coated microspheres and minimicrospheres (diameter <1.7 mm) are considered the enzyme treatment of choice. Even so, full recovery from the catabolic state of EPI with enzyme replacement therapy is never achieved in all patients.[6]

To study the effect of different enzyme preparations in the treatment of dogs with EPI, experimental studies were carried out in two dogs with cranial jejunal cannulation.[7] Food was supplemented with commercial enzyme preparations in the following sequences: powder, granules, capsules, enteric-coated tablets, and finely chopped raw pig pancreas. Jejunal ingesta were sampled at 30-minute intervals for 6 hours after feeding. Protease, amylase, and lipase activities were determined in jejunal samples and in feces. The control subjects comprised 14 healthy dogs and one subclinical EPI dog. This dog had approximately 90% pancreatic atrophy, but did not yet have clinical signs of maldigestion. In normal dogs and in the EPI dog, the highest lipase activities in the jejunal samples were achieved using raw pig pancreas. Powder achieved the second highest activities, but the other commercial porcine enzyme preparations yielded activities that were only one-tenth of those attained with the raw pancreas. Raw pancreas and commercial enzyme preparations increased the activities of proteases and amylase well beyond those found in the jejunum of the subclinical EPI dog. With the commercial powder preparation and with the raw pancreas, jejunal enzyme activity was detected immediately after feeding. Capsules and granules delayed the appearance of jejunal enzymatic activity by 1 to 2 hours and enteric-coated tablets by 5 hours. It should be noted that measuring enzymatic activity in feces was not reliable for evaluating the potency of pancreatic enzyme preparations added to food. Lipase activity was seldom found in the colon, and amylase and protease activities showed substantial variation.

The effect of the two uncoated enzyme supplements—raw chopped pancreas and porcine pancreatic powder preparation—were compared in a long-term clinical study.[8] The study included 76 dogs with an EPI diagnosis: 40 dogs were fed powdered enzymes and 36 dogs were fed raw chopped pancreas. When comparing the prevalence of clinical signs, there were no significant differences between the two groups. The study showed that in practice, the prescription of one of these supplements was largely based on economics and practicality. The raw chopped pancreas was only one-fourth as

expensive, but practical difficulties, mainly in availability, handling, and storing, were considerable compared with powdered enzyme supplements. The most common source of raw chopped pancreas was from pigs (72%), followed by cattle (19%) and lambs or reindeer (9%). The mean amount of raw chopped pancreas was 87 g/meal. It has been shown that raw pancreas can be stored frozen for several months prior to feeding. All dogs treated with powdered enzyme supplements were fed the same product (Viokase V, Fort Dodge Laboratories, IA), and the mean amount was 3 g/meal. No correlation was found between body weight and amount of enzyme fed.

Because raw chopped pancreas is not available in many countries, powder enzyme supplementation is the most common treatment for dogs and cats with EPI. Widely accepted treatment recommendations for dogs include feeding of a dose of 1 to 2 tsp of powdered pancreatic extract per 20 kg body weight at each meal.[9] For cats, a starting dose of 0.5 to 1 tsp should be administered with each meal. Enzymes should be mixed with food 20 minutes before feeding. Thereafter, pet owners are counseled to decrease the dose of pancreatic enzymes based on their pet's initial response. Most dogs require at least 1 tsp of enzymes per meal. Little additional improvement was observed after doubling or quadrupling this dose in EPI dogs with experimental pancreatic ductal ligation.[10] Side effects of porcine pancreatic extracts are rare, but it has been reported that high doses of pancreatic enzyme supplements can cause oral bleeding in dogs with EPI. Oral bleeding can be successfully managed by dose reduction in most dogs.[11]

Numerous attempts have been made to increase the efficacy of enzyme supplementation in dogs. Antacids or histamine H_2-receptor antagonists have been recommended in the therapeutic regimen to reduce gastric acid–induced destruction of orally administered enzyme. This practice is, however, costly and does not necessarily increase the efficacy of pancreatic enzyme supplementation.[9,12] In humans, a double-blind, placebo-controlled crossover study was conducted to measure the effect of acid suppression (ranitidine or omeprazole) on fat absorption in patients with cystic fibrosis. No overall significant improvement in fat absorption could be demonstrated with adjuvant therapy.[13] Concurrent oral administration of bile salts and preincubation of the meal with pancreatic enzymes for 20 to 30 minutes before feeding also did not improve the response.[14]

Besides porcine pancreatic extracts, bacterial lipase has been reported to be effective in correcting steatorrhea in dogs with experimental EPI.[15] Bacterial lipase is secreted by *Burkholderia plantarii* during fermentation. It is resistant to acid denaturation and protease digestion and does not require colipase activation for lipolytic activity. Bacterial lipase maintains activity even in the presence of bile acids. The effects of bacterial lipase were compared with those of a powdered porcine pancreatic enzyme preparation (Viokase powder, A.H. Robins Co., Richmond, VA) in alleviating steatorrhea in EPI dogs. The results of that study revealed that correcting steatorrhea required 75 times more porcine lipase than bacterial lipase by weight (240 mg vs. 18 mg). Improved fat absorption with use of bacterial lipase does not, however, improve absorption of the other nutrients, and thus, proteases and amylase are still necessary to correct protein and carbohydrate malabsorption, if present. These studies further showed that in using bacterial or porcine lipase to treat dogs with experimental EPI, a high-fat and high-protein diet improved fat absorption more efficiently than a low-fat, low-protein diet.

Enzyme preparations of vegetable origin have also been launched alongside ordinary pancreatins; these are extracted from molds or contain a protein-cleaving papain from the tropical papaya tree. Nevertheless, preparations obtained from an animal (porcine) pancreas have been demonstrated to be the ideal replacement enzymes and can in no case be replaced by vegetable ferments.[16] An experimental study in dogs has, however, shown that fungal lipase may prove to be useful in treating dogs with EPI.[17]

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CHAPTER 48

Fluid Therapy

Rance K. Sellon

Dogs and cats with gastrointestinal (GI) disease commonly need fluid therapy. The most basic reasons for fluid therapy in patients with GI disease are replenishment or maintenance of intravascular fluid volumes and correction of specific metabolic deficits, such as electrolytes, serum protein concentrations, and others, that arise secondary to GI disease. As such, there is no "one-size-fits-all" approach to fluid therapy in patients with GI disease; rather, fluid therapy should be tailored to the needs unique to the individual patient. Provision of appropriate fluid therapy requires an inventory of a variety of fluid types, access to laboratory and other technologies for patient monitoring, and a staff trained in the monitoring and care of patients receiving fluid therapy.

Pathophysiology

The need for fluid therapy in patients with GI disease arises from a number of pathophysiologic conditions. Because of malaise and anorexia, dogs and cats with GI disease may have fluid intake reduced to a level unable to offset sensible and insensible fluid losses. Patients with GI disease are also susceptible to increased fluid losses as a result of vomiting, diarrhea, and, in some cases, polyuric states. Lastly, some types of GI disease put patients at risk for fluid redistribution into third spaces, such as edema or effusion caused by hypoalbuminemia and peritonitis. These pathophysiologic processes are not mutually exclusive, and all three mechanisms could be operative in a given patient. This chapter is a broad overview of fluid therapy in patients with GI disease. Readers interested in more in-depth information regarding fluid therapy are referred to other references.[1,2]

Goals of Fluid Therapy

Some important goals of fluid therapy, and the general types of fluids commonly used to meet these goals, include the following:[1,2]

- Restoration and maintenance of circulating volume for tissue perfusion: crystalloid and colloidal fluids
- Correction of abnormalities of electrolytes, glucose: crystalloids, electrolyte, and glucose supplements
- Provision of oncotic support: synthetic and natural colloids
- Restoration of oxygen-carrying capacity: whole blood and blood products
- Provision of nutritional support: enteral and parenteral nutritional solutions

Drug Classifications

Crystalloids and colloids are the fluid types most commonly used in the treatment of dogs and cats with GI disease. Crystalloids are compositions of fluid and electrolytes in varying proportions that are divided generally into replacement fluids and maintenance fluids. Box 48-1 provides examples of each of these types of fluids. Replacement fluids, as the name suggests, are designed to replace water and electrolytes lost as a consequence of GI (or other) disease, and are characterized by higher concentrations of sodium than maintenance fluids, which have proportionally more water than replacement solutions. Colloids can be synthetic or natural. Box 48-1 also outlines examples of synthetic and natural colloids.

Rational Use in the Diagnosed Patient

Indications for Fluid Therapy

Determined by History and Physical Exam

The decision to administer fluids to a patient with GI disease should take into account historical elements (e.g., is the patient voluntarily eating and drinking?), physical examination findings, results of laboratory or other diagnostic tests, and the underlying disease process. Patients that are unwilling, or unable, to drink emerge as more likely candidates for fluid therapy than those patients that can and will drink. Dogs or cats that are dehydrated, as suggested by the physical examination and/or laboratory results, also become candidates for fluid therapy. The physical examination assessment of hydration status has potential errors in interpretation. Animals that have lost considerable body weight commonly have reduced skin turgor, prolonged skin retraction, and ocular recession even if normally hydrated. Heart rates can be elevated for reasons other than dehydration. Nausea may contribute to a degree of mucous membrane moistness in the dehydrated patient, and mucous membranes may be overly dry in the patient that has been panting. Capillary refill times may be prolonged as a result of marked sympathetic stimulation and constriction of peripheral vascular beds, or may be very rapid in patients with peripheral vasodilation or hyperdynamic states of cardiovascular shock (as occurs, e.g., with sepsis).

Determined by Laboratory Data

Laboratory abnormalities that could suggest the need for fluid therapy include hemoconcentration, prerenal azotemia for reasons

Box 48-1 Fluids Used in the Treatment of Gastrointestinal Disease of Dogs and Cats

Crystalloids

Replacement
- Lactated Ringer's solution
- 0.9% Sodium chloride
- Normosol-R
- Plasmalyte

Maintenance
- 5% Dextrose
- Plasmalyte
- 0.45% Sodium chloride/half-strength lactated Ringer's solution

Colloids

Synthetic
- Hetastarch
- Gentran
- VetStarch

Natural
- Plasma (fresh or fresh frozen)
- Concentrated albumin solutions
  - Human
  - Canine

other than heart failure or reduced cardiac output, and abnormalities in electrolytes such as hyper- or hyponatremia, hyper- or hypokalemia, and acid–base disorders. Electrolyte abnormalities are nearly impossible to predict in patients with GI disease, so baseline laboratory evaluations should be obtained to guide choices in fluid therapy. Some volume-depleted patients may have a small cardiac silhouette or small pulmonary vessels evident on thoracic radiographs. It is common for abnormalities of hydration status to mask laboratory abnormalities—for example, the dehydrated and anemic patient may initially have a normal packed cell volume—so the clinician needs to be mindful of all the pathophysiologic processes that influence a given laboratory result and assess the patient for the presence of multiple pathophysiologic processes that could confound laboratory interpretation.

Determined by Underlying Disease and Severity

The underlying disease process may also influence fluid therapy decisions. For example, adult animals with acute, self-limiting gastroenteritis without physical examination or laboratory data abnormalities may be fine without fluid therapy, or with minimal fluid therapy, whereas puppies with acute parvoviral enteritis are likely to die without fluid therapy.

Fluid Selection

The type of fluid administered to a dog or cat with GI disease is based on history, physical examination, and diagnostic test results. Patients that are dehydrated are usually candidates for replacement-type crystalloid fluids; patients that are profoundly hypotensive or hemodynamically unstable may benefit from boluses of colloid fluids in addition to initial replacement fluids. Patients with effusions from inflammatory disease, or hypoalbuminemic patients, commonly need colloidal support to help maintain a degree of effective circulating vascular volume. Patients that are not dehydrated, but for which a need for fluid supplementation is anticipated, may require little more than a maintenance type of fluid. Moderate to marked hypoalbuminemia, or hypotension/shock are often indications for colloidal fluid administration.[3]

Route of Administration

Fluids may be administered orally, intravenously, subcutaneously, or occasionally intraosseously. For most patients with GI disease, the most commonly employed routes are oral, intravenous (IV), and subcutaneous (SC). For animals, dogma has long held that patients with vomiting and diarrhea should receive fluids through routes other than oral.[4] Dogma has been challenged, however, as Mohr and colleagues[5] demonstrated that parvovirally infected puppies fared no worse, and were discharged from the hospital sooner, when oral nutrition solutions were administered. In people, oral electrolyte-containing fluids are commonly administered to diarrheic patients as the ability to absorb sodium, and thus water, remains intact in most diarrheal illnesses (see Chapter 1). Similar studies demonstrating a benefit of oral rehydration therapy in diarrheic dogs have not yet been performed, but it is likely that many would benefit from oral fluid therapy. IV fluids should be the prime consideration for patients that need rapid fluid volume replacement (e.g., shock, hypotension) and for patients with persistent vomiting. Fluids given subcutaneously may suffice for the normally hydrated patient that needs short-term fluid support, but this route is not ideal for volume replenishment given the comparatively small volumes of fluid that can be successfully given via this route. Intraosseous and intraperitoneal routes of fluid administration are typically reserved for those patients for which venous access is not possible. For a description of the technique of intraosseous fluid administration, the reader is referred to other sources.[1]

Monitoring of Fluid Administration

Once fluid therapy has been initiated, monitoring becomes an important element of the therapeutic strategy, particularly for those patients with complicated or long-term fluid needs. Assessment of therapeutic responses should be based on changes in physical examination findings; for the GI disease patient for which changes are taking place rapidly, physical examination assessments may have to be done frequently to best monitor fluid therapy responses. Attention to general attitude and appearance, heart rate, pulse quality, capillary refill time, mucous membrane color, and blood pressure are among the simplest of physical examination parameters that can be used to judge responses to fluid administration. Other parameters that are particularly useful for assessing responses to fluid therapy include urine output (may require a urinary catheter), body weight, and central venous pressure (increased with increased vascular fluid volume). Urine output in an adequately hydrated patient should be at least 1 mL/kg/h and values less than that could reflect insufficient rehydration, or oliguria/anuria secondary to renal injury. Body weight should increase in patients that are rehydrated. Increases in body weight in the face of physical examination or laboratory parameters that suggest continued volume depletion likely reflect third-space losses (interstitial edema, peritoneal or pleural effusion, GI tract fluid accumulation). Conversely, patients losing weight in the face of fluid therapy likely have had an underestimation of GI, urinary, or insensible fluid losses. Central venous pressure, if measured, should be between 5 and 10 cm water.

A number of laboratory values are likely to change with fluid therapy, and become part of the monitoring equation. Special attention should be paid to erythrocyte mass, serum total protein, serum albumin, blood urea nitrogen (BUN), serum creatinine, electrolytes, and acid–base status, typically as reflected by changes in total CO_2 and anion gap. Adjustments in fluid rate, composition (e.g.,

electrolyte or other additives), or fluid type (e.g., addition of a colloid) are all potential outcomes of monitoring of fluid therapy responses.

Contraindications and Side Effects

Although fluid therapy is often important, even lifesaving, in the patient with GI disease, fluid therapy is not without potential adverse effects. Adverse effects can be seen following administration of either crystalloids or colloids.

Administration of excessive amounts of fluids, particularly if administered intravenously, can lead to overhydration. Overhydration increases the risk of edema or effusion formation as a result of increased hydrostatic pressure. In patients with underlying cardiac disease, excessive fluid administration can provoke overt signs of heart failure (pulmonary edema, pleural or peritoneal effusion). Additionally, overhydration can dilute serum albumin concentrations and oncotic pressure, creating an additional risk factor for edema or effusion formation. A common complication of crystalloid fluid therapy is hypokalemia, particularly if potassium supplements are not added to the fluids.

Complications of colloid administration include coagulation disorders, which are more of a concern with synthetic colloids. Administration of natural colloids (plasma, albumin) can be associated with hypersensitivity reactions.[6-8] The risk of transfusion reactions associated with plasma administration can be reduced by minor crossmatching (donor serum to recipient erythrocytes), but febrile reactions associated with plasma transfusion are still possible, likely mediated through leukocyte–platelet aggregates.

Concentrated human albumin solutions have been used, primarily in dogs, for the provision of oncotic support. Although available literature suggests that hypersensitivity reactions in clinical patients are not common, deaths in normal dogs have developed secondary to administration of concentrated human albumin.[6-8] Thus, this product should be used with caution in dogs. Albumin products given to dogs with protein-losing enteropathies are likely to be of only short-term benefit because of ongoing losses, but these products can be quite helpful in perianesthetic/perioperative periods when anesthetic and surgical interventions are likely to exacerbate hypoalbuminemia and attendant consequences.

In addition to the physiologic complications that can be seen with fluid therapy, other complications are possible. Catheter or catheter site infections are possible if aseptic technique is not followed when placing IV catheters. Thrombophlebitis can be a consequence of IV catheterization, and administration of hypertonic or irritant fluid types. Blood loss can arise if patients chew connections on catheter ends. Extravasation of fluids can also occur if catheters are not secured to the patient.

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CHAPTER 49

Immunosuppressive Drugs

Rance K. Sellon

When aberrant or uncontrolled immune responses either target directly, or indirectly affect, the gastrointestinal (GI) tract, immunosuppressive drugs may be prescribed. When used for the treatment of GI disease, immunosuppressive therapy is typically administered with the goal of suppressing antibody and/or cell-mediated immune responses. A number of GI diseases of dogs and cats have either demonstrated, or suspected, pathophysiologic attributes of immune-mediated disease or dysregulated immune responses. Among the most common of GI diseases treated with immunosuppressive therapy are idiopathic stomatitis, megaesophagus secondary to myasthenia gravis, chronic enteropathies, anal furunculosis, and chronic hepatitis.

When treating dogs and cats affected by such disorders with immunosuppressive drugs, commonly accepted goals of therapy should be kept in mind. First and foremost, immunosuppressive therapy is given to control clinical signs. In some cases, control of clinical signs will be accompanied by improvements in other hallmarks of the disease being treated, for example, hypoalbuminemia in patients with protein-losing enteropathy. However, improvements in laboratory or other diagnostic features will not be appreciated in all patients despite improvements in clinical signs.[1] Thus, for patients with resolution of clinical signs of GI disease, increasing or altering immunosuppressive therapy with the specific goal of improving a laboratory or other parameter may be met with unwanted side effects or increased cost of therapy or monitoring, and should be carefully considered. The clinician should also keep as a goal of immunosuppressive therapy control of clinical signs with the lowest possible dose of drugs and longest dosing interval. Such goals also help the clinician attain a last objective of immunosuppressive therapy, which is minimization of side effects. For some clients, keeping cost to a minimum will also be a goal of therapy, and such client-driven restrictions will often dictate the immunosuppressive options possible.

Drug Categories, Mechanisms of Action, and Formulations

For dogs and cats, there are a limited number of drugs used for immunosuppressive treatment of GI disease. The most commonly used classes of drugs are glucocorticoids, calcineurin inhibitors, antimetabolites, and alkylating agents. Because of different mechanisms of action, different classes of immunosuppressive drugs are often given in combination. For most of the diseases treated, there is little high-quality (blinded, placebo-controlled) clinical evidence that supports the use of any given immunosuppressive protocol.

Glucocorticoids

Glucocorticoids are the mainstay of immunosuppressive therapy for most GI diseases needing such treatment. There are many formulations of glucocorticoids, but some of the most commonly used in the treatment of gastrointestinal disease, and their dosage suggestions, are presented in Table 49-1. It is expected that most clinicians will have an appreciation for the common side effects of glucocorticoids in dogs and cats.

Glucocorticoids have wide-ranging effects on the immune system and are beneficial for suppression of both antibody and cell-mediated immune responses. The mechanisms underlying the immunosuppressive effects of glucocorticoids are complex, and the level of understanding of these mechanisms is still evolving.[2,3] Some of the immunosuppressive effects are mediated through the interaction of glucocorticoids with cytoplasmic glucocorticoid receptors (GRs). The steroid–GR complex interacts with specific DNA sites termed *glucocorticoid-response elements*. Glucocorticoid-response elements are able to suppress, either directly or indirectly, the transcription of genes that encode proteins with proinflammatory and immune-stimulating activity. There is evidence that the antiinflammatory/immunomodulatory effects of glucocorticoids are also mediated by interaction of the glucocorticoid-GR complex with the regulatory factor nuclear factor-kappa B (NF-κB). With appropriate stimuli, NF-κB migrates from the cytoplasm to the nucleus and binds to key sites on DNA to initiate transcription of a variety of inflammatory and immune mediators. In the presence of the glucocorticoid–GR complex, NF-κB is not able to translocate to the nucleus.

Most glucocorticoids used in the treatment of canine and feline GI disease exert their effects systemically. A potential exception is the glucocorticoid budesonide. In people, budesonide has extensive first-pass hepatic metabolism and therefore is associated with fewer systemic effects than other orally administered glucocorticoids. Budesonide is used in the management of human inflammatory bowel disease (IBD).[4] A reduction of systemic effects would hold obvious appeal in the treatment of dogs or cats with IBD; however, the pharmacokinetics of budesonide have not been extensively investigated in these species. Available studies of budesonide administration to normal dogs and dogs with IBD have shown suppression of the hypothalamic–pituitary–adrenal axis, suggesting some systemic absorption of biologically active drug. However, these studies did note fewer of the other common side effects of systemically active glucocorticoids, such as polyuria, polydipsia, and increased liver enzymes.[5,6]

Table 49-1 Formulations and Dosages of Glucocorticoids Commonly Used in the Management of Small Animal Gastrointestinal Tract Disease*

Formulation	Immunosuppressive Dosage	Comments
Prednisone/prednisolone	1 to 2 mg/kg PO q12h (D, C)	Prednisolone is preferred by some clinicians for cats.
Dexamethasone	0.2 to 0.5 mg/kg PO, IV, SC q24h	Dosage suggested on the premise that dexamethasone is 4 to 5 times as potent as prednisone; may have less sodium and water retentive properties than prednisone.
Methylprednisolone acetate	20 mg SC q2wk (C)	Depo forms not recommended. If there is a need for empirical glucocorticoid therapy, use shorter-acting forms.
Methylprednisolone sodium succinate	30 mg/kg IV initially, then 15 mg/kg IV every 2 to 6 h	Immediate-acting formulation
Budesonide	3 mg/m^2 (D) 1 mg/day for "small" dogs; 2 mg/day for "medium" dogs; 3 mg/day for "large" dogs 1 mg/cat once or twice daily	Considered to have approximately 15 times the potency of prednisone; pharmacokinetic studies that establish optimal dosage guidelines have not been done in dogs or cats.

C, cat; D, dog; IV, intravenous; PO, per os; SC, subcutaneous.
*Readers are referred to chapters on the specific diseases for more details regarding therapy. Clinicians should familiarize themselves with any drug (dosing, routes of administration, adverse effects) before administration to a patient.

Calcineurin Inhibitors

Calcineurin inhibitors are a potent class of immunosuppressive drugs that includes cyclosporine and tacrolimus (FK506). Although these two drugs are structurally different, their mechanism of action depends on inhibition of the protein calcineurin. Calcineurin has serine-threonine phosphatase activity, and substrates of this enzyme include transcription factors that lead to cytokine gene activation. Inhibition of calcineurin activity causes decreased production of key cytokines, such as interleukin-2 and others that support the development of T-cell–dependent immune responses. The immunosuppressive effects of the calcineurin inhibitors encompass both B- (humoral) and effector T-cell (cell-mediated) responses.[7]

Cyclosporine is available in several proprietary and generic oral formulations. The practitioner must be aware of the different properties of the formulations as there is substantial variability in GI absorption and hepatic metabolism between formulations. Some of the available proprietary formulations include Sandimmune, Neoral, and Atopica; the latter is the only formulation specifically licensed for use in dogs and cats. Sandimmune requires more bile salt-mediated emulsification for GI absorption, and oral bioavailability is unpredictable, making Neoral, Atopica, or another microemulsified preparation preferable. Parenteral (for intravenous administration) formulations are also available, but have seen limited use in dogs and cats. Cyclosporine also comes in topical formulations, but use of these preparations has not been reported, to the author's knowledge, in dogs or cats with GI disease. Plasma trough levels of cyclosporine can be measured to determine if they are within a therapeutic window, but a common clinical practice is to evaluate drug levels if a desired clinical response is not achieved and adjust dosages if below a therapeutic level.

Evidence in the veterinary literature supports the use of calcineurin inhibitors, especially cyclosporine, in patients with stomatitis, myasthenia-induced megaesophagus, IBD, and anal furunculosis. Tacrolimus comes in formulations for both oral and topical (Protopic) administration; topical tacrolimus (0.1%) has been used successfully in the treatment of dogs with anal furunculosis.[8,9]

Antimetabolites

The antimetabolite drug most commonly used for immunosuppression in dogs is azathioprine. Azathioprine is metabolized to the active compound 6-mercaptopurine, a purine analogue that causes feedback inhibition of enzymes that synthesize purine nucleotides, essential building blocks for DNA. Incorporation of 6-mercaptopurine into DNA results in faulty DNA synthesis and messenger RNA (mRNA) transcription, and impaired T- and B-cell immune responses.[10] The most common side effect of azathioprine administration in dogs and cats is bone marrow suppression causing neutropenia, thrombocytopenia, or, rarely, anemia.[11,12] Pancreatitis is a documented complication of azathioprine administration in people, but evidence for azathioprine-induced pancreatitis in dogs is limited. Likewise, azathioprine can cause hepatic toxicity in people, but reports of dogs developing hepatotoxicity as a result of azathioprine administration are anecdotal. Azathioprine can be given to cats, albeit at much lower dosages than dogs because of an increased risk of toxicity (see Table 49-2).

Alkylating Agents

The mechanism of action of the alkylating agents involves the formation of reactive intermediates that attach alkyl groups to DNA to interfere with DNA replication and mRNA transcription. Alkylating agents impair both T- and B-cell immune responses. Chlorambucil is the most common alkylating agent used for immunosuppressive purposes in patients with GI disease, and is often used in cats when glucocorticoid responses are insufficient, or if there are reasons to avoid glucocorticoids (e.g., diabetes mellitus). Cyclophosphamide, another alkylating agent, has been used for treatment of immune-mediated hematologic diseases, but has seen little use in the management of canine and feline GI diseases (see Table 49-2).

Other Immunosuppressive Drugs

Other immunosuppressive drugs occasionally used in the treatment of immune-mediated diseases of dogs and cats are mycophenolate mofetil and leflunomide. Mycophenolate mofetil (MMF), a product of *Penicillium* spp., is converted to the active metabolite mycophenolic acid. Mycophenolic acid inhibits inosine monophosphate dehydrogenase, a critical enzyme in the synthesis of the purine guanosine. Impaired guanosine synthesis leads to decreased production of guanosine triphosphate (GTP), a nucleotide incorporated into DNA. Because lymphocyte proliferation requires de novo synthesis of GTP, MMF has a selective effect on lymphocytes, and impairs production of $CD4^+$ and $CD8^+$ lymphocytes. MMF

Table 49-2 Dosages and Side Effects of Non-Glucocorticoid Immunosuppressive Drugs Commonly Used in the Treatment of Gastrointestinal Tract Disease*

Drug	Dosage	Side Effects	Other Comments
Azathioprine	1-2 mg/kg PO q24h; often given daily for 10 to 14 days then decreased to every other day (D) 0.3 mg/kg PO q48h (C)	Neutropenia, thrombocytopenia; potential for pancreatitis, toxic hepatopathy	Believed that clinical benefits not appreciated for 2 to 3 weeks.
Cyclosporine	3 to 5 mg/kg PO q12 to 24h	Inappetence, vomiting, diarrhea, gingival hyperplasia	Expensive; better, more predictable absorption with modified formulations
Chlorambucil	2 to 6 mg/m^2 PO q24 to 48h (D) 2 mg/cat PO q48 to 72h	Neutropenia, thrombocytopenia	Does not require hepatic conversion to active metabolites
Cyclophosphamide	250 mg/m^2 PO or IV q7days 50 mg/m^2 PO q48h, or 2.2 mg/kg once daily for 4 days per week	Neutropenia, thrombocytopenia, sterile hemorrhagic cystitis	Routine evaluation of CBC is mandatory; if hemorrhagic cystitis develops, administration of the drug should cease
Mycophenolate mofetil[26]	10 mg/kg PO q8h or 20 mg/kg PO q12h (D)	Diarrhea, which can be bloody	Expensive; optimal dosing schedules have not been established
Leflunomide[27,28]	2 mg/kg PO q12h (D) 4 mg/kg PO q24h (D) 10 mg/day (C)	Anorexia, lethargy, possibly anemia	Expensive, but based on available information; a well-tolerated drug in dogs; dosing information is limited in cats

C, cat; CBC, complete blood count; D, dog; IV, intravenous; PO, per os.
*Readers are referred to chapters on the specific diseases for more details regarding therapy.

has a substantial history as an antirejection drug in canine transplantation models, including bone marrow and kidney, and has shown an ability to inhibit mitogen-stimulated proliferation of feline lymphocytes in vitro.[13,14] There are no published studies regarding the use of MMF in the treatment of animals with GI disease, but anecdotal reports of its use in dogs with myasthenia gravis–induced megaesophagus abound. MMF has been used in the treatment of human IBD,[15] and it could be of benefit in dogs refractory to other therapeutic approaches. Side effects in dogs are common and include lethargy, anorexia, and diarrhea.[16]

Leflunomide is metabolized to an intermediate that inhibits a critical enzyme in the synthesis of uridine. Like guanosine, lymphocytes synthesize uridine de novo, and impediments to uridine synthesis lead to lymphocyte death. Leflunomide has seen use in people with IBD,[17,18] but use in dogs or cats with IBD has yet to be reported.

Rational Use of Immunosuppressive Drugs in Patients with a Definitive Diagnosis

Given the immunosuppressive drug options available to the small animal clinician, an often encountered initial dilemma is deciding which drug or drugs to use in the early treatment period. As previously noted, there are no clinical studies that compare results of treatment of canine or feline GI disease with various single-agent immunosuppressive drugs, or that compare combinations of drugs. Thus, the initial selection of immunosuppressive therapy is often influenced by direct experiences, experiences of others, and owner tolerance of cost and side effects. When deliberating over the menu of drugs available, consideration of the goals of immunosuppressive therapy as discussed previously, in concert with discussions with owners to gauge tolerance for cost and adverse effects, can be useful for guiding the initial choices.

General efficacy, combined with low cost, make glucocorticoids attractive as an initial, or often sole, treatment for GI disease needing immunosuppressive therapy. When treating GI diseases that have an immunopathologic basis, immunosuppressive dosages are needed, and the clinician should not hesitate to administer such dosages in a well-evaluated patient. A common approach to immunosuppressive therapy with glucocorticoids is to administer prednisone at 2 to 4 mg/kg/day for approximately 2 weeks before a dose reduction is considered. Dosage reductions are considered after this if the desired responses have been achieved. As discussed previously, the clinician needs to carefully weigh the merits of using laboratory results over clinical features when evaluating responses to immunosuppressive therapy. The author's approach, assuming the desired clinical response has been seen after 2 weeks, is to make a dose reduction of 20% to 25%. Additional 20% to 25% reductions are prescribed typically every 2 to 3 weeks thereafter, assuming the patient's disease remains in clinical remission. A relapse usually demands reinstitution of the starting high prednisone dose. The clinician should try to find the lowest dose and greatest dosing interval needed to control clinical signs.

Because of the side effects of glucocorticoids and clients' frequent complaints about those side effects, the author is an advocate of starting azathioprine at the same time that glucocorticoids are initiated in dogs. The rationale for this approach is the use of azathioprine as a "safety net" in the event that side effects of glucocorticoids demand changes to the planned treatment approach. Azathioprine is generally well-tolerated, adds nominally to expense, and in the author's experience, often allows disease to remain in clinical remission without glucocorticoids. Azathioprine has an established history of use in patients with IBD, anal furunculosis,[19,20] and myasthenia gravis,[21] although published reports of its use in these diseases are not always placebo-controlled or blinded clinical studies.

Cyclosporine could be considered as part of the initial treatment protocol for GI disease, although the expense of the drug will limit its use in some patients. Cyclosporine is accepted as an initial line of treatment for canine anal furunculosis, although approaches using glucocorticoids or azathioprine have been described. Cyclosporine has been used successfully in the treatment of steroid-refractory IBD in dogs,[22] and has been used as part of the treatment approach to dogs with myasthenia gravis-induced megaesophagus.[23]

For patients that receive combinations of immunosuppressive drugs, another decision is the order of drug cessation. The author largely leaves such decisions to clients who will make choices based on tolerance for side effects or cost. The author does not typically taper cyclosporine, but will instead simply stop the drug. In the author's hands, azathioprine is often the last drug stopped if the drug is otherwise well-tolerated.

Responses of patients to immunosuppressive therapy can be variable. Reasons for treatment failure in the face of immunosuppressive drugs could include inappropriate dosages or dosing regimens, incomplete therapeutic regimens (i.e., the patient needs additional therapy beyond immunosuppressive drugs), poor client compliance, an incorrect diagnosis, or potentially the inherent refractoriness of the disease being treated. The intestinal epithelium is capable of upregulating expression of P-glycoprotein, a membrane protein that can pump some drugs out of a cell, in response to treatment with glucocorticoids. A potential consequence of increased P-glycoprotein expression could be poor response to glucocorticoids as was demonstrated in one study of dogs.[24]

Empirical Immunosuppressive Therapy in the Absence of a Definitive Diagnosis

Owner financial constraints commonly relegate the practitioner to empirical immunosuppressive therapy, often with glucocorticoids as first-line drugs. For most clients, empirical therapy offers the immediate advantage of reduced cost of veterinary care, particularly if favorable responses are appreciated. However, the provision of empirical immunosuppressive therapy warrants additional considerations not often needed for empirical therapy with other drugs. For some diseases, particularly lymphoma, empirical glucocorticoid treatment carries the potential risk of reduced chemotherapy responses should an owner choose at a later time to pursue chemotherapy. Some infectious diseases (e.g., pythiosis, histoplasmosis) can have features similar to idiopathic inflammatory disease of the gastrointestinal tract and could be made worse by immunosuppressive therapy. Although not commonly recognized in dogs and cats, for any given patient receiving immunosuppressive therapy there is a risk of acquisition of opportunistic infections. Poor responses to empirical immunosuppressive therapy do not rule out idiopathic inflammatory GI diseases as immunosuppressive therapy may be only one component of a given patient's therapeutic needs, and some patients require different immunosuppressive approaches to achieve clinical improvement. Lastly, empirical therapy risks delays in diagnosis of diseases that, when treated inappropriately, progress to the point of being more difficult to treat or untreatable (e.g., GI neoplasia). Empirical immunosuppressive treatment of GI disease should only be done after careful examination of the patient, elimination of as many other differentials as possible, and a conversation (ideally documented in the medical record) of the risks and benefits of such treatment. If using immunosuppressive doses of glucocorticoids in an empirical manner, shorter-acting formulations (prednisone, prednisolone, dexamethasone) are favored over intermediate or long-acting forms in case adverse events are appreciated.

Contraindications and Side Effects of Immunosuppressive Therapy

Fortunately, there are few absolute contraindications to immunosuppressive therapy in dogs and cats. It is generally accepted that immunosuppressive drugs should be avoided in patients with known infections, and should be used with caution in patients for which infectious disease is suspected. Short-term administration of immunosuppressive drugs may not exacerbate infections, but there are very few investigations in dogs and cats that specifically address this concern. Glucocorticoids should be used with caution, particularly in cats, where there is preexisting heart disease as glucocorticoids can increase intravascular fluid volume.[25] A known history of adverse reactions or toxicities to certain drugs would typically render a given patient ineligible for additional therapy with that drug, or would provoke extreme caution with additional treatment.

For patients that experience side effects, some (e.g., cytopenias) will resolve with temporary cessation of the drug; often the drug can be reinstituted at a lower dose to avoid the observed side effect. Some side effects (e.g., hepatotoxicity) may require permanent cessation of treatment with the drug. Occasionally, side effects are severe enough so as to require short-term supportive care (e.g., antibiotics for neutropenia, or fluid therapy for GI signs), which should be provided if clinically indicated.

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CHAPTER 50

Laxative Agents

Robert J. Washabau

Definition of Constipation

Constipation is an important pathophysiologic condition of both cats and dogs, but primarily of the cat. Constipation is defined as difficult, painful, or reduced defecation over a period of time ranging from days to weeks or months.[1] Physical examination findings depend on the severity and pathogenesis of constipation. Dehydration, weight loss, abdominal pain, and mild to moderate mesenteric lymphadenopathy are common findings in cats with idiopathic constipation. It is important to consider an extensive list of differential diagnoses in an individual animal, but it should be kept in mind that most cases are idiopathic, orthopedic, or neurologic in origin (see Chapters 10 and 58).[2] Left untreated or poorly monitored, constipation may progress to obstipation (permanent loss of function) and megacolon (permanent loss of form and function).[3]

Therapeutic Strategies for Constipation

Four main strategies are utilized in the management of constipation (see Fig. 10-1 in Chapter 10)[4]:

- Removal of impacted feces
- Laxative agents
- Prokinetic agents
- Surgical resection

Chapter 58 discusses each of these strategies in detail.

Established Laxative Agents

Laxatives promote evacuation of the bowel through stimulation of fluid and electrolyte transport or increases in propulsive motility. Established laxative agents are characterized as bulk-forming, emollient, lubricant, hyperosmotic, or stimulant laxatives, according to their mechanism of action (Table 50-1).[3] Newer laxative agents are more specific in their mechanism(s) of action, and include chloride channel activation, guanylate cyclase activation, μ-opioid receptor antagonism, 5-HT_4 serotonergic receptor agonism, and neurotrophin-3 activation.[5-7]

Bulk-Forming Laxatives

Most bulk-forming laxatives are dietary fiber supplements of poorly digestible polysaccharides and celluloses derived principally from cereal grains, wheat bran, and psyllium. Some constipated cats will respond to supplementation of the diet with one of these products, but many require adjunctive therapy (e.g., other types of laxatives or colonic prokinetic agents). Dietary fiber is preferable because it is well tolerated, more effective, and more physiologic than other laxatives. Fiber is classified as a bulk-forming laxative, although it has many other properties. The beneficial effects of fiber in constipation include increased fecal water content, decreased intestinal transit time, and increased frequency of defecation.[8,9] Short-chain fatty acids derived from fiber fermentation in the gut have been shown to directly stimulate colonic motility.[8,9] Fiber supplemented diets are available commercially, or the pet owner may wish to add psyllium (1 to 4 tsp per meal), wheat bran (1 to 2 tbsp per meal), or pumpkin (1 to 4 tbsp per meal) to canned cat food. To maximize the therapeutic effect, cats should be well hydrated before commencing fiber supplementation. Fiber supplementation is most beneficial in mildly constipated cats, prior to the development of obstipation and megacolon. In obstipated and megacolon cats, fiber may in fact be detrimental. Low-residue diets may be more beneficial in obstipated and megacolonic cats.

Emollient Laxatives

Emollient laxatives are anionic detergents that increase the miscibility of water and lipid in digesta, thereby enhancing lipid absorption and impairing water absorption. Dioctyl sodium sulfosuccinate and dioctyl calcium sulfosuccinate are examples of emollient laxatives available in oral and enema form. Anecdotal experience suggests that dioctyl sodium sulfosuccinate therapy may be most useful in animals with acute but not chronic constipation. As with bulk-forming laxatives, animals should be well-hydrated before emollient laxatives are administered. It should be noted that clinical efficacy has not been definitively established for the emollient laxatives. Dioctyl sodium sulfosuccinate, for example, inhibits water absorption in isolated colonic segments in vitro, but it may be impossible to achieve tissue concentrations great enough to inhibit colonic water absorption in vivo. Dioctyl sodium sulfosuccinate at a dosage of 30 mg/kg/day had no effect on fecal consistency in Beagle dogs.[10] Further studies are required to determine the clinical efficacy and therapeutic role of dioctyl sodium sulfosuccinate in the management of constipated cats.

Lubricant Laxatives

Mineral oil and white petrolatum are the two major lubricant laxatives available for the treatment of constipation. The lubricating

Table 50-1 Classification, Examples, and Doses of Established and Newer Laxative Agents

Drug Classification and Example	Dose
Rectal Suppositories	
Dioctyl sodium sulfosuccinate	1 to 2 pediatric suppositories
Glycerin	1 to 2 pediatric suppositories
Bisacodyl	1 to 2 pediatric suppositories
Enemas	
Warm tap water	5 to 10 mL/kg
Warm isotonic saline	5 to 10 mL/kg
Dioctyl sodium sulfosuccinate	5 to 10 ml/cat
Dioctyl calcium sulfosuccinate	250 mg (12 mL) given per rectum
Mineral oil	5 to 10 mL/cat
Lactulose	5 to 10 mL/cat
Established Laxative Agents	
Bulk Laxatives	
Psyllium	1 to 4 tsp mixed with food, every 24 or 12 hours
Canned pumpkin	1 to 4 tsp mixed with food, q24h
Coarse wheat bran	1 to 4 tsp mixed with food, q24h
Emollient Laxatives	
Dioctyl sodium sulfosuccinate	50 mg PO, q24h
Dioctyl calcium sulfosuccinate	50 mg PO, q12 or 24h as needed
Lubricant Laxatives	
Mineral oil	10 to 25 mL PO, q24h
Petrolatum	1 to 5 mL PO, q24h
Hyperosmotic Laxatives	
Lactulose	1 mL per 4.5 kg PO
Polyethylene glycol	25 mL/kg PO q24h as needed
Stimulant Laxatives	
Bisacodyl	5 mg PO q24h
Newer Laxative Agents	
Chloride Channel Activators	
Lubiprostone	Safe and effective doses not yet established
Guanylate Cyclase Activators	
Linaclotide	Safe and effective doses not yet established
μ-Opioid Antagonists	
Methylnaltrexone	0.15 mg/kg SQ q24 to 48h
Alvimopan	Safe and effective doses not yet established
Serotonergic 5-HT$_4$ Agonists	
Prucalopride	0.01 to 0.2 mg/kg PO q8 to 12h as needed
Neurotrophins	
Neurotrophin-3	Safe and effective doses not yet established

properties of these agents impede colonic water absorption, as well as permit greater ease of fecal passage. These effects are usually moderate, however, and, in general, lubricants are beneficial only in mild cases of constipation. Mineral oil usage should probably be limited to rectal administration because of the risk of aspiration pneumonia with oral administration, especially in depressed or debilitated cats.

Hyperosmotic Laxatives

This group of laxatives consists of the poorly absorbed polysaccharides (e.g., lactose, lactulose), the magnesium salts (e.g., magnesium citrate, magnesium hydroxide, magnesium sulfate), and the polyethylene glycols. Lactose is not effective as a laxative agent in all cats.[11] Lactulose is the most effective agent in this group. The organic acids produced from lactulose fermentation stimulate colonic fluid secretion and propulsive motility. Lactulose administered at a dosage of 0.5 mL/kg body weight q8 to 12h fairly consistently produces soft feces in the cat. Many cats with recurrent or chronic constipation have been well managed with this regimen of lactulose. The dosage may have to be tapered in individual cases if flatulence and diarrhea become excessive. Magnesium salts are not recommended in the treatment of feline constipation and idiopathic megacolon. Anecdotal reports of therapeutic successes have been reported with the polyethylene glycols.

Stimulant Laxatives

The stimulant laxatives (bisacodyl, phenolphthalein, castor oil, cascara, senna) are a diverse group of agents that have been classified according to their ability to stimulate propulsive motility. Bisacodyl, for example, stimulates nitric oxide–mediated epithelial cell secretion and myenteric neuronal depolarization.[12] Diarrhea results from the combined effect of increased mucosal secretion and colonic propulsion. Bisacodyl, at a dosage of 5 mg q24h PO, is the most effective stimulant laxative in the cat. It may be given individually or in combination with fiber supplementation for long-term management of constipation. Daily administration of bisacodyl has been linked to enterocyte injury, but this is of uncertain functional significance (see "Laxative-Induced Colonic Injury" section).[12]

Newer Laxative Agents

Chloride Channel Activators

Chloride channels are voltage-gated anion channels that allow the transport of chloride ions across cell membranes and play a critical role in fluid transport, maintenance of cell volume, and intracellular pH.[5,6]

Lubiprostone

Lubiprostone is a member of a group of compounds referred to as prostones.[13] Prostones are naturally occurring bicyclic fatty acids formed by enzymatic oxidation of the 15-hydroxyl group of prostaglandins to the keto form. Lubiprostone is approved by the U.S. Food and Drug Administration for the treatment of chronic idiopathic constipation in humans. Lubiprostone activates type 2 chloride channels in the apical membrane of intestinal epithelial cells. This activity stimulates chloride secretion, followed by passive secretion of sodium and water (see Fig. 1-17 in Chapter 1). The fluid–induced bowel distention secondarily induces peristalsis, but lubiprostone has no direct stimulatory effect on gastrointestinal smooth muscle. Insufficient safety and efficacy data are currently

available to recommend the routine use of lubiprostone in dogs and cats.

Guanylate Cyclase Activators

Activation of the guanylate cyclase-C (GC-C) receptor increases cyclic guanosine monophosphate, thereby inducing signaling pathways that stimulate chloride and bicarbonate secretion through cystic fibrosis transmembrane regulator (CFTR) chloride channel–dependent mechanisms and, to a lesser extent, CFTR chloride channel–independent mechanisms, and inhibit sodium absorption by a sodium-proton exchanger.[5,6]

Linaclotide

Linaclotide is a GC-C receptor agonist and intestinal secretagogue that improves bowel symptoms and accelerates colonic transit in chronic constipation.[14] Linaclotide has also been shown to attenuate nociceptive reflexes in response to colonic distention in three rodent models of visceral hypersensitivity.[14] Dosage is 0.15 mg/kg SQ q24 to 48h.

μ-Opioid Antagonists

Postoperative ileus has multiple pathogenetic mechanisms. A dominant theme is the activation of enteric μ-opioid receptors resulting in inhibition of enteric nerve activity.[5,6]

Methylnaltrexone

Methylnaltrexone is a quaternary derivative of the μ-opioid receptor antagonist naltrexone.[7] *N*-terminal methylation reduces lipid solubility and prevents the drug from crossing the brain–blood barrier. Methylnaltrexone's reversal of opioid-induced inhibition of enteric nerve activity increase propulsion and secretory activity. Methylnaltrexone is clearly beneficial in the treatment of opioid-induced constipation; its efficacy in the treatment of postoperative ileus has not yet been definitively established. Insufficient safety and efficacy data are currently available to recommend the routine use of methylnaltrexone in dogs and cats.

Alvimopan

Alvimopan has all of the same properties as methylnaltrexone; additionally, alvimopan accelerates colonic transit in healthy individuals, suggestive of a direct prokinetic effect.[7] Insufficient safety and efficacy data are currently available to recommend the routine use of alvimopan in dogs and cats.

Serotonergic 5-HT_4 Agonists

Serotonergic 5-HT_4 agonists bind 5-HT_4 receptors on smooth muscle cells, enterochromaffin cells, myenteric plexus neurons, and intrinsic pathway primary afferent neurons, resulting in stimulation of gastrointestinal motility (see Chapter 52).[5,6,15] Some of the 5-HT_4 agonists also have effects on secretion and visceral sensitivity.

Prucalopride

In addition to its motility effects, prucalopride also modulates cyclic adenosine monophosphate–mediated chloride secretion and visceral sensitivity. Safety and efficacy data have been reported for its use in both dogs and cats (see Table 52-1 in Chapter 52).

Neurotrophins

Neurotrophins play an important role in the development and maintenance of the central, peripheral, autonomic, and enteric nervous systems.[5,6]

Neurotrophin-3

Neurotrophin (NT)-3 reduces fluid absorption, thereby increasing the fluidity of the stool and facilitating defecation. NT-3 has also been shown to accelerate colonic transit. Insufficient safety and efficacy data are currently available to recommend the routine use of NT-3 in dogs and cats.

Laxative Withdrawal Rebound Constipation

Physical dependence is a state of adaptation that is manifested by a drug class specific withdrawal syndrome that can be produced by abrupt cessation, rapid dose reduction, decreasing blood level of the drug, and/or administration of an antagonist.[17] A small percentage of human patients with chronic constipation are dependent upon laxatives to achieve bowel movements without complaints such as severe straining, but several studies have now shown that this is not the result of prior laxative intake. There is no indication for the occurrence of "rebound constipation" after stopping laxative intake in humans,[17] and thus is not likely in dogs and cats either.

Laxative-Induced Colonic Injury

Stimulant laxatives (bisacodyl, phenolphthalein, castor oil, cascara, senna) do cause structural damage to surface epithelial cells that appears to be reversible and of uncertain functional significance. There is no current convincing evidence that chronic use of stimulant laxatives causes structural or functional impairment of enteric nerves or intestinal smooth muscle cells.[18]

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CHAPTER 51

Probiotic Agents

Mary Bowles

Probiotic agents are living organisms with low or no pathogenicity that exert beneficial effects on the health of the host. The use of probiotic agents (Box 51-1) has been advocated for general health as well as the prevention and treatment of many disorders in humans and in domestic and nondomestic animals.[1] Although controlled studies documenting the efficacy of probiotics in dogs and cats are relatively lacking, the strongest and most consistent evidence of beneficial effects resulting from probiotic administration has been related to prevention and therapy of disorders of the digestive system (Table 51-1).[2-4] Probiotics have been used as single-agent therapy or in conjunction with prebiotics as synbiotic therapy (Box 51-1).[5,6]

Probiotic Mechanisms of Action

Multiple mechanisms have been proposed to explain the beneficial effects of probiotic therapy, but most theorize an interaction between probiotic organisms and the indigenous gastrointestinal (GI) flora. Colonization of the intestine, particularly the colon, with bacteria from the environment occurs in the neonate during the first few days of life.[2,7,8] Depending upon the specific organism and the host, these bacteria may preferentially and permanently establish residence in the lumen, mucous gel layer, crypts, or epithelial cell surface of the GI tract.[9] Some bacteria provide benefit to the host through enhancement of immune responses and protection against potentially damaging agents.[2] With few exceptions, probiotic agents establish only short-term residency in the GI tract following consumption by the host. Probiotic organisms bind to epithelial Toll-like receptors thereby triggering specific innate immune responses, depending upon the particular receptor, anatomic site, and host.[10,11] Box 51-2 outlines other proposed mechanisms.[12-14]

Prebiotic Effects on Probiotic Therapy

Fiber-containing prebiotic agents can augment probiotic therapy, although the simple addition of fiber to the diet or as a supplement does not automatically guarantee effective prebiotic activity as the effect varies with fiber type. Two classes of oligosaccharides, oligofructose (fructooligosaccharide) and inulin, are soluble fibers that are considered classic and effective prebiotic agents.[15] Both classes of oligosaccharides are fermented in the colon. Oligofructose, which can be found naturally in soybeans, oats, beets, and tomatoes, undergoes rapid fermentation in the colon and provides the most benefit to bacteria residing in the proximal colon. Inulin, which is found naturally in plants such as Jerusalem artichoke, jicama, and chicory root, undergoes slower fermentation in the colon, and provides benefit to bacteria residing in both the proximal and distal colon. Although the dog and cat small intestines have minimal ability to digest prebiotic oligosaccharides, ileal and colonic bacteria are quite capable of fermenting these soluble fibers to short-chain fatty acids (acetate, butyrate, propionate) that provide metabolic fuel for colonic epithelial cells. Short-chain fatty acids decrease colonic pH resulting in pathogen inhibition, stimulation of sodium and water absorption, and suppression of abnormal colonocytes.[16]

Selection of a Probiotic Preparation

Labeling

When selecting a probiotic preparation for use in the dog or cat, a number of factors should be considered. One of these factors is the lack of regulation by the Food and Drug Administration (FDA) because probiotics are not presently classified as pharmaceutical products. Despite the advances of the past decade, most of the commercially available probiotic preparations, whether marketed for use in humans or animals, do not have adequate studies supporting manufacturer claims. Moreover, product labels have been shown in some instances to be inaccurate or incomplete in their identification and quantification of viable microorganisms.[17] Consequently, it is advisable to start the selection of a probiotic agent by using a product marketed by a reputable, science-based company. By observing this principle, the preparation selected is more likely to satisfy basic criteria for safety and efficacy (Box 51-3).[12,13,17,18] In addition to safety and efficacy data, the manufacturer's label should have information on content, handling, and advisory statements (Box 51-4).[12]

Specific Probiotic Agents

Specific identification of the organism and strain, is valuable because responses of the GI tract and immune system may vary widely depending upon the organism and strain eliciting the response. The lactic acid bacteria *Lactobacillus*, *Bifidobacterium*, and *Enterococcus* species, along with the yeast *Saccharomyces boulardii* are widely believed to be of benefit in cats and dogs with GI disorders.[2,19] Available literature indicates more specifically that *Lactobacillus acidophilus* strain DSM13241 and *Enterococcus faecium* strain SF68 are immunomodulatory bacteria capable of surviving in the canine and feline GI tract.[20,21] In a recent study of acute idiopathic diarrhea, dogs receiving *Bifidobacterium animalis* strain AHC7 as a dietary supplement experienced more rapid resolution of clinical signs compared with similarly affected dogs receiving placebo.[22] Clinical signs resolved more rapidly in dogs fed *L. acidophilus* strain NCC2628, *L. acidophilus* strain NCC2766, and *Lactobacillus johnsonii* strain NCC2767 in

Table 51-1 Canine and Feline Gastrointestinal-Related Disorders Most Likely to Benefit from Probiotic Therapy

Iatrogenic V/D	Stress D	Dietary V/D	Infectious	Miscellaneous
Medication-induced • Antibiotics • NSAIDs • Glucocorticoids	Boarding Travel Weaning Shelter/colony populations Working dogs Environmental changes	Change Indiscretion Intolerance (eg., lactose) Allergy	Viral Bacterial Protozoal	Inflammatory bowel disease Maldigestion/malabsorption SIBO Idiopathic diarrhea Hepatic encephalopathy Exocrine pancreatic disease

D, diarrhea; SIBO, small intestinal bacterial overgrowth; V, vomiting.

Box 51-1 Term Definitions

Probiotic–live microorganisms, which when administered in adequate amounts, confer a health benefit on the host.
Prebiotic–indigestible oligosaccharides that benefit the host by stimulating growth and/or activate the metabolism of a limited number of health-promoting bacteria in the GI tract.
Synbiotic–combination of a probiotic and a prebiotic for the purpose of producing a synergistic beneficial effect.

Box 51-2 Probiotic Mechanisms of Action Related to the Gastrointestinal Tract

Immunomodulation
Stimulate innate protective immune responses of host GI tract
Upregulation or downregulation of GI immune responses through Toll-like receptors
Initiate production of antiinflammatory cytokines
Suppress production of proinflammatory cytokines
Alteration of GI epithelial cell function
Promotes repair of damaged epithelial cells
Aids in epithelial cell production of antibacterial substances and protective proteins
Inhibits epithelial cell apoptosis induced by cytokines
Competitive inhibition of GI attachment of pathogens and toxins

Box 51-3 General Safety and Efficacy Criteria for Probiotic Agents in Commercial Preparations

Stable in product storage
Present in large numbers (>1 × 10^8 colony-forming units)
Resilient to technical processing
Able to survive gastric acidity and bile during GI transit
Capable of establishing temporary residence within the GI tract
Nonresistant to antibiotics
Nonpathogenic, noncarcinogenic, and nontoxic
Incapable of absorption into the systemic circulation following consumption
Capable of providing an obvious health benefit to the host

Box 51-4 Important Probiotic Product Labeling Information

Product Contents
Specific genus, species, and strain of microorganisms identified by current, scientifically recognized nomenclature
Number of live, colony-forming units per unit weight of product for each probiotic agent listed
Identification of fermentable fiber types if prebiotic agents included in product

Product Handling and Advisory Information
Storage requirements
Shelf-life
Recommended dose
Accurate description of effect on host following consumption
Warning information regarding potential adverse drug or medical condition interaction with product
Manufacturer contact information

addition to an elimination diet, compared with a control group fed an elimination diet alone.[23] Shedding of GI pathogens is also influenced by probiotic administration, and responses may vary depending upon host species and type of microorganism administered. In one study, *Enterococcus faecium* NCIB 10415 was administered to dogs, resulting in a decrease in fecal *Clostridium* species shedding, and an increase in *Salmonella* and *Campylobacter* species shedding.[24] Another study, however, reported reduction in shedding of *Campylobacter* by infected cats receiving *L. acidophilus* DSM13241.[25]

Concentration of Microorganisms

In addition to specific microorganism identification, the number of live, microbial organisms (colony-forming units [CFUs]) per unit weight of probiotic product is an important parameter that should be disclosed by the manufacturer. Ideally, the manufacturer has determined that the number of microorganisms included in a product will result in an adequate quantity of viable organisms available to the host throughout the shelf life of the preparation. Although optimal concentrations have yet to be determined, current information suggests that the number of microorganisms for each agent included in a probiotic preparation should be in the range of 1 × 10^8 to 1 × 10^{12} CFUs/g of product to achieve colonization and efficacy.[20,21,26]

Storage and Handling

Probiotic product storage and handling information should be included in the manufacturer's label. Product efficacy is directly tied to organismal viability, so product stability is of particular concern. Avoiding excessive heat, keeping the product dry, and refrigerating after opening are standard manufacturer recommendations. Even when handling instructions are strictly followed, the viability of many probiotic agents declines to an unacceptable level after 6 months of storage, or is adversely affected because of microorganism turnover during GI transit. Consequently, some manufacturers employ processing techniques such as freeze drying,

Table 51-2 Recommended Probiotic Preparations for Dogs and Cats

Product Name (Manufacturer)	Product Form	Product Probiotic Content	Oral Dose	Comments
Culturelle (Amerifit)	Capsule	*Lactobacillus rhamnosus GG* (1×10^{10} CFUs per capsule)	Dog: 1 capsule/day Cat: ½ capsule contents BID	Human product
FortiFlora Canine FortiFlora Feline (Purina Veterinary Diets)	Packet	*Enterococcus faecium SF68* (1×10^{8} CFUs per packet)	1 packet/day of cat or dog formulation Contents sprinkled on food	Veterinary product Antioxidant vitamins included Taurine included in cat product Contents of packet microencapsulated
Prostora MAX (Procter & Gamble Pet Care: Iams)	Chewable tablet	*Bifidobacterium animalis AHC7* (1×10^{8} CFUs per tablet)	Dog: day 1: 2 tabs in the AM + 1 tab in PM Days 2 to 7: 1 tab BID	Veterinary product for dogs Canine-derived probiotic agent
Proviable (Nutramax)	Proviable KP paste Proviable DC capsules	*E. faecium* *Streptococcus thermophilus* *Lactobacillus acidophilus* *Lactobacillus bulgaricus* *Lactobacillus casei* *Lactobacillus plantarum* *Bifidobacterium bifidum* (Total bacteria: minimum of 5×10^{8} CFUs per mL of paste or 5×10^{9} CFUs per capsule)	Proviable KP: Cat: 1 mL PO, BID-TID Dog: <20 lbs: 1 to 2 mL; 21 to 50 lbs: 3 to 4 mL; >50 lbs: 5 mL, PO BID-TID Proviable DC: Dog and cat: 1 capsule PO daily	Veterinary product Same formulation used in cat and dog Probiotic agents microencapsulated Prebiotics included Proviable KP paste: includes kaolin and pectin and should be administered separately from other medications by 1 to 2 hours Recommended to use for ≤72h Proviable DC capsules can be administered alone or with paste

CFUs, colony-forming units.

microencapsulation, or protective coatings to achieve sustained viability during storage and administration.[20,26]

Microorganism Species of Origin

In the future it may be beneficial for label information to include the microorganism species of origin. Until recently, probiotic agents used in dogs and cats have been derived from species other than cat or dog. A few commercially available probiotic preparations now contain canine-derived organisms. Given the specific host interactions that seem to be associated with particular strains of bacteria, it seems reasonable that same species-derived microorganisms would have the potential to enhance the therapeutic and prophylactic value of probiotic products. Future studies in dogs and cats should help determine if such enhancement actually occurs with administration of canine- and feline-derived probiotic agents.

Commercial Probiotic Products

Commercial products containing probiotics include pet foods and yogurt. Problems with microorganism content and viability limit the usefulness of these products as reliable sources of probiotic agents. To further complicate matters, current commercial pet food claims for probiotic content are not always accurate.[27] Although nonpasteurized yogurt has long been advocated as a source of probiotics, it is doubtful that viable organisms survive GI transit in sufficient numbers to reliably confer desired health benefits to the host.[27] In addition, organisms frequently contained in nonfortified yogurt, for example, *Lactobacillus bulgaricus* and *Streptococcus thermophilus*, have questionable probiotic activity. Fortified yogurt, which commonly has *L. acidophilus* and *Bifidobacterium* species added to it, may be a more scientifically sound source of probiotics.[28] Some evidence exists to support the use of yogurt fortified with *Bifidobacterium animalis* DN 173010 (e.g., Activia-Dannon),[29] but variation in viability and concentrations of microorganisms even in fortified yogurt limits the usefulness of these types of products.

Numerous commercial probiotic preparations are available that are manufactured for human or animal use. Selection of a beneficial preparation is not easily accomplished because of the minimal regulation of these products, relative lack of controlled studies, and uncertainties regarding dosing and microorganism–host interactions. Based on manufacturer reputation, product content, availability of evidence-based literature, and personal experience, Table 51-2 summarizes information for a limited number of probiotic products believed by the author to have the greatest potential for beneficial effects in the dog and cat. Two of the products listed in Table 51-2 have some unique aspects that distinguish them from other available probiotics. Prostora MAX contains canine-derived microorganisms, potentially enhancing the ability of the probiotic agent to interact with the canine gastrointestinal microenvironment. Proviable offers a somewhat different approach to probiotic therapy in that seven different probiotic agents are incorporated into one product. The potential, but not yet proven advantage, of this strategy is that multiple microorganisms expand the opportunity for beneficial interactions between the probiotic and the host microenvironment. In addition, Proviable may be offered with a prebiotic agent to help achieve more rapid resolution of acute diarrhea.

Therapeutic Regimens

Although ideal therapeutic dosing regimens have not yet been established, the products and protocols outlined in Table 51-2 all meet or exceed the minimum daily oral dose of 1×10^{8} CFUs/unit of product that is suggested by currently available information.[20] Duration of administration can range from a few days for acute GI disturbances to months for chronic disorders such as inflammatory bowel disease. For sustained effect, most microorganisms must be administered continuously as a consequence of the transient nature of probiotics in the GI tract.[2] Depletion or alteration of

the indigenous microflora as a result of antibiotic therapy is an indication for long-term probiotic therapy extending over a course of several days to weeks while the normal microflora becomes reestablished. If given concurrently with an antibiotic, the probiotic should be administered at a different time of day than the antibiotic.

As indicated in Table 51-1, probiotics have the potential for aiding in the treatment of a variety of companion animal GI disorders. The ability of probiotic agents to inhibit pathogens and parasites as well as to limit bacterial overgrowth through competition and immunomodulation supports the use of probiotic products for therapy and prevention of GI disease.[13] At the same time, traditional therapies should not be overlooked when treating specific disorders. For the time being, probiotic agents are best employed as *ancillary* therapeutic measures. At present, diarrhea-related disorders, especially those induced by medication, diet, or stressful situations, are conditions that may have the greatest potential for management and prevention with probiotics.

Contraindications and Adverse Effects

In general, adverse effects are infrequently encountered with the use of probiotic agents. Efficacy issues are more commonly encountered than safety issues or undesirable side effects. Although probiotic preparations are not subject to the stringent safety review undertaken with most pharmaceutical products, probiotic agents can receive FDA designation of "Generally Recognized As Safe" (GRAS). Because live microorganisms are being administered to the host, one of the greatest concerns is the introduction of bacteria with antibiotic resistance and plasmids conferring antibiotic resistance that can be transferred to other bacteria residing in the GI tract of the host. Although some lactic acid bacteria have antibiotic-resistant plasmids, antibiotic resistance related to the lactic acid bacteria more frequently used in probiotic preparations appears uncommon and generally does not occur because of a transmissible characteristic. In some instances, as is the case with *E. faecium* SF68, specific probiotic strains neither acquire nor transmit antibiotic resistance.[12] Because potential opportunistic, systemic infection remains a source of concern when administering live bacterial preparations, probiotic products should be used with caution or withheld from patients with weakened immune defenses. These individuals include neonatal patients (especially those ≤3 weeks of age), patients markedly debilitated as the result of a disease process, patients afflicted with severe clinical signs of intestinal infections such as canine parvovirus or feline panleukopenia, and immunosuppressed individuals in general.[4,20]

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CHAPTER 52

Prokinetic Agents

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Gastrointestinal motility disorders represent a diagnostic and therapeutic challenge. Disorders of gastrointestinal motility may result in delayed transit, accelerated transit, impaired relaxation, or inappropriate relaxation. The delayed transit disorders are the most important motility disorders of companion animals and may involve the esophagus (hypomotility and megaesophagus), stomach (delayed gastric emptying), small intestine (postoperative ileus and intestinal pseudoobstruction), or colon (constipation and megacolon) (see Section VI).

Dopaminergic D_2 Antagonist Drugs

Metoclopramide and Domperidone

The dopaminergic D_2 antagonists are a group of drugs with gastrointestinal prokinetic and antiemetic effects at peripheral (prokinetic) or central (antiemetic) dopamine D_2 receptors (Table 52-1, Figure 52-1).[1] The best representatives in this classification, metoclopramide and domperidone, reverse gastric relaxation induced by dopamine infusion in dogs, and they abolish vomiting associated with apomorphine therapy. Although the role of dopamine receptors in chemoreceptor trigger zone–induced vomiting is fairly well established, there is no definitive evidence that inhibitory dopaminergic neurons regulate gastrointestinal motility. The prokinetic effects of metoclopramide and domperidone thus may not be readily or exclusively explained by dopamine receptor antagonism. Some dopaminergic antagonists (e.g., metoclopramide) have other pharmacologic properties, for example, 5-HT_3-receptor antagonism and 5-HT_4-receptor agonism. Domperidone also has α_2- and β_2-adrenergic receptor antagonistic effects. The characterization of these drugs as dopaminergic antagonists is convenient but may not properly describe their overall in vivo effects.

Gastroesophageal Sphincter Disorders

The gastroesophageal sphincter prevents reflux of gastrointestinal contents into the esophageal body.[2,3] Reflux of gastric H^+ and pepsins, and of duodenal bicarbonate, bile salts, and proteases, induces chemical injury and inflammation of the esophageal mucosa.[3] Gastroesophageal sphincter tone appears to be under the regulation of dopaminergic neurons as both metoclopramide and domperidone increase sphincter tone. The gastric prokinetic effect of metoclopramide, although moderate, may also help to reduce the frequency, severity, and duration of reflux episodes.

Gastric-Emptying Disorders

Metoclopramide increases the amplitude and frequency of antral contractions; inhibits fundic receptive relaxation; and coordinates gastric, pyloric, and duodenal motility, all of which result in moderate acceleration of gastric emptying.[4,5] Metoclopramide appears to have continuing clinical application as a gastric prokinetic agent in the dog and cat, although the serotonergic agonists are clearly more potent. Domperidone appears to be less effective as a gastric prokinetic agent. Although effective in humans, domperidone actually decreases the frequency of corporeal, pyloric, and duodenal contractions and deteriorates antropyloroduodenal coordination in the dog by decreasing the frequency of contractions spreading from the antrum or pylorus to the duodenum.[5]

Small Intestinal Transit Disorders

Metoclopramide and domperidone are generally considered less effective in the management of the small intestinal transit disorders. Metoclopramide enhances antropyloroduodenal coordination in the dog and may be effective when delayed gastric emptying is a result of poor antropyloroduodenal coordination.[6] Domperidone has no documented effects on small intestinal transit.

Chemoreceptor Trigger Zone–Induced Emesis

The antiemetic effects of metoclopramide and domperidone are attributed to their central effects at the chemoreceptor trigger zone.[7] The antiemetic effect of metoclopramide is more important than its prokinetic effect.[1,7] Despite long-standing usage by small animal veterinarians, metoclopramide is not a very potent gastrointestinal prokinetic agent. Domperidone is 12 to 25 times more potent than metoclopramide and 50 to 60 times more potent than prochlorperazine in attenuating apomorphine-induced vomiting.

Serotonergic 5-HT_4-Agonist Drugs

Drugs acting on gastrointestinal 5-hydroxytryptamine (5-HT or serotonin) receptors have potent motility effects (see Table 52-1, Figure 52-2).[8] Serotonergic drugs that bind 5-HT_4 receptors on enteric cholinergic neurons induce depolarization and contraction of gastrointestinal smooth muscle. These drugs are not entirely selective for the 5-HT_4 receptor, however. Some of the putative 5-HT_4-receptor agonists also have 5-HT_1 and 5-HT_3 antagonistic effects on enteric cholinergic neurons, and direct noncholinergic (perhaps 5-HT_{2a}) effects on colonic smooth muscle. Cisapride,

Table 52-1 Mechanisms, Sites of Activity, Indications, and Doses of Currently Available Gastrointestinal Prokinetic Agents

Drug Classification/ Mechanism	Sites of Activity	Indications	Dose	Other Properties
Dopaminergic D_2-Antagonist Drugs				
Metoclopramide	GES, stomach, intestine, CRTZ	Vomiting disorders, gastroesophageal reflux, delayed gastric emptying, ileus/pseudoobstruction	0.2 to 0.5 mg/kg PO, IV TID; 0.01 to 0.02 mg/kg/h infusion	α_2-adrenergic antagonist β_2-adrenergic antagonist 5-HT_4-serotonergic agonist 5-HT_3-serotonergic antagonist
Domperidone	GES, CRTZ	Vomiting disorders, gastroesophageal reflux	0.05 to 0.1 mg/kg PO BID	α_2-Adrenergic antagonist β_2-adrenergic antagonist
Serotonergic 5-HT_4-Agonist Drugs				
Cisapride	GES, stomach, intestine, colon, CRTZ	Gastroesophageal reflux, delayed gastric emptying, ileus/pseudoobstruction, constipation, chemotherapy-induced vomiting	0.1 to 0.5 mg/kg PO TID (doses as high as 0.5 to 1 mg/kg have been used in some dogs)	5-HT_3-serotonergic antagonist 5-HT_1-serotonergic antagonist 5-HT_2-serotonergic agonist
Mosapride	Stomach	Delayed gastric emptying	0.25 to 1 mg/kg PO BID	None
Prucalopride	Stomach, colon	Delayed gastric emptying, constipation	0.01 to 0.2 mg/kg PO BID	None
Tegaserod	Intestine, colon	Constipation, ileus/ pseudoobstruction	0.05 to 0.1 mg/kg PO or IV, BID	5-HT_1-serotonergic antagonist
Motilin-like Drugs				
Erythromycin	GES, stomach, intestine, colon	Gastroesophageal reflux, delayed gastric emptying, constipation (dogs)	0.5 to 1 mg/kg PO IV TID	5-HT_3-serotonergic antagonist
Acetylcholinesterase Inhibitors and Cholinomimetic Agents				
Ranitidine	Stomach, colon	Delayed gastric emptying, constipation	1 to 2 mg/kg PO BID-TID	H_2-histaminergic antagonist
Nizatidine	Stomach, colon	Delayed gastric emptying, constipation	2.5 to 5.0 mg/kg PO SID	H_2-histaminergic antagonist
Bethanechol	Esophagus	Canine idiopathic megaesophagus	Dog: 5 to 15 mg/dog PO TID	
Nitric Oxide Donors				
AMU-301		Stomach	Diabetic gastroparesis	Not yet established
Prostanoids				
Misoprostol		Colon	Constipation	Dog: 2 to 5 μg/kg PO TID-QID

CRTZ, chemoreceptor trigger zone; GES, gastroesophageal sphincter; SID, standardized ileal digestible.

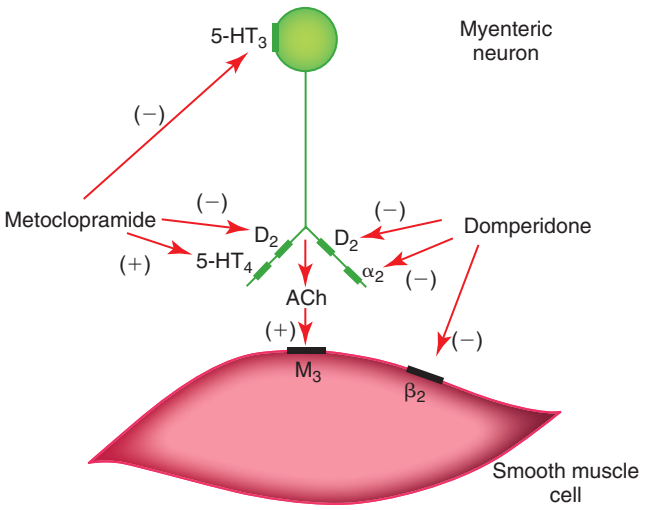

Figure 52-1 Dopaminergic regulation of gastrointestinal motility and sites of action of metoclopramide and domperidone.

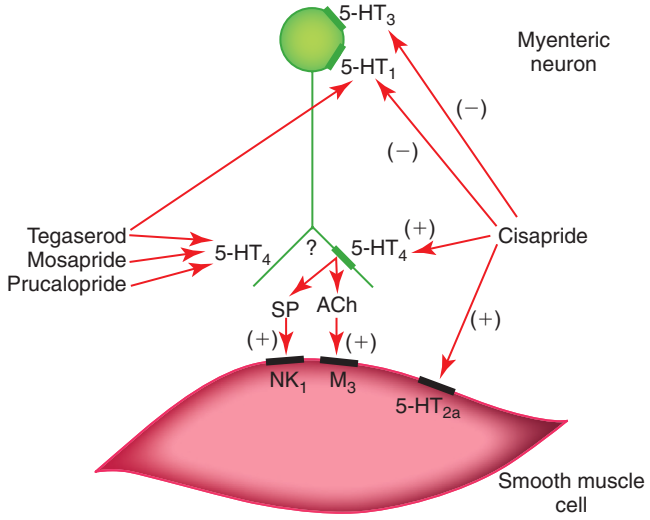

Figure 52-2 Serotonergic regulation of gastrointestinal motility and sites of action of cisapride, mosapride, prucalopride, and tegaserod.

mosapride, prucalopride, and tegaserod are the best examples in this classification. Cisapride and tegaserod have been withdrawn from several international markets because of their effect(s) on myocardial Q-T interval prolongation, although both remain available through compounding pharmacies. Mosapride is available in Japan (Pronamid, DS Pharma) and prucalopride is available in Europe (Resolor, Movetis).

Cisapride

Cisapride was widely used in the management of canine and feline gastric emptying, intestinal transit, and colonic motility disorders throughout most of the 1990s.[9,10] Cisapride was withdrawn from the American, Canadian, and certain West European markets in July 2000 following reports of untoward cardiac side effects in human patients. Cisapride causes Q-T interval prolongation and slowing of cardiac repolarization via blockade of the rapid component of the delayed rectifier potassium channel (I_{Kr}).[11] This effect may result in a fatal ventricular arrhythmia referred to as *torsades de pointes*.[11] Similar effects have been characterized in canine cardiac Purkinje fibers, but in vivo effects have not been reported in dogs or cats. The withdrawal of cisapride has created a clear need for new gastrointestinal prokinetic agents, although cisapride continues to be available from compounding pharmacies.

Gastroesophageal Sphincter Disorders

Cisapride is indicated for the treatment of gastroesophageal reflux because it stimulates gastric emptying and increases gastroesophageal sphincter pressure. Comparative studies have shown that cisapride is more potent than metoclopramide in stimulating gastric emptying and increasing gastroesophageal sphincter pressure. Cisapride can be used in conjunction with chemical diffusion barriers (e.g., sucralfate) and gastric acid secretory inhibitors (e.g., H_2-receptor antagonists; H^+,K^+-adenosine triphosphatase [ATPase] inhibitors) in the treatment of gastroesophageal reflux.[12-14]

Cisapride stimulates distal esophageal peristalsis in those animal species (e.g., cat, human being, guinea pig) in which the distal esophageal muscularis is composed of smooth muscle. The obvious exception is the dog, a species in which the entire esophageal body is composed of striated muscle. It has been suggested that cisapride might improve esophageal peristalsis in dogs affected with idiopathic megaesophagus. This would not appear to be a rational clinical application of the drug, because a smooth muscle prokinetic agent would not be expected to have much effect on striated muscle function. Indeed, the prokinetic effect of cisapride in the esophagus of human beings or cats is confined to the distal esophageal body at the transition zone from striated muscle to smooth muscle. Cisapride has no effect on proximal esophageal peristalsis in these species. Furthermore, 5-HT stimulates contraction of canine gastroesophageal sphincter smooth muscle, but is without effect on canine esophageal body striated muscle.[15] Thus, cisapride cannot be recommended for the treatment of idiopathic megaesophagus in dogs. Indeed, cisapride-induced increases in gastroesophageal sphincter pressure could diminish esophageal clearance and worsen clinical signs in dogs affected with idiopathic megaesophagus.

Gastric-Emptying Disorders

Cisapride accelerates gastric emptying in dogs by stimulating pyloric and duodenal motor activity, by enhancing antropyloroduodenal coordination, and by increasing the mean propagation distance of duodenal contractions.[5,16] Cisapride appears to be superior to metoclopramide and domperidone in stimulating gastric emptying. Dosages of cisapride in the range of 0.05 to 0.2 mg/kg enhance gastric emptying in dogs with normal gastric emptying. Dosages in the range of 0.5 to 1 mg/kg are needed to enhance gastric emptying in dogs with delayed gastric emptying induced by α_2-adrenergic agonists, dopamine, disopyramide, or antral tachygastria.[9,10]

Small Bowel Motility Disorders

Cisapride stimulates jejunal spike burst migration, jejunal propulsive motility, and antropyloroduodenal coordination following intestinal lipid infusion in the dog.[6,17] Thus, cisapride would appear to have a rational place in the treatment of postoperative ileus and intestinal pseudoobstruction. Well-designed clinical trials and evidence-based data are required to determine the effectiveness of cisapride in the treatment of these disorders.

Colonic Motility Disorders

Cisapride stimulates colonic motility,[18,19] and would appear to have a rational place in the treatment of idiopathic constipation. Disruption of the normal colonic motility patterns results in constipation in domestic cats. Cisapride improves colonic motility in cats that are mildly or moderately affected with idiopathic constipation; cats with long-standing hypomotility and dilation are usually less responsive. A recent evidence-based data review of cisapride's efficacy in the treatment of human constipation and constipation-predominant irritable bowel syndrome was carried out by the Cochrane Collaboration.[20] These authors concluded, "no clear benefit could be demonstrated with cisapride."[20]

Cis-*Platinum–Induced Emesis*

Cis-Platinum-induced emesis is mediated by 5-HT_3 serotonergic receptors, either in the chemoreceptor trigger zone (cat) or in vagal afferent neurons (dog). Selective antagonists of the 5-HT_3 receptor (e.g., ondansetron, granisetron, tropisetron, dolasetron) abolish vomiting associated with *cis*-platinum chemotherapy. Cisapride antagonizes these 5-HT_3 receptors and inhibits vomiting associated with *cis*-platinum chemotherapy. The potency of cisapride's 5-HT_3 antiemetic effect (median effective dose [ED_{50}] = 0.6 mg/kg IV; ED_{100} = 2.6 mg/kg IV) is less than its 5-HT_4 gastric prokinetic effect. Thus, cisapride could be recommended as an antiemetic agent for the cancer chemotherapy patient only if ondansetron, granisetron, tropisetron, or dolasetron were not immediately available or were too cost prohibitive.[7] Metoclopramide is equipotent with cisapride in inhibiting *cis*-platinum emesis, but it has the distinct disadvantage of adverse central nervous system side effects, for example, drowsiness, extreme weakness, and body tremors. Cisapride has no effect on nausea and vomiting mediated by dopaminergic D_2 receptors (e.g., apomorphine, uremia) or histaminergic H_1 receptors (e.g., motion sickness).

Mosapride

Mosapride citrate, a substituted benzamide, is a novel 5-HT_4-receptor agonist that increases gastric emptying in rats and dogs, and increases electrically evoked contractions in the isolated guinea pig ileum.[21,22] Mosapride stimulates acetylcholine release from the myenteric plexus via activation of 5-HT_4 receptors, but has no real affinity for D_2 dopamine, 5-HT_1, 5-HT_2 receptors, or α_1-adrenoceptors. Mosapride restores gastric motility in dogs with vincristine-induced gastric hypomotility,[23] and therefore may be clinically useful in other gastric-emptying disorders. Mosapride is apparently without effect on distal gastrointestinal tract motility. Mosapride is marketed as Pronamid by DS Pharma Animal Health in Japan.

Prucalopride

Prucalopride is a potent partial benzamide agonist at 5-HT_4 receptors, but is without effect on other 5-HT receptors or cholinesterase enzyme activity. Prucalopride dose dependently (0.02 to 1.25 mg/kg) stimulates giant migrating contractions and defecation in the dog.[24-26] The prucalopride effect is observed most prominently in the first hour after administration, suggesting that the prucalopride effect is a direct effect on the colon rather than on total gut transit time. Oral and intravenous doses appear to be equipotent, again implying a high oral bioavailability. Prucalopride also enhances defecation frequency in healthy cats.[27] Cats treated with prucalopride at a dose of 0.64 mg/kg experience increased defecation within the first hour of administration. Fecal consistency is not altered by prucalopride at this dosage.

Prucalopride also appears to stimulate gastric emptying in the dog.[28] In lidamidine-induced delayed gastric emptying in dogs, prucalopride (0.01 to 0.16 mg/kg) dose dependently accelerates gastric emptying of dextrose solutions. The prucalopride effect is equipotent following oral and intravenous administration suggesting that prucalopride may have a high oral bioavailability. Prucalopride is marketed as Resolor by Movetis in Europe.

Tegaserod

Tegaserod is a potent partial nonbenzamide agonist at 5-HT_4 receptors and a weak agonist at 5-HT_{1D} receptors.[29,30] Tegaserod has prokinetic effects in the distal gastrointestinal tract. Intravenous doses of tegaserod (0.03 to 0.3 mg/kg) accelerate colonic transit in dogs during the first hour after intravenous administration.[29] The highest doses of tegaserod (0.1 and 0.3 mg/kg) have no greater efficacy than lower doses (0.03 mg/kg), suggesting the possibility that tegaserod may stimulate canine colonic motility through a receptor-independent mechanism, or that tegaserod may act at sites other than 5-HT_4 receptors at higher doses.

The motor mechanisms responsible for tegaserod-induced canine colonic propulsion are unclear. High-amplitude propagated phasic contractions are thought to be responsible for mass movements, but they were not observed during tegaserod infusion. Contraction, amplitude, and motility indices were not different postprandially among treatment groups, so the mechanism of the tegaserod effect requires more detailed investigation in the dog.

Gastric effects of tegaserod have not been reported in the dog, so this drug may not prove as useful as cisapride in the treatment of delayed gastric-emptying disorders. Tegaserod at doses of 3 to 6 mg/kg PO normalizes intestinal transit in opioid-induced bowel dysfunction in dogs,[31] and it may be useful in other disorders of intestinal ileus or pseudoobstruction.

Tegaserod was approved by the U.S. Food and Drug Administration in September 2002, but was removed from the American market in 2007 because of reports of prolongation of the Q-T interval and delayed cardiac repolarization. Tegaserod is marketed as Zelnorm by Novartis in Europe.

Future Research in 5-HT-Receptor Pharmacology

The 5-HT_4 receptor appears to hold the most interest and promise for future drug development. 5-HT_4-receptor activation can cause relaxation or contraction depending on the region, cell type, and animal species. In the dog, the effects of selective 5-HT_4-receptor agonists suggest that these receptors are present on jejunal mucosa, ileal mucosa, gastric cholinergic neurons, and circular colonic smooth muscle cells. Development of 5-HT_4 ligands is somewhat constrained by the effects these drugs have on cardiac 5-HT_4 receptors and the delayed rectifier potassium channel (I_{Kr}). Some, but not all, 5-HT_4 agonists prolong the Q-T interval and delay cardiac repolarization. Molecular biology experiments have revealed differences in the carboxyl terminus of smooth muscle and cardiac muscle 5-HT_4 receptors, but these amino acids differences are distant from the receptor binding site. Thus, receptor subtypes may exist but they may not be important from a functional or therapeutic standpoint.

Motilin-Like Drugs

Erythromycin

The antibiotic properties of erythromycin and other macrolides were discovered in the early 1950s. Since that time, erythromycin has been widely used in treating patients with Gram-positive and Gram-negative bacterial and mycoplasmal infections. Physicians and veterinarians noted that erythromycin therapy was accompanied by frequent gastrointestinal side effects, including nausea and vomiting. This occurrence suggested to researchers that erythromycin might have effects on gastrointestinal motility. It was subsequently demonstrated that microbially effective doses of erythromycin stimulate retrograde peristalsis and vomiting in dogs, and that lower microbially ineffective doses of erythromycin stimulate migrating motility complexes and antegrade peristalsis similar to that induced by the endogenous gastrointestinal hormone, motilin (see Table 52-1, Figure 52-3).[32-34]

Gastroesophageal Sphincter Disorders

Motilin, erythromycin, and erythromycin analogues (e.g., LY-267108) increase gastroesophageal sphincter pressure in cats and dogs.[35] Erythromycin also increases gastroesophageal sphincter pressure in cats in which the basal pressure has been lowered experimentally by esophageal acid perfusion or following intravenous isoproterenol administration.[35] These studies suggest that erythromycin should be useful in treating cats, and perhaps dogs, with gastroesophageal reflux and reflux esophagitis.

Gastric-Emptying Disorders

Erythromycin accelerates gastric emptying by inducing antral contractions similar to phase III of the interdigestive state.[36-39] The strong contractions associated with phase III normally occur only

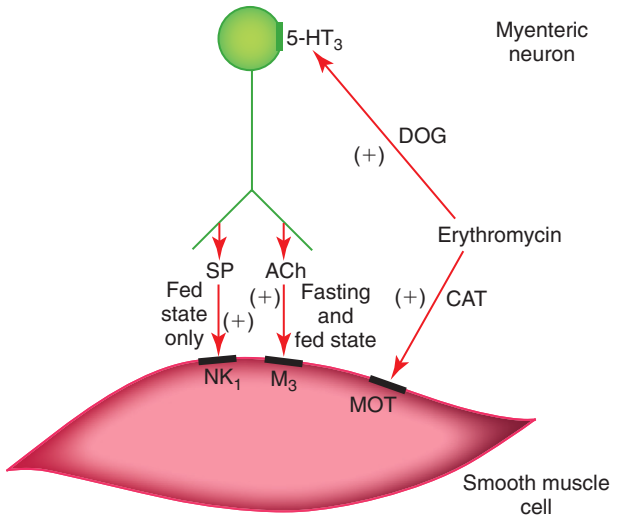

Figure 52-3 Motilin regulation of gastrointestinal motility and sites of action of erythromycin.

during the fasted state when they clear the stomach of large indigestible solids. After meals, intravenous or oral erythromycin accelerates gastric emptying of solid meals in dogs. EM574 is 250 times more potent than erythromycin in inducing phase III contractions in dogs and it has no antibacterial activity.[37,38] EM574 is as effective as cisapride in normalizing gastric contractility and emptying in dogs with clonidine-induced gastroparesis in dogs.[37,38]

Colonic Motility Disorders

Erythromycin accelerates regional colonic transit in the dog.[40] Erythromycin has been shown to stimulate canine but not feline colonic smooth muscle contraction in vitro.[41] These results suggest that erythromycin may be useful in the treatment of canine colonic motility disorders.

Acetylcholinesterase Inhibitors and Cholinomimetic Agents

Ranitidine and Nizatidine

Ranitidine and nizatidine, classic histamine H_2-receptor antagonists, stimulate gastrointestinal motility by inhibiting acetylcholinesterase activity (see Table 52-1, Figure 52-4).[42-44] As parasympathetic potentiating agents, ranitidine and nizatidine stimulate gastric emptying and small intestinal and colonic motility. The prokinetic effects of ranitidine and nizatidine appear to be more prominent in the proximal gastrointestinal tract (i.e., gastric emptying). Other members of this classification, for example, cimetidine and famotidine, apparently have no effect on gastrointestinal motility.

Bethanechol

Bethanechol is a cholinomimetic agent that binds muscarinic cholinergic receptors and stimulates motility throughout the gastrointestinal tract.

Esophageal Motility Disorders

Smooth muscle prokinetic agents, for example, cisapride and metoclopramide, have limited clinical application in the treatment of canine idiopathic megaesophagus. Cisapride and metoclopramide stimulate distal esophageal peristalsis in those animal species (e.g., cat, human being, guinea pig) in which the distal esophageal muscularis is composed of smooth muscle. The domestic dog has evolved with a purely striated muscle esophageal muscularis, which has a different regulation and therapeutic responsiveness.[13] Bethanechol stimulates esophageal propagating contractions in some dogs affected with idiopathic megaesophagus and is therefore a more appropriate prokinetic agent for the therapy of this disorder.[45]

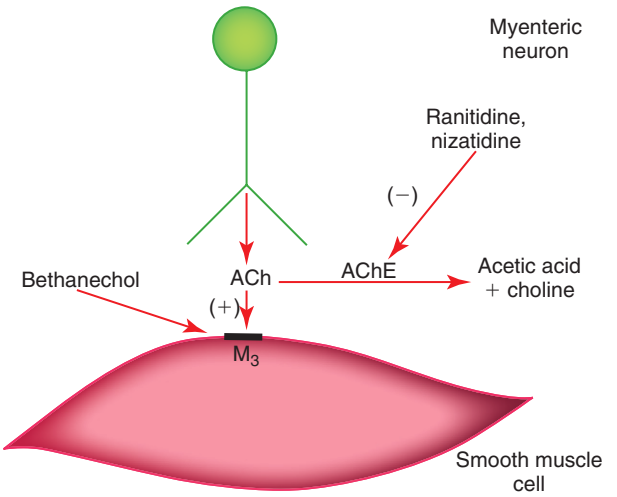

Figure 52-4 Cholinergic regulation of gastrointestinal motility and sites of action of ranitidine, nizatidine, and bethanechol.

Gastric-Emptying Disorders

Ranitidine and nizatidine stimulate gastric antral contractions at gastric antisecretory dosages (ranitidine, 1.0 to 2.0 mg/kg PO BID; nizatidine, 2.5 to 5.0 mg/kg PO BID) and may be useful as gastric prokinetic agents in dogs and cats.[43,44,46]

Colonic Motility Disorders

Infusions of ranitidine at doses of 3 mg/kg induce canine colonic propagating contractions in vivo.[46] Ranitidine and nizatidine also stimulate feline colonic smooth muscle contraction in vitro.[47] These data suggest that ranitidine and nizatidine may be useful in the treatment of feline or canine colonic motility disorders.[42]

Nitric Oxide Donors

Delayed gastric emptying is recognized as an important cause of upper gastrointestinal tract pathology (e.g., anorexia and vomiting) in companion animals.[14] Delayed gastric emptying has been reported in infectious and inflammatory gastric diseases, diabetes mellitus, and radiation injury in the dog.[48,49] Delayed gastric emptying is also associated with several secondary conditions, including electrolyte disturbances (e.g., hypokalemia, hypocalcemia), metabolic disorders (e.g., hypoadrenocorticism, hypergastrinemia, uremia), concurrent drug usage (e.g., cholinergic antagonists, β-adrenergic agonists, opiates), acute stress (e.g., sympathetic stimulation, spinal cord injury), and acute abdominal inflammation.[48,49]

Diabetes mellitus is the most common endocrinopathy of the domestic dog.[50] Long-standing undiagnosed or untreated diabetes mellitus is associated with significant gastroparesis in the dog,[51,52] just as it is in humans. The pathogenesis of gastroparesis in diabetes mellitus is complex and probably multifactorial, involving one or more of the cellular elements (neurons, smooth muscle cells, interstitial cells of Cajal) regulating gastric motility.[53] An important pathophysiologic mechanism appears to be the loss of neuronal nitric oxide synthase, the enzyme responsible for the production of nitric oxide, an inhibitory neurotransmitter that is required for relaxation of smooth muscle and therefore a critical component of normal gastrointestinal motility. In the absence of nitric oxide, the stomach cannot relax, resulting in bloating, satiety, nausea, and vomiting.[54]

Cisapride, metoclopramide, and erythromycin have all been used with variable effect in diabetic gastroparesis. Therapy aimed instead at restoring nitrergic neurotransmission could have intrinsic beneficial effects in canine diabetic gastroparesis. AMU-301, a nitric oxide (NO) donor, is recognized as an effective treatment for diabetic gastroparesis in streptozotocin-induced (STZ) diabetic rat models of delayed gastric emptying,[55] and may eventually prove useful in spontaneous canine diabetes mellitus (see Table 52-1, Figure 52-5).

Prostaglandin E_1 Analogues

Misoprostol is a prostaglandin E_1 analogue that reduces the incidence of nonsteroidal antiinflammatory drug–induced gastric injury. The main side effects of misoprostol therapy are abdominal discomfort, cramping, and diarrhea. Dog studies suggest that prostaglandins

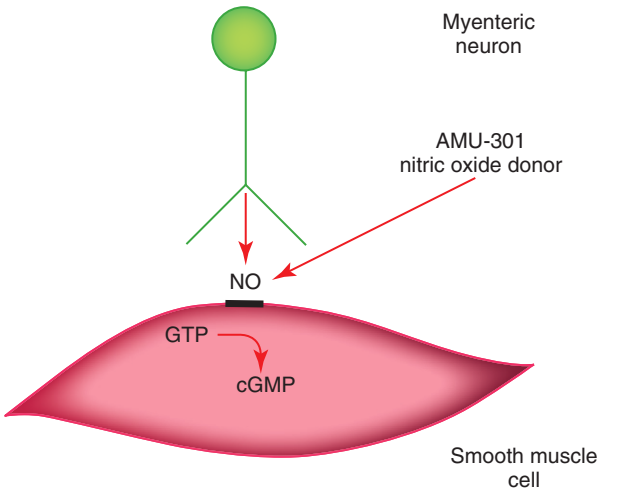

Figure 52-5 Nitric oxide regulation of gastrointestinal motility and sites of action of nitric oxide donors.

may initiate a giant migrating complex pattern and increase colonic propulsive activity.[56] In vitro studies of misoprostol show that it stimulates feline and canine colonic smooth muscle contraction.[57] Given its limited toxicity, misoprostol may be useful in dogs and cats with severe refractory constipation.

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CHAPTER 53

Vitamins and Minerals

Craig G. Ruaux

Definition

Vitamins and minerals are components of the diet that are necessary for normal cellular physiology but do not provide any significant caloric input. In a dietary context, the term *minerals* refers to the ionized form of predominantly low-molecular-weight alkali metals or transition metals such as magnesium, cobalt, selenium, and zinc. Vitamins, by comparison, have more complex molecular structures. Vitamin and mineral malabsorption and systemic deficiencies are common consequences of gastrointestinal disease.

Formulations and Doses

Vitamin and mineral supplements are available in a variety of over-the-counter formulations, for both human and animal use. Many of these products contain a substantial variety of vitamin and mineral compounds in combination with various amino acids, fatty acids, and putative micronutrients. There is a distinct lack of objective, peer-reviewed literature to support the need for or use of these complex mixtures of vitamins and minerals, particularly in the otherwise healthy companion animal consuming a well-formulated, balanced diet. Many of the components of these multivitamin supplements have rational uses in gastrointestinal diseases; however, the doses necessary to achieve therapeutic effect are often substantially higher than is feasible using multivitamin preparations. Therapeutic formulations of vitamins for parenteral use in companion animal species are available from several manufacturers in a variety of formulations.

Rational Use in the Diagnosed Patient

Vitamin and Mineral Deficiencies in Gastrointestinal Disease

Vitamin and mineral deficiencies are commonly recognized in human patients with inflammatory bowel disease.[1] The mechanisms whereby micronutrient deficiencies may come about include reduced voluntary intake because of inappetence, increased losses as a result of diarrheal disease, compromised uptake as a consequence of loss of absorptive surface area, loss of specific mucosal receptors, or compromised fat absorption in diseases characterized by steatorrhea. In the veterinary literature, the greatest attention has been paid to (a) vitamin deficiencies resulting from fat malassimilation and (b) deficiencies in cobalamin (vitamin B_{12}) and folic acid or folate (vitamin B_9) as a result of loss of specific receptors. Hypovitaminosis D, with concurrent disorders of calcium homeostasis, has been reported in dogs in association with protein-losing enteropathies,[2,3] while in the cat severe organic acidemias have been recognized in patients with gastrointestinal disease and subnormal serum cobalamin concentrations.[4,5] Hypocobalaminemia has been identified as a negative prognostic factor in dogs with chronic enteropathies.[6]

Recent studies have focused on the prevalence of cobalamin deficiency in the cat and dog with gastrointestinal disease.[7,8] In both species, cobalamin deficiency was common in patients with gastrointestinal disease. In an open-label, uncontrolled study, cobalamin supplementation in cats with gastrointestinal disease and severe hypocobalaminemia was associated with positive clinical benefit and normalization of biochemical parameters.[9]

Cobalamin malabsorption because of intestinal disease cannot be successfully treated with dietary supplementation. Parenteral therapy is essential in deficient patients.[9] A dose range previously described for use in cats with cobalamin deficiency as a consequence of intestinal disease is 250 µg/cat injected subcutaneously, once a week for 6 weeks, once every 2 weeks for 6 weeks, and once a month thereafter.[9] The concentration of cobalamin in standard injectable multivitamin preparations (5 µg/mL) is insufficient to supply this amount of cobalamin in a reasonable injection volume. Therefore a pure preparation of cobalamin is recommended, in addition to multivitamin products, in dogs and cats with documented cobalamin deficiency.

Reduced serum concentrations of folic acid/folate most commonly occur in companion animals because of loss of specific duodenal mucosal receptors. Although subnormal serum folate concentrations have been recognized cats with gastrointestinal disease,[10] the clinical significance of this finding, or of similar findings in dogs, is currently unclear. At the time of writing there is no well-defined threshold for folic acid supplementation in either species, and no peer-reviewed literature that specifically addresses the benefit, if any, of folate supplementation in adult patients with gastrointestinal disease. Empirically, treatment with oral or injectable folic acid (1 to 5 mg/dog or 1 mg/cat PO daily) results in dramatic increases in serum folate concentrations in most animals (unpublished data).

Vitamin and Mineral Deficiencies in Liver Disease

Liver disease patients often present with vitamin and/or mineral deficiencies. Several factors, including reduced voluntary intake, fat malabsorption, reduced gastrointestinal mucosal function, and loss of hepatic reserves, all contribute to the development of vitamin and mineral deficiencies.

Water-soluble vitamins such as folic acid, thiamine, cobalamin, niacin, and riboflavin are cofactors for many enzymatic reactions carried out in hepatic cells. Deficiencies in these vitamins are detected frequently in cats with hepatic lipidosis.[11] Most water-soluble vitamins do not have substantial body stores and daily replacement from dietary sources is necessary. Administration of multivitamin supplements is cost-effective and simple, and should be included in any nutritional support plan for patients with liver disease. In the cat, cobalamin malabsorption because of small intestinal disease is commonly documented in association with liver disease.[5]

In animals with long-standing liver disease, fat malabsorption and subsequent deficiencies of fat-soluble vitamins can occur. Vitamin E deficiency may reduce cellular defenses against oxidant-mediated damage, potentially playing a role in copper-associated hepatoxicity.[12,13] Empirically, regular supplementation of vitamins E, A, and D by intramuscular injection at 3- to 4-month intervals is recommended in companion animals with long-standing liver disease, particularly if this is complicated by steatorrhea. Cats with hepatic lipidosis should be screened for vitamin K deficiency, particularly if there is any evidence of bleeding tendencies. If detected (ideally via protein-induced vitamin K absence [PIVKA] assay), subcutaneous vitamin K administration at 1 to 5 mg/kg/day for 2 to 3 days is indicated.

Niacin Therapy for Hyperlipidemia

Niacin therapy has been recommended in humans and companion animals with hyperlipidemia syndromes, particularly when dietary fat restriction has failed.[14,15] Niacin acts through several different mechanisms to reduce circulating lipids. These mechanisms include inhibition of hormone-sensitive lipase, thus reducing fatty acid mobilization, stimulation of hepatic high-density lipoprotein catabolism, and direct inhibition of hepatic fatty acid synthesis.[16] Taken alone in high doses, niacin is associated with pruritus and skin flushing in many human patients.[17] When used for control of hyperlipidemia in dogs, niacin is administered at 25 to 100 mg/dog/day.[14] As with many other nutritional interventions in animals, large-scale controlled studies documenting benefit of niacin therapy are lacking.

Elemental Zinc Therapy in Copper-Accumulation Hepatopathies

Hepatic copper accumulation is a feature of several diseases in dogs. Copper accumulation hepatopathy is well recognized as an autosomal recessive disorder in the Bedlington Terrier.[18] In several other breeds, including the Doberman Pinscher, Cocker Spaniel, West Highland White, Skye Terrier, and Labrador Retriever, there is evidence of excessive copper accumulation in some liver diseases.[19,20] In addition to chelation therapy and the feeding of a low-copper diet, micronutrient interventions to decrease hepatic copper accumulation include supplementation with ascorbic acid and elemental zinc.

Administration of zinc between meals leads to increased metallothionein expression in the enterocytes. Copper in the diet is bound with high affinity within the mature enterocyte and lost in the feces as the enterocyte is shed.[21] Zinc is given at a loading dose of 100 mg per os twice daily for 3 weeks, followed by a maintenance dose of 50 mg orally twice daily. Vomiting and nausea may both occur as side effects of zinc therapy; administration with a small amount of food may reduce these side effects. Ascorbic acid supplementation increases urinary excretion of copper and zinc, as well as increasing the intestinal synthesis of metallothionein.

Rational Use in the Undiagnosed Patient

Water-soluble vitamin B-complex formulations are commonly used empirically in the management of many chronic disease conditions. To the best of the author's knowledge, no peer-reviewed publications directly address the utility of multivitamin supplementation in any disorder of companion animal species. Most water-soluble vitamins have minimal potential for toxicity or adverse effects, thus water-soluble vitamin supplementation in companion animals with gastrointestinal disease can be considered safe and of potential, but unproven, benefit.

Empirical use of cobalamin supplementation in companion animals with chronic gastrointestinal disease is becoming increasingly common. Although mild symptomatic improvement may be seen in some patients with empirical cobalamin supplementation, all efforts should still be made to achieve a definitive diagnosis and appropriate therapy for the primary gastrointestinal disease.

Contraindications and Side Effects

Empirical use of fat-soluble vitamin supplements, particularly formulations containing more than one vitamin, should be approached with caution because of the potential for hypervitaminosis syndromes, particularly hypervitaminosis A in the cat and hypercalcemia as a result of hypervitaminosis D.[22-24] Empirical use of water-soluble vitamins, particularly B-complex preparations, carries minimal risk of side effects at appropriate doses.

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CHAPTER 54

Oropharynx

STRUCTURE AND FUNCTION

Kendall Taney

Structure of the Oropharynx

Oral Cavity

The oral cavity extends from the lips to the oropharynx, or more specifically to level of the palatine tonsils.[1] The lateral boundaries are the cheeks and the dorsal boundary is the hard palate and part of the soft palate.[1,2] The ventral boundary is the tongue and floor of the mouth. The oral cavity encompasses the vestibule and the oral cavity proper. The vestibule is the potential space between the lips or cheeks and the teeth and gums. The oral cavity proper extends from the alveolar ridge and teeth to the oropharynx.[1] The oral cavity proper contains the teeth, hard palate and part of the soft palate, portions of the osseous tissue of the skull and mandible, and the tongue.

Dogs and cats have anisognathic jaws as the mandible is narrower than the maxilla and the teeth of the maxilla and mandible do not meet directly in occlusion.[1] The dentition and jaw structure in carnivores facilitate capture of prey and tearing of tissue versus the grinding and crushing action of the teeth and jaws in humans and other omnivores. The dentition of the dog is described as diphyodont, heterodont, and thecodont.[1] Diphyodont means having two sets of teeth, such as a primary set that erupts soon after birth followed by a permanent set that remains in place for the remainder of life. Heterodont refers to having more than one shape of tooth, such as the pointed canines, which are used for grasping and holding food and the more blunt caudal molars that are used for grinding and crushing food. Thecodont teeth are held firmly within the sockets or alveoli by a type of fibrous, nonmobile joint termed a *gomphosis*.[1-3] The fibrous structure that anchors the teeth to bone is more commonly referred to as the periodontal ligament. The alveolar processes of the paired maxillary and mandibular bones surround the roots of the teeth. It is composed of a cortical plate, cribriform plate, and trabecular bone. The cortical plate forms the outer wall of the alveolus. The cribriform plate is a thin layer of bone within the alveolus, which appears radiographically as the lamina dura. Trabecular bone is the supportive hard tissue between the cortical plate and the lamina dura.[1]

The hard and soft palates separate the oral and nasal cavities. The bony structure of the hard palate is composed of the paired incisive bones, palatine processes of the maxilla, and palatine bones. These bones are covered by cornified stratified squamous epithelial soft tissue, called the *hard palate mucoperiosteum*. The mucosa of the hard palate is nonelastic and has six to 10 transverse ridges or rugae. Located just caudal to the maxillary incisors on midline is a mound of tissue called the *incisive papilla*. On either side of the papilla are the incisive ducts, which travel through the palatine fissures of the incisive bones to communicate with the vomeronasal organ.[1-5] The greater palatine branch of the maxillary branch of the trigeminal nerve (cranial nerve [CN] V) supplies sensory innervation to the hard palate. The main arterial supply is from the paired greater palatine arteries that branch off from the maxillary arteries.[2,4] The soft palate begins at the caudal termination of the hard palate and continues into the pharyngeal region; it is discussed further with the oropharynx.

An important structure within the oral cavity is the tongue, which is responsible for prehension and manipulation of a food bolus during mastication and deglutition. It is also involved in grooming and intake of fluids. The tongue is divided into four sections: tip, margin, body, and root. It becomes thicker caudally toward the root. Arterial blood supply to the tongue is provided by the paired lingual arteries.[2] Motor innervation of the tongue is from the hypoglossus. Sensory innervation is provided by the lingual branch of the trigeminal (CN V), facial (CN VII), glossopharyngeal (CN IX), and vagus nerves (CN X).[2,4] The dorsal surface of the tongue is covered by cornified lingual papillae. The papillae can be mechanical or may contain taste pores which provide information to the sensory nerves.[2] Five types of papillae are present in the tongue of the adult dog: filiform, fungiform, vallate, foliate, and conical. A sixth type, called *marginal papillae*, is a functional type present only in neonates. The marginal papillae are located on the margins of the tongue and help create an airtight seal in the mouth during nursing. They begin to disappear soon after weaning. Filiform papillae are numerous and are located on the rostral two-thirds of the tongue. They are heavily cornified and may aid in grooming; thus they are mostly mechanical in function. The filiform papillae in the cat are especially stiff and long, and are oriented in a caudal direction.[4] The fungiform papillae are also located on the rostral two-thirds of the tongue but are mostly concentrated on the tip and sides of the tongue. Each fungiform papilla may contain up to eight taste pores. There are anywhere from three to six total vallate papillae in the dog. They are arranged in a V shape at the base of the tongue. Vallate papillae may also contain taste pores. The foliate papillae do contain taste buds and are located on the caudal third of the tongue immediately rostral to the palatoglossal folds. Finally, the conical papillae are located on

the caudal third of the tongue. Their function is mainly mechanical and tactile and they do not contain taste pores.[1,2] A visible median groove divides the most rostral two-thirds of the dorsal tongue. The ventral surface is covered by a smoother, less cornified mucosa.[1] A band of tissue called the *lingual frenulum* extends from the floor of the mouth to the base of the tongue.

The tongue is able to prehend and manipulate food as a result of its composition of intrinsic and extrinsic skeletal muscles. The intrinsic propria lingua muscle is innervated by the hypoglossal nerve (CN XII) and serves to retract and depress the tongue. It has four types of muscle fibers: superficial longitudinal, deep longitudinal, perpendicular, and transverse. These muscle fibers allow the tongue to perform complex movements during prehension, fluid intake, mastication, bolus formation, and deglutition and also function to prevent the tongue from being bitten. The extrinsic muscles are the styloglossus, hyoglossus, and genioglossus. These extrinsic muscles are also innervated primarily by the hypoglossal nerve (CN XII). The origin of the styloglossus muscle is the stylohyoid bone. The styloglossus muscle has three heads and the tongue can be pulled backward when all three heads are contracting together.[2] Each head can also act to depress the tongue. The hyoglossus muscle originates from the basihyoid and thyrohyoid bones to the root and caudal two-thirds of the tongue. Its action is to depress and retract the tongue. The genioglossus muscle lies beneath the tongue in the intermandibular space and its origin is on the medial surface of the mandibles. A portion of the genioglossus makes up the lingual frenulum. The caudal fibers can act to draw the tongue forward and the rostral fibers can curl the tip of the tongue downward.[2]

Other important structures involved in the function of the oropharynx are the salivary glands. These accessory digestive organs secrete a serous and mucous fluid (saliva) that is important for lubrication of a food bolus for transport to the upper digestive tract. Many different salivary glands contribute to saliva formation and they are regulated by the autonomic nervous system (see Chapter 1). There are several groups of numerous, small, disseminated glands that secrete small amounts of saliva. These are the lingual, labial, buccal, and palatine salivary glands. The larger salivary glands contribute to the bulk of saliva formation and are the paired parotid, mandibular, sublingual, zygomatic, and, in cats only, the molar glands.[1] The parotid gland is located close to the surface of the masseter muscle. The parotid duct exits into the vestibule on the buccal mucosa at the level of the maxillary fourth premolar. The zygomatic salivary gland, which is located ventral to the rostral portion of the zygomatic arch, has a duct that exits in the vestibule just caudal to the parotid duct. There may also be several small minor zygomatic duct openings in addition to the major opening.[1-4] The parotid duct termination is commonly called the *major papillae* and the larger zygomatic duct opening is called the *minor papillae*. The mandibular gland is located just caudal to the angle of the mandible between the linguofacial and maxillary veins. The sublingual gland is divided into monostomatic and polystomatic portions. The monostomatic portion of the gland is located primarily within the capsule of the mandibular salivary gland with a few lobules of tissue located close to the mandibular and sublingual ducts near the root of the tongue. The polystomatic portion is a group of small, scattered lobules that empty through several minor sublingual ducts into the oral cavity between the tongue and mandible.[1] The mandibular and sublingual salivary glands are intimately associated with one another as they share a common capsule. Their ducts are adjacent to one another and terminate in the same location. The openings of the ducts of the mandibular and the monostomatic portion of the sublingual gland are located beneath the tongue in a fold of mucosal tissue called the *sublingual caruncle*. Salivary mucoceles are most commonly caused by a defect in the sublingual gland or duct. Because of the close proximity of the mandibular and sublingual glands, treatment for salivary mucoceles requires excision of the mandibular and sublingual gland ducts to the level of the lingual nerve.[6-8] Buccal and lingual molar glands are present only in the cat. The buccal molar gland is located below the mucous membrane of the lower lip and empties into the vestibule through several small ducts. The lingual molar gland is located just lingual to the mandibular first molar in a fold of tissue. This gland also has several small openings unlike a common duct.[1]

Oropharynx

The pharynx is the common passageway for the respiratory and digestive systems. It provides a connection between the nasal and oral cavities to the trachea and esophagus and is pivotal in directing air, food, and fluids into the correct system. The pharynx encompasses the nasopharynx, oropharynx, and laryngopharynx. The nasopharynx is part of the respiratory system. It is located dorsal to the soft palate and extends from the choanae to the caudal free edge of the soft palate and the palatopharyngeal arches.[3] This caudal border is where the laryngopharynx begins. The oropharynx is part of the digestive system and lies between the soft palate, the base of the tongue, and the epiglottis. The laryngopharynx receives air from the nasopharynx and directs it to the trachea, and accepts food and water from the oropharynx and directs it to the esophagus. It is a part of both the respiratory and digestive systems and extends from the base of the epiglottis to the esophagus.[3]

The anatomic borders of the oropharynx are indistinct but can be correlated with certain structures. The dorsal border of the oropharynx is the ventral surface of the soft palate. The soft palate is the muscular continuation of the hard palate and is covered by stratified squamous epithelium on the ventral surface. Dorsal to the epithelium there are numerous palatine glands, which open on the ventral surface of the soft palate. The next layer is the muscular layer and includes the paired palatine muscles and the end portions of the paired tensor and levator veli palatini muscles. The arterial vascular supply of the soft palate includes the minor palatine arteries, the ascending pharyngeal artery, and the major palatine arteries. Venous drainage occurs through the palatine plexus.[2] The right and left pterygopharyngeal muscles originate from the pterygoid bones and pass laterally and dorsally along the pharynx and the caudal part of the soft palate to form the base for the palatopharyngeal arches. These arches are the caudal continuation of the soft palate and also demarcate the nasopharynx from the laryngopharynx.[2,4] The paired palatoglossal arches or folds are located at the rostral border of the soft palate and demarcate the end of the oral cavity and the beginning of the lateral borders of the oropharynx. These arches are not well-defined structures compared to humans because dogs and cats lack a palatoglossus muscle. When the tongue is pulled rostrally and laterally the fold is more visible and extends from the body of the tongue to the rostral border of the soft palate.[2] Soft palate defects are caused by disturbances during development of the secondary palate. These defects can occur on midline between the palatine muscles, or less commonly can be unilateral or bilateral and are located lateral to the palatine muscles. In bilateral defects of the soft palate, a remnant of tissue remains that is composed of portions of the levator and tensor palatini muscles, connective tissue, and mucosa.[9] In contrast to an abnormal or absent soft palate, brachycephalic breeds commonly have an elongated soft palate, which can interfere with the function of the glottis and epiglottis or the normal passage of air.[2,10]

The lateral walls of the oropharynx are termed the *fauces*. The fauces contain the palatine tonsils that reside within the tonsillar fossa. The tonsils are aggregates of lymphoid tissue located in the pharyngeal mucosa. They are not encapsulated like typical lymph nodes. The tonsils function as host defense at the mucosal level. Only efferent lymphatic drainage occurs as tonsillar tissue does not filter lymph.[2,4] The palatine tonsils are the only discrete bodies of lymphoid tissue. The other tonsils such as the pharyngeal and lingual are more diffuse. The pharyngeal tonsil is unpaired and is known as the adenoid in humans. The lingual tonsils are distributed over the entire surface of the base of the tongue.[11] The palatine tonsils arise from the second branchial cleft epithelium. The palatine tonsils often increase in size over time as an increase in lymphatic tissue and the system of crypts occurs, likely as a consequence of antigenic stimulation.[2,11] These crypts serve as physical antigen traps and the tonsils themselves form immunocompetent lymphocytes.[8] The palatine tonsils can be visible in some animals or they may be completely within the tonsillar fossa. Everted tonsils are more often seen in brachycephalic breeds, perhaps as a result of increased negative airway pressure causing eversion of the tonsils and laryngeal saccules.[10] The medial wall of the fossa is formed by the tonsillar fold that comes from the ventral surface of the lateral portion of the soft palate.[2] The deep portion of the tonsil is attached to the lateral wall of the pharynx. Efferent drainage of the palatine tonsils is into the medial retropharyngeal lymph node. Blood supply is derived from the tonsillar artery, which is a branch of the lingual artery. The palatine plexus provides venous drainage.[2]

Function of the Oropharynx

Prehension and Mastication

The most important functions of the oral cavity and oropharynx are their roles in prehension, mastication, bolus formation, and deglutition or swallowing. Prehension is the grasping and manipulation of food. In dogs and cats, prehension is generally achieved with the use of the tongue, teeth, and mandible. The lips play a very minor role in prehension and act more to keep food and fluids in the oral cavity. The olfactory nerve (CN I), optic nerve (CN II), trigeminal nerve (CN V), hypoglossal nerve (CN XII), and the cerebral cortex control the voluntary act of prehension.[12,13] Vertebrates with complete cheeks, such as pigs, sheep, and horses, use suction to draw liquid upward and use their tongue to transport it intraorally. In contrast, vertebrates with incomplete cheeks, including most carnivores, are unable to seal their mouth cavity to generate suction and must instead rely on their tongue to move water into the mouth. The cat accomplishes this through a rapid lapping mechanism that differs in function from the scooping mechanism of the dog.[14]

Mastication is the process of breaking down food into smaller pieces and coating it with saliva to prepare a food bolus for deglutition. The masticatory muscle group is composed of the paired temporalis muscles, masseter muscles, lateral and medial pterygoid muscles, and the digastricus muscles. The masseter, pterygoids, and temporalis muscles contain special type 2M skeletal muscle fibers, sometimes referred to as *superfast fibers*.[4,15] Masticatory muscle myositis, a disease characterized by painful inflammation, scarring, and contracture of the masticatory muscles, can be diagnosed by measuring serum 2M antibody. Autoantibodies against this specific type of myosin in these fibers are responsible for the immune-mediated process.[16] An increase in titer along with clinical signs confirms the diagnosis.[17] The muscles of mastication are innervated by the mandibular branch of the trigeminal nerve (CN V) except for the caudal belly of the digastricus muscle, which is innervated by the facial nerve (CN VII).[2] All of the muscles, except for the digastricus, act to close the jaws. The digastricus muscle contracts to open the jaws. The large size of the masseter and temporalis muscles and the action of the pterygoid muscles act to keep the jaws closed even at rest. Prehension, mastication, and bolus formation are voluntary whereas deglutition is strictly involuntary.

Deglutition

Deglutition is the transport of a bolus of food or liquid from the mouth to the stomach.[12] Normal deglutition requires precisely timed contraction and relaxation of numerous muscles of the oral and pharyngeal regions (Table 54-1).[18] After prehension and mastication the food bolus stimulates sensory receptors in the oropharynx that inhibit the muscles of mastication and allows swallowing to occur. The structures involved in deglutition include the tongue, hard and soft palate, pharyngeal muscles, esophagus, and gastroesophageal junction.[19] Coordination of swallowing is controlled by the trigeminal (CN V), facial (CN VII), glossopharyngeal (CN IX), vagus (X), and hypoglossal (CN XII) nerves and their nuclei. These nerves and nuclei are themselves controlled by areas of the reticular formation known as the swallowing center.[20] All of these nerves provide sensory and motor innervation except for the hypoglossal (CN XII), which provides only motor innervation.[21] The trigeminal nerve (CN V) carries sensory fibers from the oral cavity and motor fibers for the muscles of mastication and the soft palate muscles. The facial nerve (CN VII) contains sensory fibers from visceral receptors in the soft palate and nasopharynx, and motor fibers to the stylohyoid and omohyoid muscles. The glossopharyngeal nerve (CN IX) contains sensory fibers to the pharynx and some areas of the tongue. The vagus nerve (CN X) and the motor fibers of the glossopharyngeal nerve (CN IX) innervate nearly all of the muscles of the pharynx. The vagus nerve carries both visceral efferent and visceral afferent fibers to the pharynx. The visceral sensory nerves of the vagus nerve transmit impulses from the base of the tongue, pharynx, and esophagus to the medulla oblongata.[19]

Deglutition is divided into three phases: oropharyngeal, esophageal, and gastroesophageal. The oropharyngeal phase is controlled by the trigeminal (CN V), facial (CN VII), glossopharyngeal (CN IX), vagus (CN X), and hypoglossal nerves (CN XII). The oropharyngeal phase is further subdivided into three stages: oral, pharyngeal, and pharyngoesophageal.[12,13,19] The oral phase is voluntary and is controlled by cranial nerves V, VII, and XII. The food bolus is transferred into the oropharynx by the base of the tongue.

Once the food bolus reaches the pharynx, the involuntary pharyngeal phase begins. Sensory receptors in the oropharynx are stimulated and transmitted by cranial nerves V, IX, and X. The swallowing center in the medulla oblongata initiates the deglutition reflex and causes progressive contraction of the pharyngeal muscles to continue to propel the food bolus. To prevent aspiration the soft palate is elevated to seal off the nasopharynx and the entrance to the trachea is covered by the glottis and epiglottis (Figure 54-1). The pharyngeal phase is controlled by cranial nerves V, VII, IX, X, and XII. The final stage of oropharyngeal deglutition is the pharyngoesophageal phase. Cranial nerves IX, X, and the swallowing center control this stage. The cricopharyngeus and thyropharyngeus muscles of the cranial esophageal sphincter relax to allow the food bolus to pass into the cranial portion of the esophagus. The sphincter closes after passage of the bolus to aid in retention and to prevent aerophagia. A primary peristaltic wave in the esophagus is initiated after passage of the bolus (see Chapter 55).[12,13,19,20]

Table 54-1 Muscles and Motor Nerves Involved in Prehension, Mastication, and Deglutition

Muscle	Innervation	Action
Lingua propria, intrinsic tongue muscle (P, D)	Hypoglossus	Protrude the tongue, coordinate complex movements, prevent tongue from being bitten
Hyoglossus, extrinsic tongue muscle (P, D)	Hypoglossus	Retract and depress the tongue
Styloglossus, extrinsic tongue muscle (P, D)	Hypoglossus	Draw the tongue backward or depress the tongue
Genioglossus, extrinsic tongue muscle (P, D)	Hypoglossus	Depress the tongue, draw the tongue forward, curl the tip downward
Temporalis muscle (P, M)	Mandibular branch of trigeminal nerve	Closing the jaws
Masseter muscle (P, M)	Mandibular branch of trigeminal nerve	Closing the jaws
Medial and lateral pterygoid muscles (P, M)	Mandibular branch of trigeminal nerve	Closing the jaws
Digastricus muscle–rostral belly (P, M)	Mandibular branch of trigeminal nerve	Opening the jaws
Digastricus muscle–caudal belly (P, M)	Facial	Opening the jaws
Hyopharyngeus (D)	Glossopharyngeal and vagus	Constriction of the rostral pharynx
Thyropharyngeus (D)	Glossopharyngeal and vagus	Constriction of the middle part of the pharynx
Cricopharyngeus (D)	Glossopharyngeal and vagus	Constriction of the caudal part of the pharynx
Stylopharyngeus (D)	Glossopharyngeal and vagus	Dilation, elevation, and drawing of the pharynx forward
Palatopharyngeus (D)	Glossopharyngeal and vagus	Constriction and drawing of the pharynx forward and upward
Pterygopharyngeus (D)	Glossopharyngeal and vagus	Constriction and drawing of the pharynx forward
Tensor veli palatini (D)	Mandibular branch of the trigeminal	Stretching of the soft palate
Levator veli palatini (D)	Glossopharyngeal and vagus	Raising of the caudal part of the soft palate
Palatinus (D)	Glossopharyngeal and vagus	Shortening and curling of the posterior border of the soft palate

D, swallowing function; M, masticatory function; P, prehensile function.

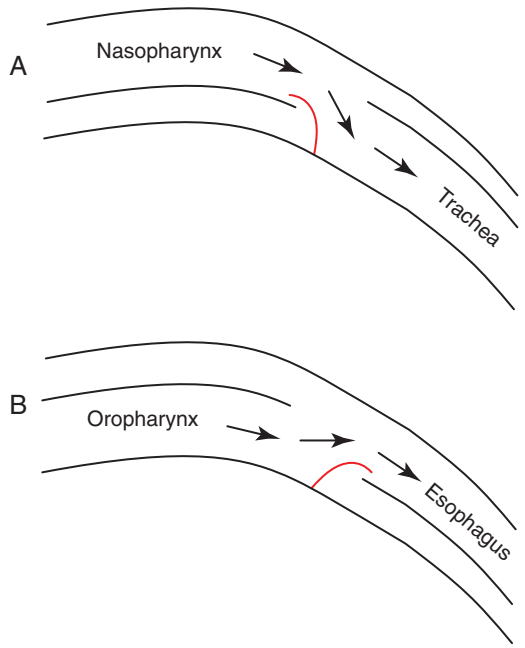

Figure 54-1 Diagram showing the changing position of the epiglottis (highlighted in the red zone) during inspiration (**A**) and deglutition (**B**). During inspiration, the epiglottis moves forward to close off the oropharynx and prevent food or liquids from entering the trachea. During deglutition the epiglottis moves caudally to cover the entrance to the trachea and again prevent movement of food or liquid into the trachea.

The beginning of the gastrointestinal tract is a complex group of structures that all act to promote nutrient intake, provide immunologic protection, and prevent aspiration and aerophagia, as well as other functions such as grooming and defense. The precise coordination of nerves, muscles, and other structures is very complicated. Any abnormality in these structures or their function can result in significant morbidity for the animal if alimentation is not precisely coordinated. Diagnosis of dysphagia requires intimate knowledge of the anatomy of the oral cavity and oropharynx as well as the neurologic control of this region.

INFLAMMATION

Linda DeBowes

Stomatitis

Clinical Manifestations

Stomatitis refers to inflammation within the oral cavity and clinical manifestations depend on the site(s), extent of inflammation, amount of pain, and the interference with normal function. Inflammation may range from superficial mucosal inflammation, erosion, and shallow to deep ulceration. Stomatitis includes inflammation of the gingiva; the buccal, vestibular, and sublingual mucosa; the tongue; and the palate.

The major clinical sign often is halitosis. Depending on the severity of stomatitis, there may be hypersalivation, drooling, decreased food intake, dysphagia, lethargy, depression, and weight loss (Figure 54-2). Patients with extensive inflammation and ulcers are often in pain and are apprehensive about being touched around their head or mouth. Oral examination should be attempted with

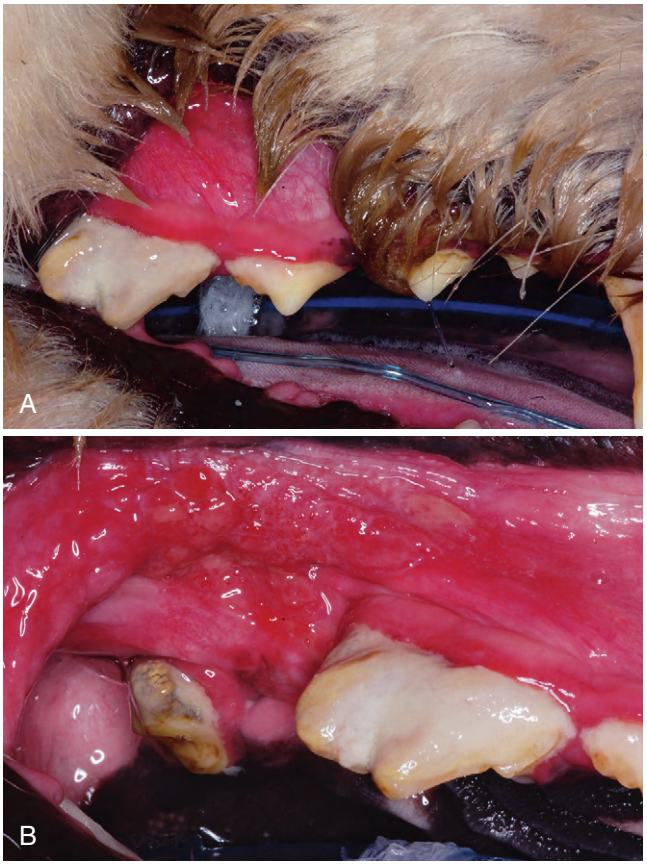

Figure 54-2 **A,** A dog with severe stomatitis showing drooling. **B,** Proliferative and ulcerated buccal mucosa in this patient.

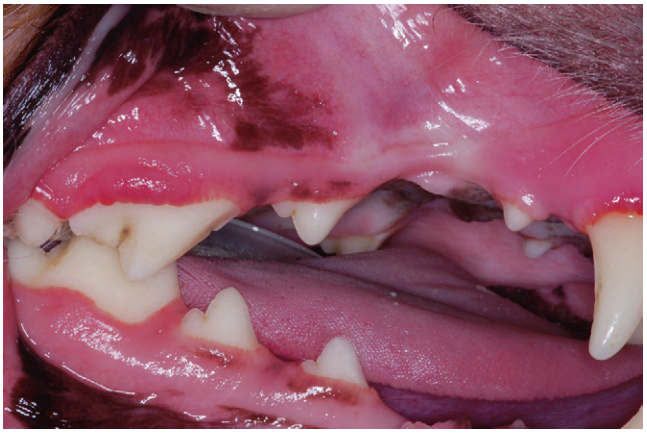

Figure 54-3 Inflammation and rounding of the gingival margin in a dog with gingivitis.

these patients; however, when the lesions are too painful, this is done under anesthesia unless anesthesia is contraindicated.

Gingivitis is inflammation of the gingiva and may be limited to the marginal gingiva or include the attached gingiva (Figure 54-3). Focal areas of gingival hyperplasia may result from chronic inflammation. Contact ulcers are focal areas of inflammation and ulceration located on the buccal mucosa where it contacts plaque biofilm (Figure 54-4). Periodontitis involves the gingiva as well as the other tissues of the periodontium (i.e., cementum, periodontal ligament, alveolar bone). Oral examination may reveal gingival

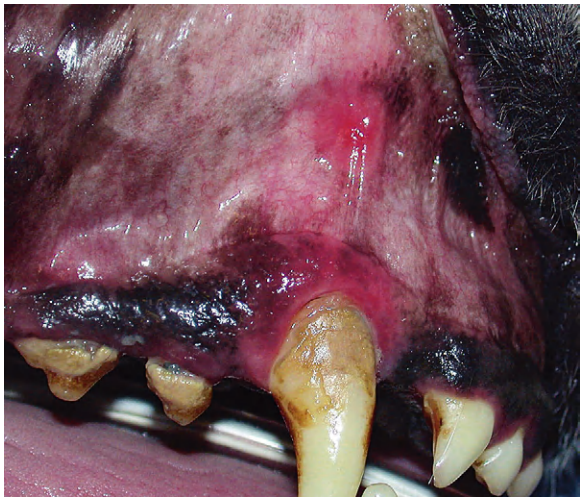

Figure 54-4 Contact ulcer on the buccal mucosa opposite calculus on the canine tooth.

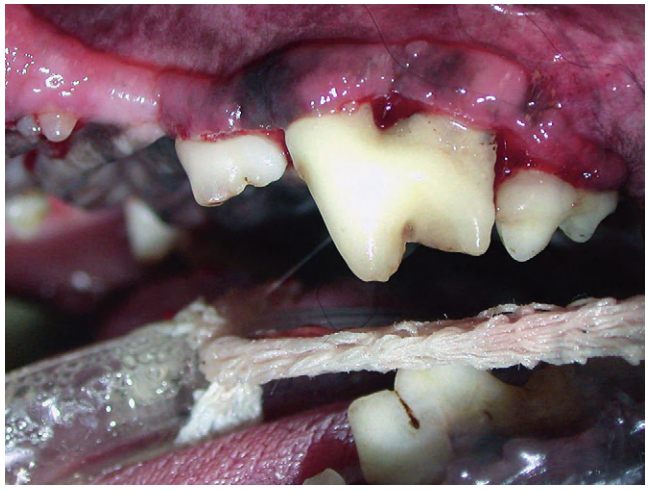

Figure 54-5 Gingival bleeding, recession, and exposed roots in a dog with periodontitis.

recession, gingival hyperplasia, root exposure, and mobile teeth (Figure 54-5).

Patients with stomatitis may have severe inflammation and ulceration of the gingiva, buccal mucosa, tongue, and palate (Figure 54-6). Inflammation of the tongue is often along the lateral margins and there may be ulceration are severe cases (Figure 54-7). Palatal inflammation and ulceration is usually linear or focal and range from superficial to deep ulceration. Patients with severe stomatitis may be in significant pain. Clinical signs may be severe halitosis, hypersalivation, drooling, and changes in behavior. The patients often refuse dry food and will eat only soft food. In very severe cases they refuse soft food as well. When cats with caudal stomatitis open their mouths to eat or yawn this can trigger intense pain, and they may vocalize, aggressively rub or scratch at their face, run away from their food, and have activities that the owners describe as a seizure. On physical examination there may be minimal external signs. In severe cases there is blood-tinged or thick-yellowish saliva, and saliva may adhere to the fur around the lips and on the front legs. Cats often have a matted and unkempt appearance. The inflammation of the mucosa is often disproportionately severe compared with the minimal amount of plaque and calculus on the teeth.

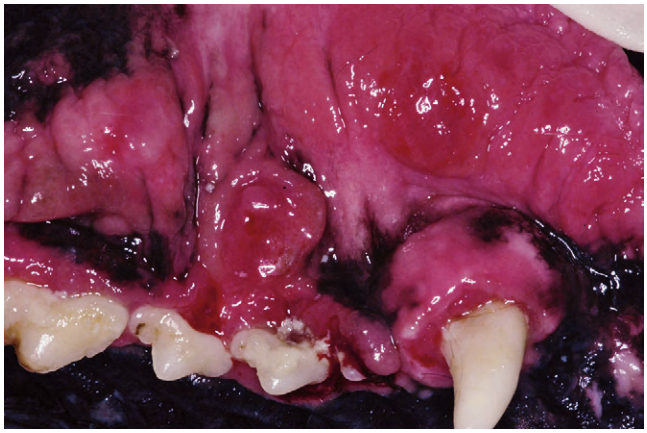

Figure 54-6 Dog with severe stomatitis, buccal and gingival inflammation, and ulceration.

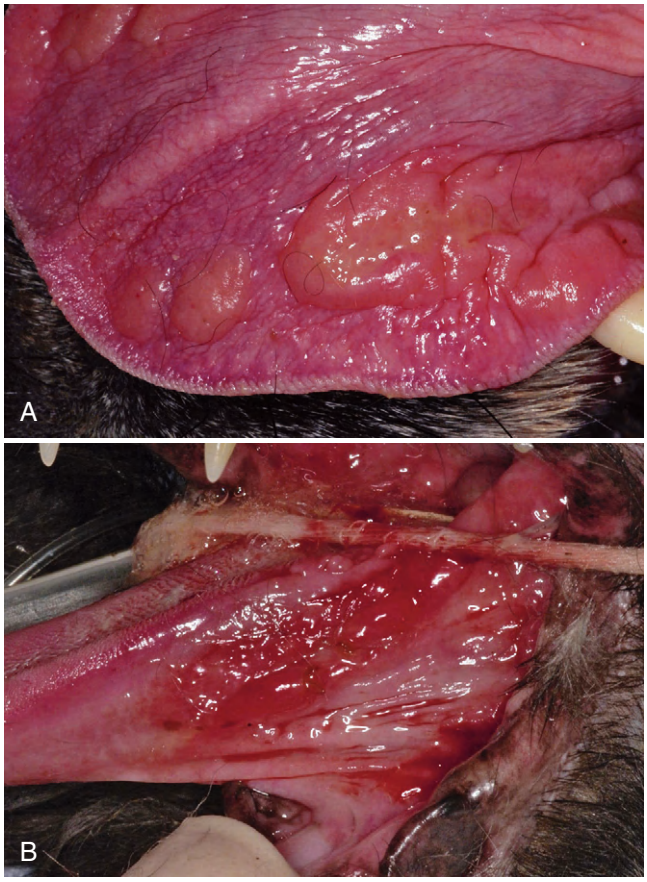

Figure 54-7 **A,** Lingual inflammation in a dog with periodontal disease. **B,** Lingual inflammation in a cat with caudal stomatitis.

The inflammation in cats with caudal stomatitis initially may be limited to the pterygomandibular raphe (Figure 54-8). Over time many cats with caudal stomatitis will also develop anterior stomatitis (Figure 54-9). Pharyngeal hyperplasia, in severe cases, can result in a narrowing of the pharyngeal opening, contributing to pain on swallowing (Figure 54-10). Oral examination of cats with severe caudal stomatitis may be difficult, but visualization is often possible if the mouth is opened very slowly and carefully. Inflammation of the tongue may be local or generalized and present as erythematous areas, erosions, or ulcers. Cats with lingual ulceration may have

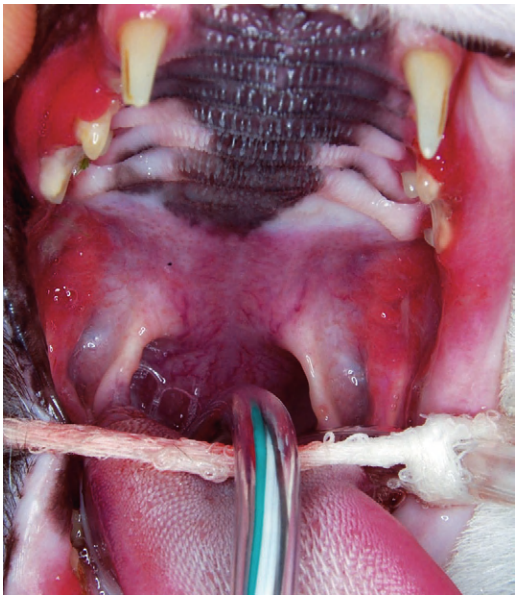

Figure 54-8 Caudal stomatitis in a cat.

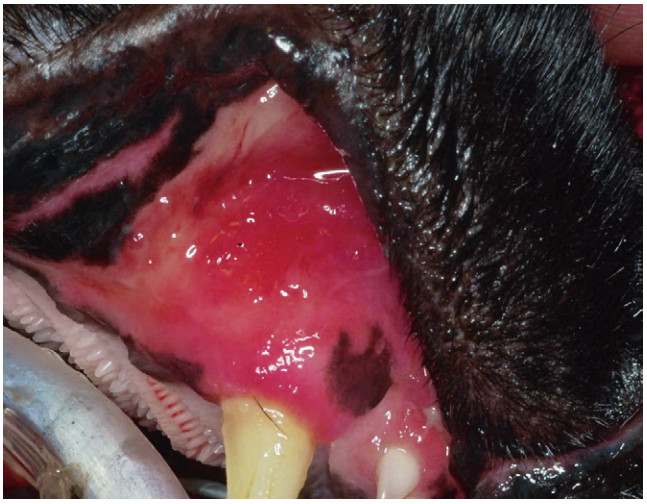

Figure 54-9 Anterior stomatitis.

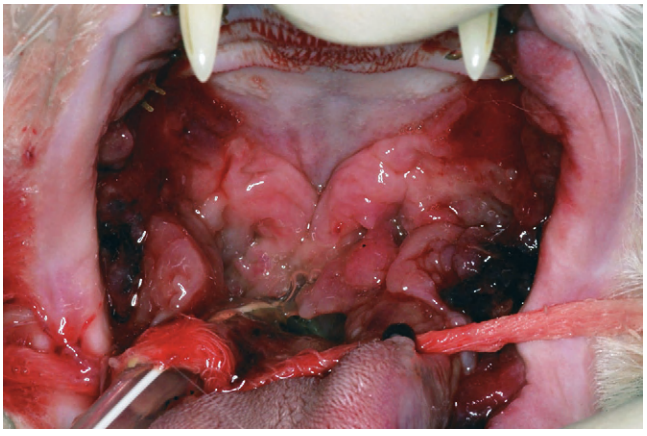

Figure 54-10 Narrowing of the pharyngeal opening in a cat with caudal stomatitis.

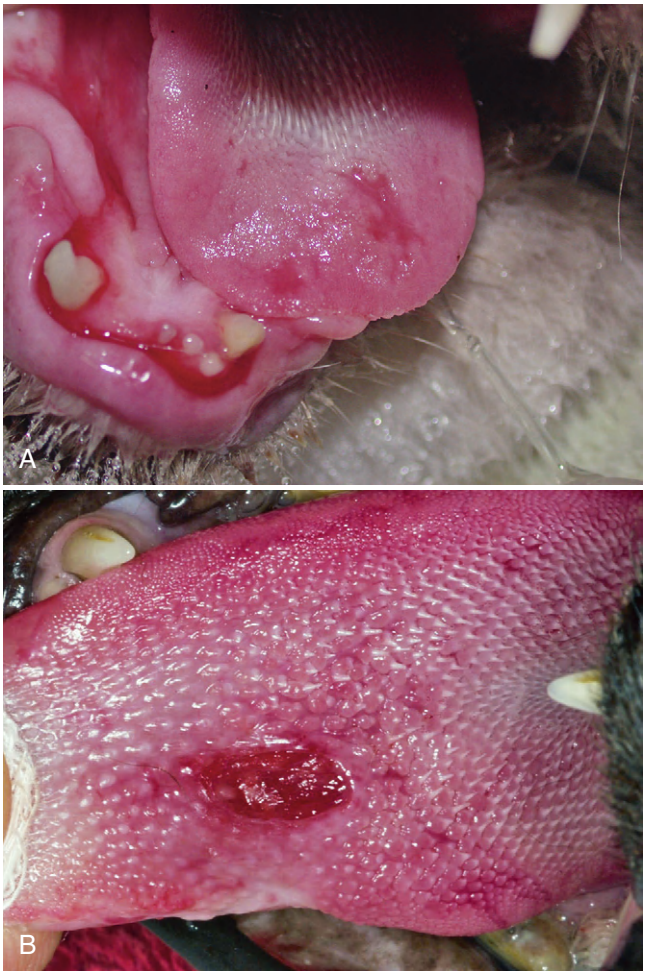

Figure 54-11 **A,** Lingual ulcers in a cat with feline calicivirus infection. **B,** Oral ulceration in a cat with lingual oral neoplasia (hemangiosarcoma).

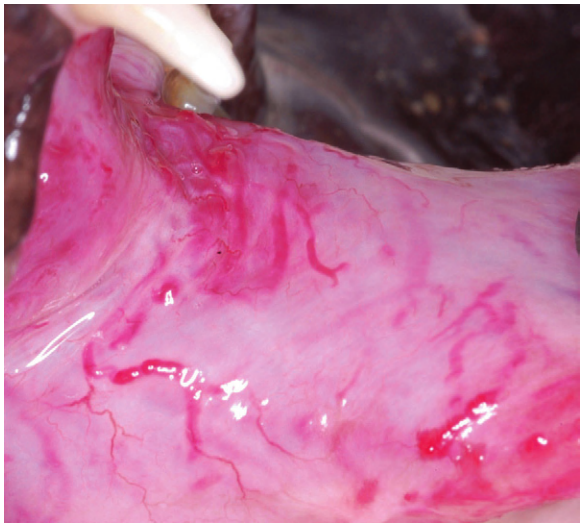

Figure 54-12 Sublingual hemangiosarcoma in the cat shown in Figure 54-11.

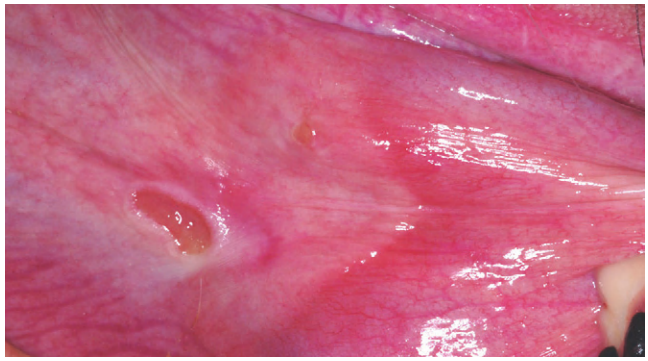

Figure 54-13 Sublingual eosinophilic granuloma in a dog.

clinical manifestations of upper respiratory tract infection. Lingual ulcers may be located anywhere but the most common areas are the rostral one-third of the tongue (Figure 54-11). Lingual ulcers associated with feline calicivirus (FCV) and feline herpesvirus (FHV)-1 are seen with the acute phase of the infection and when there is a recurrence of signs in a carrier cat.

Sublingual masses generally occur at the base of the tongue with varying degrees of inflammation, ulceration, and proliferation. When a lingual mass is present, especially if the base of the tongue is involved, the patient may have difficulty eating or drinking (Figure 54-12).

Eosinophilic diseases affecting the oral cavity occur more frequently in cats than in dogs.[1] The canine breed reported most commonly with eosinophilic granulomas is the Siberian Husky. Affected dogs have lesions primarily on the palate or tongue.[2,3] Eosinophilic granulomas have also been reported in Cavalier King Charles Spaniels.[4-6] Clinical signs may not be present and the lesions may be found incidentally on physical examination. Lesions on the palate or tongue are usually linear with raised margins, and a reddish color in the center but no ulceration (Figure 54-13). Eosinophilic granulomas in cats occur primarily at the base of the tongue, are proliferative with varying degrees of ulceration, and may have a similar appearance to sublingual squamous cell carcinoma. Clinical signs may include excessive licking and abnormal tongue movement with difficultly in eating or drinking.

Oral candidiasis may result in single or multiple erosions or ulcers of the mucocutaneous junctions and oral mucosa. Ulcers are nonhealing and erythematous, and are covered by whitish-gray plaques.[2,7]

Pemphigus vulgaris in dogs may be associated with severe inflammation and ulceration of the gingiva and oral mucosa. Ulcerated tissues are very erythematous and friable. Patients are usually in pain, are depressed, have difficulty eating, and prefer soft food. The severity of the inflammation is more than is expected with the minimal amount of plaque and calculus and inflammation is present even in edentulous areas.

Lymphoma in the oral cavity may be seen as raised, inflamed gingival tissues, or as a mass lesion.[8]

Patients with systemic diseases may have oral lesions as part of the presenting clinical signs. Vasculitis as a consequence of systemic disease may lead to oral lesions including ulcers and necrosis of oral mucous membranes and the tongue. Additional oral lesions that may be associated with systemic diseases include congestion, hemorrhage, glossitis, uremia-related oral ulceration, and lingual necrosis, especially at the tip of the tongue.[2]

Pathogenesis

Inflammation of the oral tissues is a common pathologic response when disruption of the normal oral mucosal barrier allows an inflammatory response in the epithelium or connective tissues.[9]

The depth and severity of an ulcerative lesion depend on the severity of the insult and inflammatory response. Erosion involves only the epithelium, ulceration occurs when the epithelium is lost, and deep ulcers occur when there is sloughing of inflamed necrotic material.

The masticatory mucosa of the gingiva, hard palate, and the dorsal surface of the tongue is a tough layer of keratinized stratified squamous epithelium that provides protection from compressive and shear forces.[10] This protective layer is less likely to be damaged with resulting inflammation compared with other areas in the oral cavity.

The lining of the oral mucosa is composed of nonkeratinized stratified squamous epithelium that is attached to underlying structures by loose, elastic connective tissue. The tightly adherent epithelial cells and intercellular ground substance compose the primary mucosal barrier and protect the underlying tissues against fluid loss and the ingress of potentially harmful environmental agents (e.g., microbial toxins and antigens). This permeability barrier also isolates organisms in the epithelial layer from larger molecules (e.g., antibodies, complement) in the subepithelial tissues. When antigens penetrate the mucosal barrier, antigen–antibody complexes, complement activation, and infiltration of inflammatory cells result in tissue destruction. Oral organisms on the surface of the epithelium do not penetrate the mucosal barrier unless the organism acquires a greater virulence or the host defenses are compromised.[10]

The protective function of the mucosal barrier may be damaged by trauma, immune-mediated disease, soluble toxins, altered mucosal barrier, and xerostomia.[10] When the mucosal layer is damaged or there is a decrease in cell renewal, epithelial and subepithelial inflammation may occur. Xerostomia and dehydration may result in ulceration and infection because of the role of salivary mucins in maintaining healthy epithelium.

Epithelial cell renewal is affected by age, stress, inflammation, chemotherapy, and radiation treatments. Mild epithelial inflammation stimulates cellular proliferation while severe inflammation suppresses cell proliferation.[10] Chemotherapeutic agents and radiation treatments limit the proliferative ability of the epithelium and connective tissue. Depending on the neoplastic disease and planned cancer treatment, the oral cavity should be evaluated and oral disease (e.g., dental) managed prior to treatment to prevent complications associated with mucositis.[11]

Oral ulcers occur in some forms of pemphigus. Autoantibodies are directed against components of the epidermis or subdermal tissues and the level at which cell separation occurs determines the depth of the ulceration.

In addition to limiting the proliferative ability of the epithelium and connective tissue, ionizing radiation has a direct effect on the large molecules that make up intercellular ground substance. These changes allow for an increase in vascular permeability, resulting in tissue edema and an inflammatory infiltration.

Secondary bacterial infections occur commonly when the mucosal tissues are compromised. When the normal endogenous microflora is altered, such as following prolonged broad-spectrum antibiotic therapy, oral candidiasis can occur.

The pathogenesis of periodontal disease depends on microbial plaque stimulating an initial inflammatory response. The host defense cells are stimulated to produce and release mediators capable of destroying the alveolar bone and periodontal connective tissue. Genetics plays a role in determining the host inflammatory response.[12,13]

Patients infected with *Cryptococcus neoformans* occasionally have oral involvement as part of the clinical manifestations of local or systemic disease. The lesions may include diffuse ulceration of the buccal mucosa, tongue, gingiva, hard palate, and lips as well as gingival proliferation. The more common clinical signs of cryptococcosis include sneezing, snuffling, nasal discharge, skin lesions, and a nasal mass.[8,14,15]

Vasculitis as a manifestation of systemic or local disease affects the circulation and oxygenation of tissues and may lead to destruction or necrosis of these tissues.[16]

Etiology and Differential Diagnosis

Stomatitis is defined as the inflammation of soft tissues of the oral cavity occurring as a result of mechanical, chemical, thermal, bacterial, viral, electrical, or radiation injury, or as a reaction to allergens or as a secondary manifestation of systemic disease.[17]

Mechanical causes of stomatitis include swallowing, chewing, or biting on abrasive substances (e.g., pinecones, sticks, plants, rocks). An object may become lodged in the mouth causing continuous mechanical trauma, inflammation, and infection until it is removed.

Caustic and irritating substances that come into contact with oral soft tissues cause inflammation, primarily on the dorsal one-third of the tongue, but inflammation can occur in other places as well. Examples of caustic and irritating materials are certain plants with small spikes, household products (e.g., cleaning supplies, bleach), foreign bodies (e.g., grasses, bark, wood, fertilizers, embedded hair), and medications (e.g., pancreatic enzymes). Biting on electrical cords can cause severe palatal and lingual inflammation and necrosis of soft tissues.

Focal areas of inflammation and ulceration of the maxillary or mandibular mucosa are common signs associated with squamous cell carcinoma, osteomyelitis, or other neoplasms. Inflammation and draining fistulas at the mucogingival line may be from endodontic infection or less commonly periodontal infection.

Caudal stomatitis in cats is secondary to altered immune function; however, the etiology has not been determined.[18] Various theories have been presented, including associations with FCV and *Bartonella henselae*.[19] FCV does appear to be associated with caudal stomatitis.[19-21] The role of FHV-1 in caudal stomatitis is unknown; however, in one study the majority of cats with caudal stomatitis were shedding both viruses.[21]

Eosinophilic diseases in most cases are attributable to hypersensitivity reactions to insects (e.g., fleas and mosquitoes), environmental antigens (e.g., atopic dermatitis, foods), or other antigenic stimulation. Eosinophilic granulomas in some cats may be a result of imbedded insect parts; in many cases, however, the specific etiology remains unknown.[1] Pemphigus vulgaris, bullous pemphigoid, and pemphigus foliaceus may have oral manifestations. Of these, pemphigus vulgaris is most likely to have oral manifestations and up to 75% to 90% of dogs with this disease have involvement of the oral cavity. Oral lesions are the initial clinical signs in 50% of cases.[2]

Painful oral ulceration and inflammation may occur following radiation treatment or chemotherapy.

Extension of diseases such as neoplasia (e.g., squamous cell carcinoma) and infection into the oral cavity can occur, resulting in inflammatory lesions within the oral cavity.[22]

Systemic diseases also may have oral manifestations. Renal failure and vasculitis (e.g., rickettsial diseases) from any cause may result in oral manifestations (Figure 54-14).[16] Mucosal erosion and ulceration may be present in patients with systemic lupus erythematosus. Bacterial (e.g., *Francisella tularensis*, *Leptospira canicola*), fungal

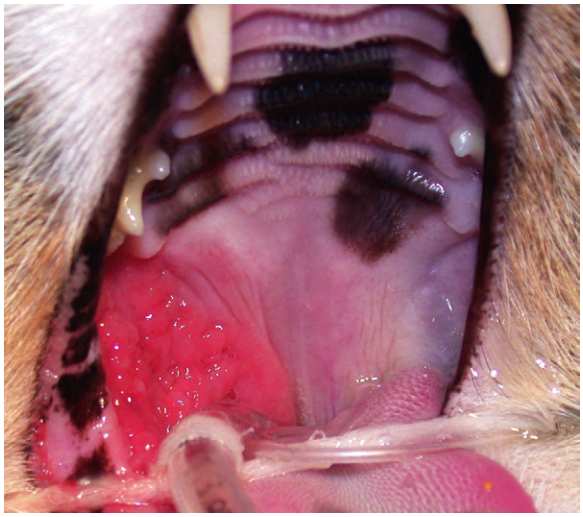

Figure 54-14 Oral squamous cell carcinoma in a cat.

(e.g., *C. neoformans*), and viral infections, neoplasia, and drug reactions all have the potential for oral manifestations.[8,23,24]

Diagnosis

Diagnosis of stomatitis begins with a complete history and physical examination. It is usually possible to determine when oral lesions may be a manifestation of a systemic disease. Diagnosis of systemic diseases is beyond the scope of this chapter.

Stomatitis caused by irritating or inflammatory materials may be diagnosed based on the history and oral examination. Contact irritants (e.g., rubber toys, chemicals) may be suspected based on history and response to removal. Traumatic stomatitis is often identified based on the history and oral examination; however, an oral examination under anesthesia may be required to identify the cause (e.g., penetrating foreign body) and consequences of the trauma. Embedded materials (e.g., plant materials) may not be visually apparent and biopsy and histopathology should be performed if embedded materials are suspected.

Caudal stomatitis in cats is a clinical diagnosis and is present only when there is inflammation of the pterygomandibular raphe. This is important because there are specific treatments for caudal stomatitis that do not apply to stomatitis elsewhere in the mouth. Histologic examination reveals inflammation and does not add to the diagnosis; however, when neoplasia is suspected based on the clinical appearance, histological examination should be undertaken (see Figure 54-14).

Periodontal disease and the extent of disease are diagnosed by oral examination and dental radiography. Buccal and lingual inflammation associated with periodontal disease (e.g., contact ulcers) is also a clinical diagnosis.

Eosinophilic granuloma (complex) is diagnosed by histopathology (rules out other problems); the underlying etiology, however, may require additional evaluation (e.g., dietary trials).[1]

Histopathology is necessary for the diagnosis of pemphigus vulgaris, oral candidiasis, and neoplasia.[7]

Treatment

Initial treatment is removal of any topical substances that may have caused the stomatitis. Oral hygiene to reduce bacterial load, pain management, treatment of secondary bacterial infections, and nutritional support should be considered. Oral manifestations of systemic diseases are treated as for any stomatitis in addition to the treatment of the primary systemic disease.

Pain management is especially important initially when there is severe inflammation and ulceration. Oral antimicrobial rinses (e.g., 0.12% chlorhexidine gluconate) are often used until the epithelium has healed. Secondary bacterial infections may occur in cases that do not rapidly resolve and systemic antibiotics may be necessary in addition to the topical rinses.[25]

Periodontal disease treatment planning is based on the extent of disease. Complete periodontal treatment planning is beyond the scope of this chapter.[13]

Eosinophilic granuloma complex may be treated with short courses of glucocorticoids if the lesions are mild and occur only once to twice a year.[1] If lesions are progressive in severity or frequency, a more complete evaluation for the cause should be undertaken. Higher doses and longer durations of glucocorticoids, antibiotics, and cyclosporin may be used in the more severe cases.[1]

Treatment of caudal stomatitis has been widely debated over the years; however, the first treatment should be extraction of all premolar and molar teeth. In some patients with severe anterior stomatitis accompanying the caudal stomatitis, extraction of the canine and incisor teeth may also be necessary. Medical treatment following surgical extractions may include antibiotics, glucocorticoids, or cyclosporin. Medical management should not be used in place of extractions for long-term management. Clindamycin, amoxicillin-clavulanate acid (Clavamox), and metronidazole are commonly used oral antibiotics. If glucocorticoids are used as an adjunct to extraction, they should be used at the lowest doses necessary. Cyclosporin has been used for the management of cats with persistent clinical signs following extractions. Cats should be treated for at least 8 weeks to assess the clinical response.[26] Potential side effects of cyclosporin are gingival hyperplasia, excessive shedding, and hypertrichosis.[27,28] The immunosuppressive effects of cyclosporin may result in development of infections or the emergence of an existing subclinical infectious disease (e.g., toxoplasmosis).[29-31] Although lactoferrin, gold salts, and other miscellaneous treatments have been recommended, there is no evidence that they have any clinical benefit. Newer therapies that have been proposed are omega interferon (Virbagen Omega, Virbac) and T-cell receptor (TCR) peptides (TCR Vax). Anecdotally, cats with an incomplete response to extractions have improved with Virbagen Omega; however, this product is not licensed in the United States. The administration of a TCR vaccine for treatment of caudal stomatitis in cats has been proposed (www.imulan.com). TCR Vax is undergoing field trials and is not yet commercially available.

Pemphigus vulgaris is difficult to treat and multidrug therapy is often necessary. High-dose glucocorticoid administration either alone or in combination with another immunomodulatory medication is usually recommended. Azathioprine is the secondary immunomodulatory medication most commonly used.[32] Gold salts, chlorambucil, and tetracycline-niacinamide are other options for the treatment of pemphigus. Alternative therapeutics may be tried when the response to the commonly used drugs is not adequate. Intravenous immunoglobulin (IVIg) has been suggested as an alternative therapeutic for treating dogs.[32] IVIg used in humans for the treatment of pemphigus has shown beneficial results and a better quality of life when compared with other therapeutics.[33]

Mucositis secondary to chemotherapy or radiation treatment is managed with palliative care. Pain medications, topical rinses (e.g., CET rinse), and soft foods are used during the healing phase. Infections (e.g., candidiasis) and systemic complications may occur during treatment or after treatment.[25]

Prognosis

The prognosis for resolution of clinical signs in cats with caudal stomatitis is dependent on the treatment, severity of disease, concurrent viral (e.g., FCV) infection, and duration of disease. An excellent response following extraction may be achieved, especially when treated at an early stage. Extraction of the premolars and molars carries the best long-term prognosis for resolution.[34] The prognosis is poor to guarded when extractions are not done and when tooth roots have not been removed. Cats that do not have a successful or significant improvement in clinical signs following extraction are medically managed. There is a varied response in these cats and some may have excellent responses. In one study, cyclosporin treatment resulted in remission in four of eight cats and fair to good improvement in the other cats.[26]

Eosinophilic granuloma, especially in dogs, may spontaneously regress. Eosinophilic granulomas in cats may respond well to three monthly subcutaneous injections of a long-lasting glucocorticoid. Cyclosporin for treatment and maintenance is reported to be beneficial.[26]

Radiation mucositis is an acute reaction and should start to heal by 10 to 14 days after treatment has ceased. However, the prognosis depends on the amount of radiation that the tissue was exposed to. The prognosis is guarded in patients with severe mucositis and poor healing.[25] Postradiation osteonecrosis has a poor prognosis and a comprehensive assessment and oral care should be done before radiation therapy.[35]

Pemphigus vulgaris has a guarded prognosis because of the potential for secondary infections, high doses of medication necessary to control the disease, and the difficulty of maintaining the patient in remission.

Pharyngitis

Clinical Manifestations

The pharynx is divided into three areas: nasopharynx, oropharynx, and laryngopharynx. Clinical manifestations vary depending upon the location and extent of the inflammation, the etiology, and the involvement of adjacent structures. The most common clinical manifestations include dysphonia (voice change), snoring, coughing, gagging, dysphagia, inappetence, and hypersalivation. When stomatitis occurs concomitantly with pharyngitis there may be clinical signs of each. Secondary tonsillitis is often present in association with pharyngitis. Clinical manifestations of tonsillitis are similar to those of pharyngitis (Figure 54-15).

Nasopharyngeal foreign bodies can cause coughing, sneezing, epistaxis, gagging, discomfort on pharyngeal palpation, and open-mouth breathing.[36] Obstructive masses may result in dyspnea, stridor, open-mouth breathing, snoring, and gagging.[36-38]

Disease involving extrapharyngeal sites have additional clinical manifestations and signs of disease (e.g., neurologic signs, ocular discharge, repeated head shaking) depending on the involved site, disease process, and extent of disease.[38]

Pathogenesis

The pharyngeal tissues have the same mucosal barrier as in the oral cavity. Therefore pharyngitis has the same pathogenesis for inflammation as stomatitis.

Etiology and Differential Diagnosis

Pharyngeal inflammation can occur from trauma, caustic or irritating substances, infectious diseases, obstructive masses, foreign bodies and as an extension of rhinitis, sinusitis, caudal stomatitis, and drainage of a local abscess (e.g., retrobulbar abscess) (Figure 54-16).[36,39] Caustic or irritating substances are similar to those causing stomatitis. Pharyngitis caused by chronic coughing, regurgitation, or vomiting may cause irritation resulting in pharyngitis. Severe cases of caudal stomatitis in cats can extend into the oropharynx. Sino-orbital aspergillosis may extend into the palate and nasopharynx resulting in clinical signs of pharyngitis.[21,40,41]

Nasopharyngeal diseases include lymphoma and inflammatory polyps.[40,41] Feline inflammatory polyps that expand into the nasopharynx as well as other obstructive masses in the oral cavity or nose, may obstruct the flow of air and the exaggerated respiratory efforts result in laryngeal inflammation (Figure 54-17).[38] The etiology of feline inflammatory polyps has not been determined.[38] Tissue from 41 inflammatory polyps was evaluated by polymerase chain reaction for the presence of FCV and FHV-1; negative findings

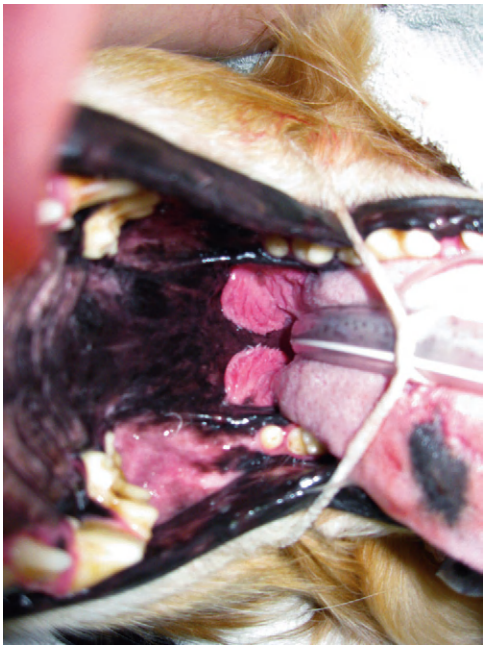

Figure 54-15 Bilateral tonsillar enlargement with histologic evidence of chronic inflammation and fibrosis.

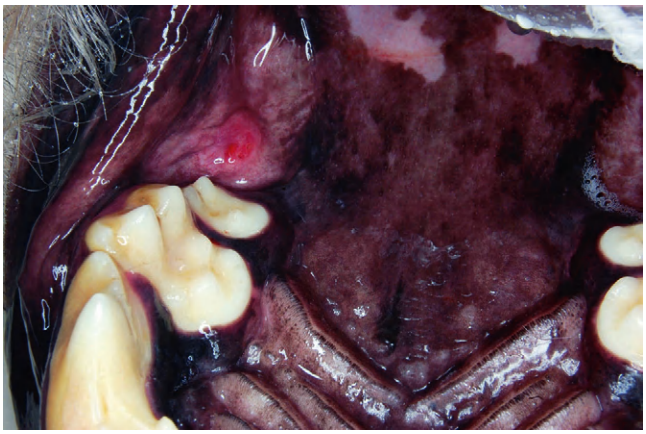

Figure 54-16 Focal area of inflammation and drainage from a retropharyngeal abscess.

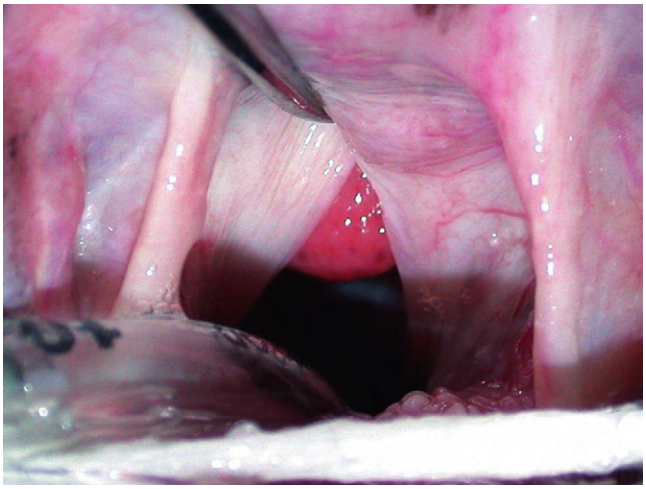

Figure 54-17 Feline inflammatory polyp.

suggested that these viruses are not involved with the pathogenesis of inflammatory polyps.[38]

Diagnosis

History and oral examination will lead to the clinical diagnosis of pharyngitis. Direct oral examination may be sufficient in diagnosing topical contact with caustic or irritating substances, trauma, foreign bodies, or mass lesions. Rhinoscopy and retroflex nasopharyngoscopy may be required for adequate visualization and collection of tissue for histopathology.

Radiography is generally not necessary in diagnosing the etiology of pharyngitis. Radiography may be necessary for diagnosing pharyngitis from a radiodense penetrating foreign body (e.g., needle) or pharyngitis secondary to extrapharyngeal disease.

Treatment

Removal or treatment of the primary etiology applies to all patients with pharyngitis. In addition, pain management, topical antimicrobial rinses, systemic antimicrobials, and fluid and nutritional support should be considered for each patient.

Topical irritants, depending on the source, should be removed as much as possible by rinsing the mouth. Foreign bodies are removed using direct visualization.[36]

Nasopharyngeal inflammatory polyps in cats with normal bulla may be treated (removed) by traction avulsion.[38] A novel approach to removal of polyps using an endoscope passed into the nasopharynx via a gastrotomy has been described.[42]

Nasopharyngeal stenosis in cats may be treated by balloon dilation under general anesthesia.[43,44] Restenosis may occur and it may be treated with another balloon dilation. When retreatment is necessary, the application of topical steroids or an antifibrotic agents may be tried to decrease the degree of another restenosis.[43]

Prognosis

There is an excellent prognosis in acute primary pharyngitis when the source of topical trauma or irritant can be removed. Nasopharyngeal foreign bodies may have a varied prognosis depending on the ability to remove the foreign body atraumatically and manage local complications that can occur from a perforation of the nasopharynx. The prognosis is worse when there has been a perforation.

Feline inflammatory polyps have an excellent response to removal. Feline nasopharyngeal stenosis has a good to excellent response following balloon dilation.[43] The prognosis for other problems that may cause pharyngitis depends on the underlying disease and its response to treatment.

Sialadenitis

Clinical Manifestations

Enlarged, painful salivary glands, hypersalivation, dysphagia, repeated attempts at swallowing, pain on opening the mouth, xerostomia, decreased food intake, and depression are all potential manifestations of sialadenitis.

Pathogenesis

The pathogenesis of salivary gland inflammation may be idiopathic, infectious (e.g., bacterial, viral, mycotic), traumatic, secondary to xerostomia or dehydration, ductal obstruction, or organic disease of the gland (e.g., Sjögren syndrome). Acute bacterial infections of the salivary gland are usually a result of an ascending infection. Xerostomia or dehydration may contribute to the development of ascending bacterial infection by decreased salivary flow and alteration of the normal oral flora.[45,46] Hematogenous spread of infection from other areas also may cause a bacterial sialoadenitis.[47]

Etiology and Differential Diagnosis

Ascending bacterial infections are most likely to be caused by anaerobic periodontal pathogens.[48] Decreased salivary gland flow may occur secondary to dehydration, salivary duct obstruction, or decreased saliva production. Acute salivary gland inflammation or chronic inflammation with fibrosis may decrease salivary gland production. Systemic disorders that may lead to inflammation include autoimmune sialadenitis (e.g., Sjögren syndrome) and vasculitis.[49] Sialadenitis is uncommon in dogs and cats. Differentials for enlarged salivary glands include sialadenitis, sialadenosis, and infiltrative disease.

Diagnosis

Diagnostic tests may include fine-needle aspirate cytology, culture and sensitivity, histopathology, ultrasound, and radiography (e.g., films and contrast sialography). Fine-needle aspirate cytology of enlarged salivary glands is the initial diagnostic test and may reveal the presence of salivary gland inflammation.[50] Bacterial culture and sensitivity of exudate from the orifice of the salivary duct or the salivary gland is recommended.[47] Ultrasound of the salivary gland can help to differentiate obstructive from nonobtrusive sialadenitis and identify masses and abscess formation.[51] Radiography, including plain films and contrast sialography, may identify radiopaque salivary calculi and ductal or glandular changes. Histopathology may reveal neutrophils in the ducts and small abscesses in the interstitium.[47]

Treatment

Sialadenitis is treated with supportive care, antiinflammatories, and antibiotics.[52] Abscesses may be treated by antibiotics in addition to drainage using ultrasound guidance.[51]

Prognosis

Ascending bacterial infections and acute sialadenitis may be treated very successfully if there are no ductal or glandular obstructions. Salivary duct obstruction generally has a good prognosis, especially in acute cases.

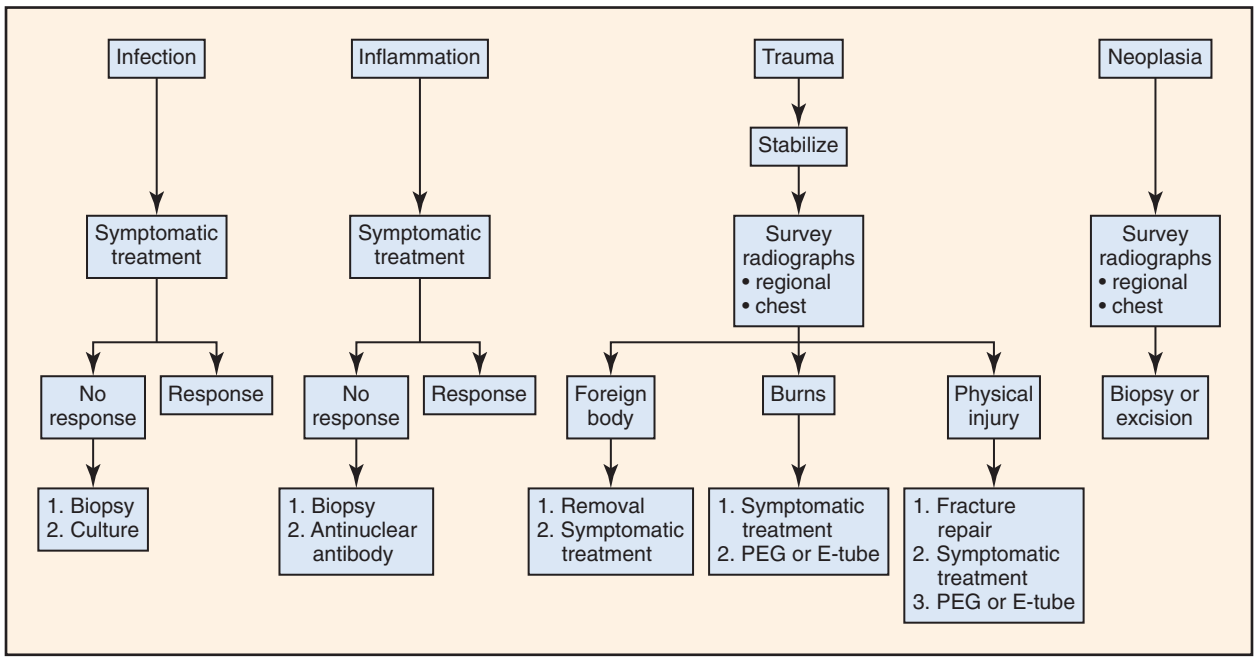

Figure 54-18 Medical investigation of a morphologic oropharyngeal motility disorder. E, Esophageal; PEG, percutaneous endoscopic gastrostomy.

DYSMOTILITY

Robert J. Washabau

Etiology

Oropharyngeal motility in health requires the highly coordinated propagation of food and water in the oral, pharyngeal, and cricopharyngeal stages of swallowing.[1-4] Oropharyngeal dysmotility is associated with the primary clinical signs of dysphagia, gagging, and salivation (see Chapter 13).[5] Dysmotility syndromes are broadly classified as anatomic or functional in origin. The anatomic disorders are those processes that interfere with oropharyngeal motility because of infection, inflammation, trauma, and neoplasia (Figure 54-18). The functional disorders are of three main types: oropharyngeal dysphasia, cricopharyngeal dysphagia, and cricopharyngeal achalasia (Figure 54-19).

Physiology and Pathophysiology

The oropharyngeal phase of feeding is entirely under voluntary control. Feeding is guided by social conditions for domesticated animals, and by the fight-or-flight response for animals in the wild. The oropharyngeal phase of feeding consists of three stages: prehension, mastication, and deglutition (swallowing).[5] see Structure and Function section for more detail on the process of swallowing.

The first stage of oropharyngeal motility begins with the prehension of food and water with teeth and tongue. Land animals have evolved diverse means to acquire water, including absorption through the skin and the extraction of moisture from food, but most rely on drinking. Vertebrates with complete cheeks, such as pigs, sheep, and horses, use suction to draw liquid upward and use their tongue to transport it intraorally. In contrast, vertebrates with incomplete cheeks, including most carnivores, are unable to seal their mouth cavity to generate suction and must rely on their tongue to move water into the mouth. When the tongue sweeps the bottom of a shallow puddle, the process is referred to as *licking*.[6,7] When the puddle is deeper than the tongue excursion into the liquid, it is called *lapping*. The domestic cat and dog lap by a subtle mechanism based on water adhesion to the dorsal side of the tongue. Fluid inertia is exploited to defeat gravity and pull liquid into the mouth. The competition between inertia and gravity sets the lapping frequency.[6,7]

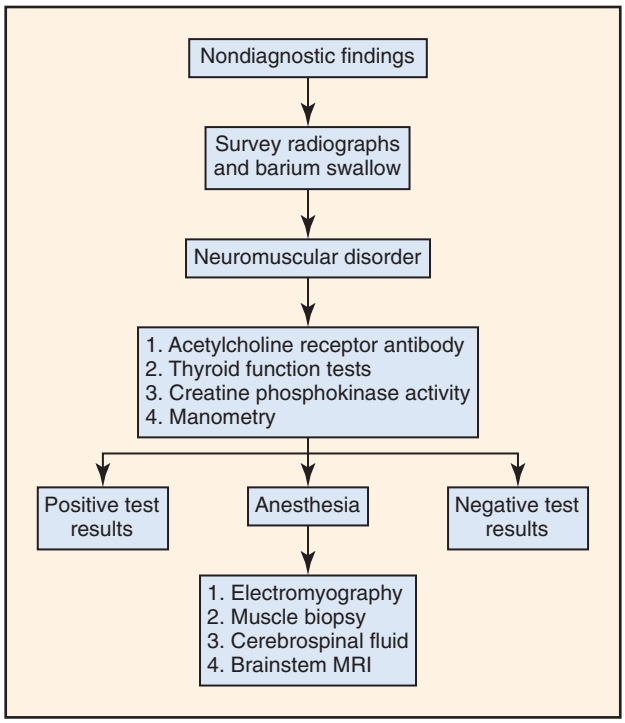

Figure 54-19 Medical investigation of a functional oropharyngeal motility disorder. MRI, Magnetic resonance imaging.

Table 54-2 Differentiation of Clinical Signs: Diseases of the Oral Cavity, Esophagus, and Stomach

Clinical Sign	Oral Cavity	Esophagus	Stomach
Dysphagia	Always present	Sometimes present	Absent
Regurgitation	Absent	Present	Absent
Vomiting	Absent	Absent	Present
Salivation	Usually present	May be present	May be present
Gagging	Often present	Usually absent	Absent
Ability to drink	Abnormal	Normal	Normal
Bolus formation	Abnormal	Normal	Normal
Dropping food	Present	Absent	Absent
Ejection time	Immediate	Delayed (minutes to hours)	Delayed (minutes to hours)
Character of food	Undigested	Undigested	Digested, bile stained, acidic pH
Odynophagia	Occasional	Frequent	Absent
Swallowing	Multiple	Single to multiple	Usually single

Mastication is the next stage in the process of breaking down food into smaller pieces and coating it with saliva to prepare a bolus for deglutition (swallowing).

In the final stage, rostral to caudal pharyngeal contractions propel the bolus from the base of the tongue to the cricopharyngeal or cranial esophageal sphincter opening. The cricopharyngeus relaxes during the final stage, and the bolus passes into the cranial esophageal body. Following bolus passage, the cricopharyngeus subsequently contracts, pharyngeal muscles relax, and the oropharyngeal phase is repeated until the completion of feeding.[1-4]

Prehension, *mastication*, and *deglutition* are controlled by the hypoglossal nerve (tongue movement), trigeminal and facial nerves (jaw movement), and glossopharyngeal and vagus nerves (pharynx constriction and relaxation, and soft palate movement) (see Table 54-1).[8] Disorders of the cranial nerves, neuromuscular junction, and striated musculature can result in significant oropharyngeal dysphagia.

Dysphagia, gagging, and hypersalivation are the most important clinical signs with oropharyngeal disorders. Other signs include difficulty in drinking water or forming a solid bolus; excessive mandibular or head motion; persistent forceful ineffective swallowing efforts; dropping of food from the mouth; nasal discharge because of misdirection of food into the nasopharynx; excessive salivation; foaming from the mouth; coughing; failure to thrive; and reluctance to eat (Table 54-2). Regurgitation, a common sign of esophageal disease, is less frequently reported with diseases of the oropharynx.

Clinical Examination

Physical examination findings are dependent upon both pathogenesis and disease severity. Many anatomic abnormalities (e.g., neoplasia, stricture, inflammation, foreign body) are readily apparent on physical examination alone. Animals with functional disorders, on the other hand, may have few anatomic abnormalities. Focal or generalized muscle atrophy and diminished or absent gag reflex may be the only abnormal findings in animals with functional disorders of the oropharynx. Figures 54-18 and 54-19 outline an approach to the diagnosis oropharyngeal dysmotility. The diagnosis of an anatomic abnormality is usually straightforward and, except for tissue biopsy or culture, does not usually require any additional diagnostic testing. (Examples of each of the anatomic disorders may be found in: "Inflammation", "Neoplasia", "Granuloma", and "Trauma" sections.) Survey radiography, ultrasound, computerized tomography, and magnetic resonance imaging (MRI) may be performed to assess for either the severity of local traumatic injury or for distant metastasis.[4] The diagnosis of the functional motility disorders is more difficult and likely requires the use of videofluoroscopy[3,5,9] and/or electrophysiology.[2] If these techniques are not readily available in the private practice setting, cases could be referred to a specialty center.

Diagnosis

Videofluoroscopy is useful in the further classification of the functional disorders.[3,5] The videofluoroscopy findings of *oral* stage dysphagias are typified by weak tongue-thrust action, retention of contrast medium in the oropharynx, and loss of contrast medium from the mouth. Aspiration pneumonia is not a typical finding in oral stage dysphagias. Videofluoroscopic findings consistent with a *pharyngeal* stage dysphagia include incomplete pharyngeal contraction with adequate cricopharyngeal relaxation, slow induction and slow progression of peristaltic-like contractions from the rostral to the caudal pharynx, and laryngotracheal aspiration. Aspiration pneumonia is a typical finding in pharyngeal stage dysphagias. In *cricopharyngeal* stage dysphagia, the cricopharyngeus fails to relax (achalasia) or relaxes at an inappropriate time (incoordination) following pharyngeal contraction.

Electromyography may be useful in distinguishing oropharyngeal dysphagia and cricopharyngeal dysphagia from cricopharyngeal achalasia. Fibrillation and positive sharp waves observed in oropharyngeal musculature suggest that the disorder involves the structures of the oral cavity and pharynx instead of the cricopharyngeus.

Other diagnostic tests that may be warranted after an oropharyngeal dysphagia or cricopharyngeal dysphagia has been diagnosed are serology for nicotinic acetylcholine receptor antibody, antinuclear antibody, thyroid function test, serum creatine phosphokinase activity, muscle biopsy, and brainstem magnetic resonance imaging (see Figure 54-19). Esophageal disorders are the major differential diagnoses for the oropharyngeal dysmotility syndromes.

Oropharyngeal Dysphagia

Oropharyngeal dysphagia represents a disruption in the coordinated transport of food and water from the oropharynx to the hypopharynx. If morphologic abnormalities (e.g., infection, inflammation, trauma, neoplasia) can be excluded, neuromuscular disease is the likely underlying pathogenesis. The precise etiology is often more difficult or impossible to identify. Some cases are associated with

Table 54-3 Treatment of the Functional Oropharyngeal Motility Disorders

Disorder	Diagnostic Test	Therapy
Myasthenia	Ach R Antibody	Pyridostigmine
Myositis	Antinuclear antibody	Glucocorticoids
Hypothyroidism	TSH, T_4/T_3	Thyroid hormone
Brainstem disease	MRI, CSF tap	Nutritional support

Ach R, acetylcholine receptor antibody; CSF, cerebrospinal fluid; T_4/T_3, thyroxine/triiodothyronine; TSH, thyroid-stimulating hormone.

brainstem disease (e.g., meningioma), cranial nerve neuropathy, myasthenia gravis, polymyositis, muscular dystrophy, and hypothyroidism. A unique form of oropharyngeal dysphagia bearing some resemblance to muscular dystrophy has been described in the Bouviers des Flandres breed.[10-12] Fluoroscopy demonstrates absence of aboral pharyngeal contraction, incomplete bolus transport, and dropping of food and water. Differentiating between oropharyngeal dysphagia, cricopharyngeal dysphagia, and cricopharyngeal achalasia is crucial, as the treatment for cricopharyngeal achalasia (myotomy or myectomy) could significantly exacerbate clinical signs in dogs affected with more proximal oropharyngeal dysphagia. Table 54-3 outlines treatments for each of the causes of oropharyngeal dysphagia. For those of known or unknown etiology, long-term management may require permanent gastrostomy or enterostomy tube feedings. Consequently, the prognosis for the oropharyngeal dysphagias is guarded at best, and affected animals will require significant home care.

Cricopharyngeal Dysphagia

Cricopharyngeal dysphagia is a rare swallowing disorder of the cricopharyngeus (cricoesophageal sphincter) characterized by cricopharyngeal asynchrony or dyssynchrony. Affected animals have many of the same clinical signs as seen with oropharyngeal dysphagia. Cricopharyngeal dysphagia or asynchrony is an incoordination between contraction of the dorsal cranial and middle pharyngeal contractor muscles (i.e., the hyopharyngeal, pterygopharyngeal, and palatopharyngeal muscles) and relaxation of the cricopharyngeus.[13,14] Cricopharyngeal dysphagia likely represents an abnormality of the central pattern generator with incomplete coordination of the contraction–relaxation cycle of oropharyngeal and cricopharyngeal motility. Cricopharyngeal myotomy or myectomy have been recommended in the treatment of this disorder. Although some animals have improved with this therapy, others have not.[14-16] The prognosis for this disorder is guarded as well, and the patients may be at increased risk for aspiration pneumonia.

Cricopharyngeal Achalasia

Cricopharyngeal achalasia is a neuromuscular disorder of young dogs characterized by (a) hypertension of the cranial esophageal sphincter (cricopharyngeus) and (b) inadequate relaxation of the sphincter with swallowing. In this disorder, the lesion is purely sphincteric. Proximal oropharyngeal motility is entirely normal. The underlying pathogenesis has not been elucidated, but a dysfunction in the inhibitory neuron mediating sphincteric relaxation has been postulated. To reduce sphincteric hypertension, calcium channel antagonists have been used to treat this disorder, but without success.[17] (Calcium channel antagonists are more effective in smooth muscle sphincters versus the striated muscle of the cricopharyngeus.) Myotomy or myectomy should be considered and will usually resolve the dysphagia seen in this disorder.[14-16] The cricopharyngeal and thyropharyngeal muscles can be approached through a standard, ventral midline approach, with 180-degree rotation of the larynx on its longitudinal axis, or through a lateral approach, with 90-degree rotation of the larynx. Cricopharyngeal myotomy involves transecting the cricopharyngeal muscles to the level of the pharyngeal mucosa. Several authors have combined cricopharyngeal myotomy with partial or complete thyropharyngeal myotomy. Cricopharyngeal myectomy entails removal of a portion of the cricopharyngeal muscles, rather than simple incision. The muscle fibers are separated from the mucosa and excised. Both procedures (myotomy and myectomy) appear to be effective. Myectomy may be more permanent in its effect.

Treatment/Management

General Principles

Except for cricopharyngeal achalasia, which is treated surgically by cricopharyngeal myotomy or myectomy, oropharyngeal and cricopharyngeal dysphagias are best treated medically. Cricopharyngeal myotomy appears to be of no benefit in oral, pharyngeal, or cricopharyngeal stage dysphagias; indeed, more proximal dysphagias may be worsened by cricopharyngeal myotomy.

Medical (Drugs and Diet)

The medical therapy for oropharyngeal and cricopharyngeal dysphagias is mostly supportive and consists of nutritional support (e.g., gastrostomy tube feeding) on a temporary or permanent basis. Elevated feedings and different food consistencies may be attempted, but these efforts are often of little clinical benefit. In early cases of myasthenia gravis, acetylcholinesterase inhibitors (e.g., pyridostigmine, 1 to 3 mg/kg PO, BID-TID) may yield substantial clinical improvement.[18,19] Glucocorticoid therapy (prednisone, 1 to 2 mg/kg PO, BID) also improves clinical signs in many myasthenic and polymyositis patients, although many cases of canine myasthenia gravis appear to resolve spontaneously without immunosuppressive therapy.[20] Thyroid hormone replacement therapy (levothyroxine, 22 µg/kg PO, BID) should be attempted in animals with documented hypothyroidism.

NEOPLASIA

Antony S. Moore

Most oral tumors are diagnosed at an advanced stage of growth and therefore many pets show similarly advanced clinical signs. Regardless of the tissue of origin, cats and dogs with oral tumors present for drooling, halitosis, and (occasionally) dysphagia. Most patients have shown signs for 3 months or less, but some may show signs for 6 to 12 months before diagnosis. With more routine dentistry performed, some tumors are diagnosed at an earlier stage, and this has been reflected in recent changes to prognosis (specifically, early diagnosis of oral melanoma in dogs may confer a reasonable chance for long survival). Loose teeth at dentistry may be the first signs of oral squamous cell carcinoma (SCC) in cats. Biopsy of any ulcerated mucosal tissue is warranted in older cats with dental disease.

Before obtaining a biopsy or attempting surgical resection of an oral tumor, all dogs and cats should have their general good health confirmed with a minimum database, including hematology and

urinalysis. Thoracic radiographs should be obtained to rule out macroscopic pulmonary metastases or other intercurrent disease. Fine-detail radiographs of the affected area, including the dental arcade, provide information on tumor infiltration. Radiographs should not be relied on for surgical margins because more than 50% of the bone must be replaced by tumor before lysis is evident radiographically. Computed tomography (CT) is a more accurate method of delineating the margins of a tumor and will allow planning of surgical margins or radiation therapy. Local lymphadenopathy should be further investigated by fine-needle aspiration (FNA) or biopsy performed at the same time as tumor biopsy. In one study of 100 dogs with oral melanoma, 60% of enlarged lymph nodes had cytologic evidence of metastases, but metastases were also detected in 40% of normal-size lymph nodes.[1] Thus, even normal-size lymph nodes should be aspirated. A preoperative biopsy of the primary tumor will guide the veterinarian as to the type of surgery needed and the prognosis.

The first surgical excision is the most likely to result in tumor control. The tumor should not be scraped or peeled from underlying bone, as recurrence is certain and the tumor bed will be enlarged. A definitive aggressive first surgery, such as maxillectomy or mandibulectomy, should be performed.

General Comments about Surgery

In general and regardless of the tissue of origin, incomplete surgical resection is commonly associated with recurrence, which emphasizes the importance of early diagnosis and obtaining wide surgical margins by mandibulectomy or maxillectomy at the first surgery. In two studies 65% of oral tumors treated by maxillectomy with incomplete margins recurred, compared with 22% of tumors with complete histologic margins.[2] Similarly 62% of oral tumors treated by mandibulectomy with incomplete margins recurred, compared with 15% of tumors with complete histologic margins.[3]

Surgical techniques for mandibulectomy and maxillectomy have been described in detail, and the reader is referred to surgical texts for descriptions beyond the scope of this chapter; newer techniques for resection of large oral masses have been published.[4,5]

Although the mandibular lymph nodes are regularly assessed when examining a dog with an oral tumor, metastases may involve other lymph nodes in the neck without involving the mandibular nodes. A single surgical approach was described that allowed biopsy of ipsilateral parotid, mandibular, and medial retropharyngeal lymph nodes. Lymph nodes that would have been considered difficult to evaluate by FNA (parotid and medial retropharyngeal) provided useful diagnostic and prognostic information.[6] The surgeon should also be aware that lymphatic drainage from the cranial mandible is commonly bilateral to mandibular nodes.

Both mandibulectomy and maxillectomy are tolerated well by dogs, with median hospitalization times ranging from 2 days for simple excision to 8 days for total hemimandibulectomy. Owner satisfaction with aggressive oral surgery remains a concern for veterinarians and their patients' families. In a telephone survey of caregivers for 27 dogs with oral tumors that had been treated with either aggressive surgical resection, satisfaction with the surgical procedure was assessed.[7] Overall, 85% of owners were pleased with their decision to treat their dogs, and the longer the dog had lived, the more likely the caregiver was to be satisfied. Although difficulty in eating was noted for 44% of the dogs (most commonly after maxillectomy; 64%), pain was thought to be less after surgery for most animals. All clients found the cosmetic appearances of their dogs acceptable after facial hair regrew. The quality of the pets' lives was perceived by the owners to be most improved after rostral mandibulectomy (100%) and least improved after partial mandibulectomy.

Mandibulectomy and maxillectomy are poorly tolerated in cats compared with dogs. One study reviewed 42 cats treated with mandibulectomy for oral cancer. Tumor control was seen in 56% of cats at 1 year after surgery and in 49% of cats 2 years after surgery; in addition, 60% and 57% of the cats were alive during the same time periods. Cats with SCC (43% were alive 2 years after surgery) had shorter survival than cats with fibrosarcoma (67%) or osteosarcoma (83%). Morbidity was high in cats compared with reports from dogs, with 72% of cats dysphagic or inappetent immediately after surgery and 12% never regaining the ability to eat. Despite acute morbidity in 98% and long-term morbidity in 76% of cats, 83% of the owners surveyed were satisfied with the outcome of mandibulectomy.[8] Cats that have undergone mandibulectomies need to have special attention paid to dental care, and teeth may need to be removed if they are causing abrasion. Nutritional support should be considered mandatory in cats with oral tumors, particularly if they are undergoing extensive treatment. A gastrostomy or esophagostomy tube should be placed during aggressive surgery or for the duration of radiation treatment and until the cat is able to eat by itself. Antibiotics, corticosteroids, and analgesics should be administered as needed to minimize discomfort.

Benign Oral Tumors

Epulides and Ameloblastomas

Dogs

A number of different terms have been used to describe tumors arising from the components of teeth. Some tumors retain the ability to induce reactive proliferation of connective tissue, and thus odontogenic tumors are often described as "inductive." Reclassification of what used to be termed *epulides* has resulted in the term *epulis* being reserved only for fibromatous epulis of periodontal ligament origin. Fibromatous epulides are slow-growing gingival masses that rarely exceed 2 cm in diameter. In dogs, they may be single or multiple but are always discrete and located near teeth, particularly the premolars; they are most common in the maxilla. Poor oral hygiene may be a predisposing factor for these tumors. One study found that dental plaque deposition was common in dogs with fibromatous epulides; approximately half the affected dogs had severe dental tartar, and a further 30% had moderate dental tartar.[9]

Acanthomatous ameloblastoma (previously acanthomatous epulis) occurs in dogs, but not cats. It is a rapidly progressive tumor that has a high epithelial component and infiltrates readily into bone. It is usually found in the mandible, particularly around the canine teeth, and should be considered malignant.

Cats

Epulides, arising from the periodontal ligament, are rare in cats.[9a] In this species, giant cell epulides have a more aggressive clinical behavior compared with the fibromatous type, including rapid growth, presence of ulceration, and rapid recurrence after surgery; all of which combined confer a worse prognosis. The most common noninductive tumor in cats is the calcifying epithelial odontogenic tumor, which contains amyloid deposits within its stroma and may be pigmented. Inductive fibroameloblastomas have almost exclusively been described in cats age 18 months or younger and appear as a rapidly growing fleshy mass, usually located rostrally in the mouth.

Treatment

Dogs

Local excision of a fibromatous or ossifying epulides may be all that is required. In one study, 104 dogs with fibromatous epulides were treated by marginal excision; only six dogs had a slow-growing regrowth between 6 and 7 months after surgery.[9]

Local gingival excision of an acanthomatous epulis is rarely curative, as these tumors deeply invade bone in a similar manner to SCC and other oral malignancies. Of 23 dogs with a marginal excision, the tumor recurred in 21 (91%) within 1 month.[9] Wide surgical margins that include a section of normal bone encompassing the tumor (maxillectomy or mandibulectomy) should be curative for small acanthomatous epulides. Similarly aggressive surgical excision should be curative for larger acanthomatous epulis; however, adequate margins may be difficult to obtain.

Radiation therapy is very effective for the treatment of acanthomatous epulis. In one series of dogs with acanthomatous epulis, 80% were free of tumor 3 years after ^{60}Co radiation therapy.[10] Where the tumor was located within the oral cavity, and whether bone was involved were not important to outcome.

Chemotherapy is not warranted, as systemic spread has not been reported for any epulis. Cryosurgery has been used for treatment of epulides, but recurrence is common, presumably because of poor ability to freeze bone. This modality should not be used if it will delay more definitive treatments.

Cats

In cats, radiation therapy appears to confer similar long-term tumor control for cats with epulides, calcifying epithelial odontogenic tumors, and fibroameloblastomas and may be preferred to surgery for tumors that are large and would require significant portions of bone to be removed.

Malignant Oral Tumors

The most common malignant neoplasm in the oral cavity of dogs is melanoma, which accounts for approximately 35% of tumors. The next most common is SCC (25%), with fibrosarcoma as the third most common (16%). Other less common tumors encountered include osteosarcomas and nerve sheath tumors. In cats, SCC accounts for 60% to 80% of all oral tumors. Fibrosarcoma is the only other commonly reported malignant tumor, and accounts for 10% to 20% of feline oral tumors; all other individual tumor types account for less than 3% of oral tumors.

Oral Melanoma

Dogs

Oral melanoma is the most common oral malignancy in dogs. Unlike cutaneous melanomas, which are often benign, melanomas of the canine oral cavity are uniformly malignant. Aggressive local growth and distant metastasis are common. These tumors are most common in Poodles, Dachshunds, Scottish Terriers, and Golden Retrievers. This is a disease of older dogs. In one study, the median age of affected dogs was 11 years.

Most melanomas arise in the gingiva. In descending order of frequency, melanomas are also found on lips, tongue, and hard palate. Although masses are frequently pigmented, amelanotic tumors are common. Because these tumors often surround the bony structures and invade bone, surgical excision is often difficult.

In general oral melanomas should be considered to be potentially malignant regardless of their histologic appearance. On the other hand, a recent study found that shorter survival times were seen for dogs with oral melanomas that were larger, had high numbers of mitotic figures per 10 high-power fields, had marked nuclear atypia, and had more inflammation or necrosis (these characteristics were added into a numerical score). In that study six of the nine dogs alive at the end of the study had a score of less than 10, and only one of the 46 dogs that died had a score of less than 10 (so the system is not perfect).[11] Melanomas of the lips appear to have less aggressive behavior, with lower metastasis rates after local therapy. In one study, dogs with melanoma of the lips had a median survival of 22 months with a 30% death rate caused by melanoma, compared with a median survival of 5 months with a 68% death rate caused by melanoma for dogs with oral mucosal melanoma.[11]

Metastasis of oral melanoma is probably an early event; however metastases are often not detected until long after the primary melanoma is resected. The growth rate of metastases may vary, and it is this variation, rather than when metastasis occurs, that determines survival time.

Cats

Although oral melanoma is common in dogs, it is rare in cats, accounting for less than 3% of oral cancers. Oral melanomas in cats have a similar clinical appearance to those in dogs and are often ulcerated. Based on case reports, and anecdotal information, the metastatic rate for this tumor approaches 100% (usually lymph nodes and lungs but also to other systemic sites) and progression is usually rapid.

Treatment

Dogs

Surgery remains the mainstay of treatment for oral melanoma and should consist of mandibulectomy or maxillectomy. Radiation has a role in local tumor control. Chemotherapy with platinum compounds, perhaps combined with immunotherapy, may offer the best adjunctive treatment for metastatic disease.

Most dogs with oral melanoma are euthanized because of progression or recurrence of local disease. If surgery is aggressive from the outset, it may prolong survival as well as provide palliation. Aggressive local therapy should include resection of underlying bone. Mandibulectomy or maxillectomy should be the first surgery used to treat oral melanoma in dogs. Less aggressive surgeries do not prolong survival and make subsequent surgery more difficult. Most studies report local recurrence rates ranging from less than 15% for melanomas treated by mandibulectomy to 48% for tumors treated by maxillectomy. In three studies, dogs treated with aggressive surgery had a median survival time of 7 to 9 months compared with seven dogs that did not have surgery and survived a median of 2 months. Lingual melanomas may have a lower rate of metastasis than mucosal melanomas, and are often of a lower histologic grade. Regardless of the surgery performed, most dogs with oral melanoma develop metastases; consequently, adjuvant chemotherapy is recommended.

Radiation therapy has a role in the treatment of melanoma, particularly when surgery is not possible. Melanoma responds best when radiation therapy is delivered in large doses per fraction, and because metastatic disease is often the cause of death in dogs with melanoma, a palliative course of radiation is also appealing from a quality of life perspective. For dogs that have tumors that cannot be treated by surgery, coarsely fractionated radiation therapy causes a complete response in 50% to 75% of patients. If the melanoma can be reduced to microscopic disease, then the prognosis is much better. For dogs with small, rostrally located melanomas the risk of late effects of radiation therapy becomes greater as their survival times are likely to be long. For these dogs the use of small doses per

fraction, as used in more conventional radiation therapy, could be considered. In one study, dogs with microscopic disease, those with no bony lysis on radiographs, and those with rostrally located tumors all had a lower chance of recurrence and lived longer. Overall median survival was 7 months. Dogs with no poor prognostic factors lived longer than those with increasing numbers of negative factors.[12]

Metastatic disease occurs in the majority of patients and often occurs within 6 months of treatment, although metastases may not be visible for longer than 1 year after surgery. After metastases develop, dogs may still survive a long time, depending on the growth rate. Dogs may tolerate pulmonary metastatic disease with very little apparent effect on their quality of life.

Chemotherapy may improve survival times in dogs with oral melanoma when used as an adjunct to surgery but rarely when used to treat gross or metastatic disease. Platinum compounds appear to be the most efficacious. Carboplatin caused responses in 28% of dogs with unresectable oral melanoma, including one dog with a complete response lasting nearly 3 years. Overall response duration was 5.5 months.[13] Higher dosages, and the occurrence of gastrointestinal toxicity were associated with a higher likelihood for response.

Combinations of chemotherapy with either surgery or radiotherapy appear to make the most therapeutic sense for dogs with oral melanoma. One study reported weekly radiotherapy for 6 weeks (also given with weekly low doses of carboplatin or cisplatin before treatment) to dogs that had been treated surgically to microscopic disease. In this group of 39 dogs recurrence was seen in six dogs (15%) a median of 4 months after treatment, and metastases were seen in 20 dogs (51%) a median of 10 months after treatment. The median overall survival was more than 1 year.[14] Survival times were longer than previously reported for dogs with oral mucosal malignant melanoma. The implication is that surgical debulking to microscopic disease may improve local control, and allow the benefit of chemotherapy in treating metastatic disease to be seen.

Immunotherapy has a role in treating melanoma in dogs. In early 2010, the USDA gave full licensure to a xenogeneic human tyrosinase DNA vaccine to treat dogs with melanoma, following a period of conditional licensure starting in 2007 in which the vaccine was available to veterinary oncologists in the US for treatment trials in spontaneous melanoma in dogs. The vaccine is now available in the US as Oncept (produced by Merial) for use by veterinary oncology specialists. The vaccine is given as an initial series of four treatments, using a specifically designed needleless transdermal injector, 2 weeks apart, and then a booster every 6 months. Recent data analysis of 58 dogs with stages II and III oral melanoma treated by surgical excision and Oncept showed that dogs that received vaccine had a longer median survival time (median not reached) compared with historic controls. 75% of dogs were alive 15 months after surgery, compared with 5 months for dogs treated by surgery alone.[15]

Cats

All cats that had surgical excision of oral melanoma developed metastatic disease within 5 months of surgery. In two of these cats metastases were diffuse throughout the body. Radiation therapy appears to be helpful in local tumor control as it is in dogs; however, even though responses are reported in approximately 60% of cats, metastasis is common and survival times are similar to those with surgery. Carboplatin may have efficacy against metastases but is unproven. With the exception of one report,[16] the use of Oncept in cats has been reported anecdotally that one macroscopic anti-tumor response was seen. The safety and toxicity appears to be the same as for canine patients. The Bioject transdermal device can be used on feline skin, but the angle of injection is different, using the skin of the caudal thigh and injecting cranially into the semimembranosus/tendinosus muscles.

Squamous Cell Carcinoma

Dogs

Most oral SCCs are found rostrally within the mouth; most occur in the maxilla. SCC is usually found in the gingival tissue, although the tongue and tonsils can be affected. Gingival tumors may extend to cause lysis of underlying bone. SCC usually occurs in older dogs with no apparent breed or gender predilection. Tumors of the tonsil and tongue behave more aggressively than SCC arising at other sites. Papillary SCC occurs more often in young dogs as a progressive disease with a high rate of lytic bone involvement; however metastases are rare.[16a]

Metastasis of gingival SCC is uncommon, and metastasis to the lungs at time of diagnosis is rare. Regional lymph nodes are frequently enlarged at diagnosis and should be sampled for cytology or histopathology; however, they usually do not contain metastases. Regional lymph node metastasis is uncommon both before and after therapy, occurring in 10% of dogs in a five-case series.

Tonsillar SCC is considerably more aggressive than gingival SCC and occasionally may occur bilaterally. Most dogs present with dysphagia, anorexia, and pain, and clients may have noticed a cervical swelling, which is usually lymph node metastasis that occurs very early in the course of disease. In fact, the primary tumor may be quite small but lymphadenopathy may be marked. Most dogs have shown these signs for 1 month or less. SCC of the tongue has a similarly high metastatic rate to tonsillar SCC.

Cats

SCC is the most common oral tumor of cats. White coat color appears to increase the risk of developing cutaneous SCC, but there is no influence of coat color, gender, or breed on the occurrence of oral SCC. Affected cats have an average age of 12 years. Although SCC in cats can affect any mucosal surface in the mouth, the tongue is most commonly involved. The frenulum and ventral surfaces are often ulcerated, and although the tumor is deeply invasive it is rare for the dorsum of the tongue to be affected. This site predilection has been suggested to be because of increased carcinogen exposure caused by coat grooming in cats and the risk is higher in cats exposed to insecticidal collars and certain foods.[17] The mucosa adjacent to the caudal maxilla or mandible is the next most commonly affected site. SCC may invade the underlying bone and extend to involve the palate, pharynx, or angle of the jaw occasionally invading the periocular space causing exophthalmos as well as nasal and ocular discharge. Invasion of mandibular bone can cause a marked periosteal reaction that mimics a primary bone tumor both clinically and radiographically. Although oral SCC may progress to invade the tonsillar area, it is uncommon for the tonsil to be the primary site in cats.

Treatment

Dogs

In dogs the relatively low metastatic rate of gingival SCC makes this malignancy a good candidate for local therapies, such as surgery and radiation. Aggressive surgery is necessary to obtain adequate surgical margins, and with this approach median survival in reports ranged from 9 to 18 months. Recurrence is more frequent than metastasis after surgery. Incomplete surgical resection is commonly associated with recurrence, which emphasizes the importance of confirming wide surgical margins by histopathology after mandibulectomy or maxillectomy. Adjunctive radiation therapy may improve tumor control when complete excision cannot be achieved at

surgery. Dogs with rostrally located tumors and dogs with smaller tumors appear to have longer remissions following either surgery or radiotherapy. Median progression-free survival in one study of radiotherapy was approximately 17 months. Local mucositis is the most common acute side effect of radiation therapy, and dogs may require antiinflammatory medications, antibiotics, pain relief (opioids, such as codeine or fentanyl), and appetite stimulants. It may be necessary to place a feeding tube in a dog undergoing radiation therapy for an oral tumor. For small dogs, or dogs with a large radiation field, prophylactic tube placement is recommended. It is rare for acute side effects to persist beyond 3 weeks after therapy.

A combination of radiation and surgery gives the best control for gingival SCC, and postsurgical radiation should be considered for dogs with large tumors or for dogs with tumors that have incomplete margins on histopathology. This combined modality approach is the treatment of choice for larger, caudal or incompletely excised SCC. Chemotherapy is rarely warranted for rostral gingival SCC in dogs because of the low metastatic rate for this tumor. Chemotherapy should always be considered for SCC of the tongue, tonsil, and caudal location of the mouth because of the high metastatic rate of such tumors. Platinum compounds are probably the drugs of choice for metastatic SCC. Piroxicam, a nonsteroidal inhibitor of cyclooxygenase-2 (COX-2), showed efficacy against canine oral SCC although the duration of response may be in the order of 6 months. The mechanism by which piroxicam exerts its antitumor effects on SCC is still unclear, although it may affect tumor angiogenesis. Combination carboplatin and piroxicam may have increased efficacy over either drug itself.

The prognosis for dogs with tonsillar SCC is very poor. Surgery alone is not generally effective for treating tonsillar SCC because of their high metastatic rate, which manifests early in the course of the disease. The best survival rates for this tumor have come when dogs were treated with a combination of surgery, radiation therapy, and chemotherapy. Even with this approach, the median survival was still only 8 months. Piroxicam also shows efficacy against canine tonsillar SCC, with similar response rates and duration as for oral mucosal SCC.

Surgery for lingual SCC in dogs has variable outcome, and recurrence is common unless wide surgical margins are obtained. In one study, dogs with small tumors were treated with surgery alone and had a median survival time of 8 months. In some cases, complete removal of the tongue is indicated and requires that dogs have food supplemented with water to maintain hydration, or they learn to suck water as a horse would. This surgery was well tolerated by owners and dogs. Recurrence of tongue tumors is also common after radiation therapy. Metastatic disease usually determines survival; 43% of dogs in one study developed metastasis to lymph nodes, lung, or bone, so chemotherapy is indicated.

Cats

The best treatment for oral SCC in cats has yet to be decided. In one study comparing surgical treatment with radiation either alone or in combination with hyperthermia or platinum drug, there was no influence of treatment modality on survival.[18] Surgical removal of visible tumor is rarely successful as oral SCC is deeply invasive into both soft-tissue stroma and sometimes bone, thus often making local excision incomplete. CT scanning prior to surgery may assist the surgeon in deciding on the extent of surgery needed to obtain appropriate margins. Maxillectomy or mandibulectomy may allow the surgeon to obtain tumor-free margins but recurrences are still common. Cats treated in this way rarely live longer than untreated cats. Recurrence or metastases occur in cats within a median of 2 months after resection of all visible tumor tissue. For SCC limited to the mandible, mandibulectomy may delay recurrence to between 4 and 9 months after surgery. Still the major indication for surgical excision is as an adjunct to multimodality therapy.

Because recurrence is still a problem following even radical surgery, radiation therapy either alone or following surgery has been used to treat oral SCC. Tumor response to radiation is often dramatic initially, but usually of short duration, and the reported median survival is still only about 3 months. To date, the addition of chemotherapy or cell sensitizers does not seem to improve on these figures.

The best results have been reported in a small series of seven cats with SCC limited to the mandible; they were treated with a combination of mandibulectomy, lymph node resection, and radiation that included the surgical site of regional lymph node resection. The median disease-free period for this group of cats was 11 months and the 1-year survival rate was 57%. All cats developed recurrence.

Chemotherapy alone or in combination with radiation therapy has done little to improve survival in cats with oral SCC, and further trials are needed to further define the role of this modality. Response rates to platinum drugs, mitoxantrone, doxorubicin, or cyclophosphamide have been approximately 20%. Piroxicam, a nonsteroidal antiinflammatory agent, appears to have limited efficacy in cats as oral SCC has a very low rate of COX-2 expression; however, this treatment remains unexplored in the cat.

Other treatment modalities, such as cryosurgery or photodynamic therapy, do not appear to be successful, in part because of the increased sensitivity of the oral mucosa to toxicity, and because the tumor invades bone or deep into tissue, preventing adequate light or cold penetration.

Nutritional support is mandatory for cats with oral SCC. Clients should be counseled about care and nursing, and a gastrostomy or esophagostomy tube should be placed for the duration of treatment and until the cat is able to eat by itself. In one study, half of the cats required a gastrostomy tube for 2 weeks or less. Antibiotics and antiinflammatory drugs may be necessary to treat secondary bacterial infection and inflammation in these cats, and analgesics should be administered as needed to minimize discomfort.

Fibrosarcoma

Dogs

Fibrosarcoma is the third most common oral malignancy in dogs and occurs at an average age of 7 years. These tumors arise most commonly in the gingiva and are equally likely to be located around the maxilla or the mandible. The hard palate is uncommonly involved except by extension of a maxillary tumor. Tumors are usually large, with diameters of greater than 4 cm.

Histologic reports of these tumors should be interpreted cautiously. Occasionally, a tumor may be termed a *fibroma*, which implies that the process is benign. In fact, all sarcomas encompass a spectrum of disease and fibromas of the oral cavity should be treated as aggressively as fibrosarcomas. One report described tumors that were histologically diagnosed as fibromas, nodular fasciitis, or granulation tissue. Although all of these lesions are considered histologically benign, they invade bone and metastasize in some dogs and should therefore be termed *histologically low-grade, biologically high-grade fibrosarcomas*. Bony invasion should be interpreted as a sign of malignancy regardless of the pathology report.

Metastasis is uncommon in fibrosarcoma, particularly at the time of diagnosis, but is reported in approximately 25% of patients in the latter stages of disease, most commonly to regional lymph nodes.

Especially in young dogs, which may have more aggressive tumors, mandibular lymph nodes should be palpated and subjected to FNA or biopsy. Systemic metastases from oral fibrosarcoma may be a late event, so the incidence may prove higher than has been reported as local tumor control improves.

Cats

Fibrosarcoma is the second most common oral malignancy in cats, but unlike oral SCC, which has a predilection for the sublingual tissues, there does not appear to be a site predilection for feline oral fibrosarcoma. Fibrosarcoma is invasive when it occurs in the oral cavity, just as it is at other sites in cats; advanced lesions may invade surrounding bone and muscle. Lesions may be ulcerated causing dysphagia and other signs similar to oral SCC, and most cats are presented because an owner noticed swelling or a mass.

It is rare for metastases to be noted at the time of presentation, and no cat has been reported to have metastatic disease after surgery. Many of these cats had short survival following surgery before any subclinical metastases become apparent, therefore the reported low metastatic rate may not be accurate.

Treatment

Dogs

The treatment of choice for fibrosarcoma of the oral cavity in dogs is complete surgical excision. Maxillectomy and mandibulectomy are well tolerated by dogs and are necessary to obtain adequate surgical margins. In series of dogs treated with aggressive surgery, the median survival was 12 months. Even after such surgery, local recurrence is seen in nearly 40% of dogs, although this appears to depend on surgical expertise. Incomplete surgical resection is commonly associated with recurrence, which emphasizes the importance of early diagnosis and confirming wide surgical margins by histopathology.

The response of oral sarcomas to radiation therapy is not as good as for soft-tissue sarcomas at cutaneous sites, but still good compared with incomplete surgery alone. In one study the median survival for dogs with oral sarcomas was 18 months compared with 75 months for dogs with tumors at other sites.[19] In another study, the median progression-free survival was 26 months.[20] As with melanomas and carcinomas, dogs with smaller tumors had longer remissions.

Little has been reported regarding chemotherapy in the treatment of oral fibrosarcomas, although the metastasis rate of nearly 30% documented in one study shows that with local control rates improving with more aggressive surgery and radiation therapy, metastasis is the cause of death in as many dogs as is local recurrence.[20] Doxorubicin has been noted to produce objective responses in soft tissue sarcomas, and metronomic cyclophosphamide in combination with piroxicam appears to delay regrowth of sarcomas at other sites.

The optimum treatment for oral fibrosarcoma probably involves combined surgery and radiation therapy to dosages that exceed 50 Gy. Chemotherapy is investigational but may improve survival rates through control of metastases. Control rates similar to those seen with soft-tissue sarcomas at other locations could be expected with this combined approach.

Cats

In cats, as in dogs, surgical excision should be as aggressive as possible. Adequate postsurgical nursing care and nutritional support should be provided as described for cats with oral SCC. Survival times after surgery are generally higher than for cats with oral SCC, with 67% of cats with fibrosarcoma and 83% of cats with osteosarcoma alive 2 years after complete excision.

Radiotherapy improves local control of soft-tissue sarcomas at other sites in cats, and should be considered for cats with unresectable or histologically incompletely resected oral sarcomas.

Salivary Gland Tumors

Dogs

These tumors occur in older animals with no obvious gender predilection. Poodles and possibly Spaniel breeds are at higher risk for developing this disease. Malignant salivary gland tumors are more common than benign tumors and account for more than 95% of reported cases. On the other hand, enlargement of the salivary gland in a dog is more likely to be an inflammatory process than a tumor. Most owners notice a swelling or mass in the neck. Signs may include anorexia, dysphagia, and pain on opening the mouth. The most commonly affected salivary gland is the parotid gland (50% of dogs), with mandibular (30%), sublingual (12%), and zygomatic glands less frequently affected.

Lymph node metastasis may occur, and metastases to nodes were confirmed in approximately 20% of affected dogs at presentation in one study.[21] Dogs with enlarged nodes should have a biopsy or a FNA. Pulmonary metastases are rare, occurring in less than 10% of dogs at presentation in one study. Staging has proven prognostic for dogs with salivary carcinoma; the occurrence of metastases to lymph nodes or systemically gives a worse prognosis with a median survival of approximately 6 months following surgery alone. On the other hand, in one large study, histologic features did not appear to be prognostic; approximately 60% of tumors were poorly differentiated, and most showed more than 50% necrosis and vascular emboli, but this had no effect on outcome.

Cats

Approximately 5% of salivary tumors in cats are adenomas. Little is reported about salivary adenocarcinoma in cats. The average age of affected cats is 11 years but ranges from 2 months to 20 years. Siamese cats are predisposed to this tumor. Commonly, cats are presented for an enlarging mass on the side of the face or below the ear. Less commonly the mucosal gingiva or other oral site may be ulcerated. Oral tumors that are "undifferentiated" adenocarcinomas are usually of salivary derivation. Ulceration of the overlying skin is common, possibly a result of pruritus. Pruritus may be exacerbated by secondary otitis externa from parotid tumors, and deeper invasion may result in facial nerve damage or vestibular signs. Salivary adenocarcinomas can be very invasive into surrounding musculature and may even extend along the skin of the neck to involve the thoracic wall and scapula.

Approximately 80% of cats have metastases to regional lymph nodes at the time of first diagnosis. However; fewer than 20% have distant metastasis at the time of diagnosis. Interestingly, clinical stage (i.e., whether the tumor had metastasized to nodes) was not prognostic in a study of 31 cats with salivary carcinomas, although the multiple methods of treatment reported probably confuses the issue. This implies that the finding of metastasis should not necessarily preclude treatment.

Treatment

Dogs

Surgery alone and radiation therapy with surgery were the most successful modes of treatment in a study of 24 dogs. Both groups had median survival times of 2 years, with a number of animals alive

beyond 4 years. Chemotherapy is rarely reported. In one study a plethora of protocols was reported, but none improved survival.

Cats

Cats with salivary adenocarcinoma that were not treated lived between 5 and 6 months and were euthanized because of weight loss and enlargement of the tumor. Surgery is considered the primary treatment for salivary adenocarcinoma; however, surgical cure is often difficult because of deep invasion into the oral cavity and around the jugular vein and associated structures. Complete excision may be associated with long-term control in cats, particularly if used in combination with radiotherapy or chemotherapy. The primary surgery should be as aggressive as possible, however, so that a minimal amount of tumor tissue is present when adjunctive therapy is instituted.

Good local control of these tumors has also been seen when radiation therapy was used, but metastases are common, and therefore adjunctive chemotherapy is usually necessary. Chemotherapy for salivary adenocarcinoma has not been evaluated in a controlled clinical trial; however, based on one study where chemotherapy was used in combination with surgery, adjunctive therapy should be considered. Combination therapy using surgery, radiation therapy, and chemotherapy is the treatment most likely to be successful in cats with salivary adenocarcinomas. The median survival for 31 cats treated with any combination of these modalities was 17 months.[21]

TRAUMA

Kevin Stepaniuk

Etiology

Oropharyngeal trauma includes trauma of the soft (oral mucosa and underlying connective tissue, muscles, tongue, tonsils) and hard tissues (teeth and maxillofacial bone) of the oropharynx.

Soft Tissue

Trauma secondary to wooden sticks, plant material, sharp dental chews, projectiles, insects, chemicals, electricity, blunt and crushing trauma, and self-trauma secondary to behavioral problems is common. *Stomatitis* is the term used to refer to generalized inflammation of the oral cavity. Regional areas of inflammation such as caudal mucositis, buccal mucositis, gingivitis, periodontitis, glossitis, and the like are more descriptive and provide better clues to underlying pathogenesis and etiology.[1]

Oropharyngeal Foreign Body

Oropharyngeal foreign bodies are common. Breeds that commonly carry wooden sticks in their mouth can suffer oral lacerations, punctures, abrasions, and impalement.[2] Puncture wounds from sticks introduce bacteria into deeper tissues and may cause retrobulbar abscesses or cellulitis, glossitis, and actinomycosis cervicofacialis.[3] Foreign plant material can migrate and cause trauma, draining tracts, and granulomas.[4] Sticks and bones may lodge across the palate between contralateral dental arcades resulting in oral ulcerations, gingival recession, and periodontal disease.[5] Foreign bodies in or under the tongue lead to chronic inflammation, ulceration, granuloma formation, and sublingual edema.

Chemical and Pharmaceutical Trauma

Chemical injury secondary to ingestion of caustic substances leads to erosions and ulcerations of the oral mucosa.[6] Cleaning chemicals, batteries, and disinfectants are common sources of chemical injury to the oropharyngeal mucosa (Figure 54-20). Erroneous Internet information may lead owners to attempt home remedies that result in further chemical trauma.[7]

Insect bites and stings damage the oral mucosa and induce local inflammatory reactions.[8] Venom found in the mucosa of toad skin may also cause acute oral inflammation. With some species of toad, death of the patient within minutes to hours results from cardiovascular and systemic collapse.[9,10]

Medical prescriptions often have unanticipated side effects if they are retained in the oral cavity. Pancreatic enzyme supplementation, for example, causes oral mucosal ulceration and hemorrhage if not properly adminstered.[11,12] Differentials for traumatic and chemical ulcers includes chronic ulcerative paradental stomatitis (Figure 54-21), inflammatory diseases secondary to trauma, and autoimmune diseases.

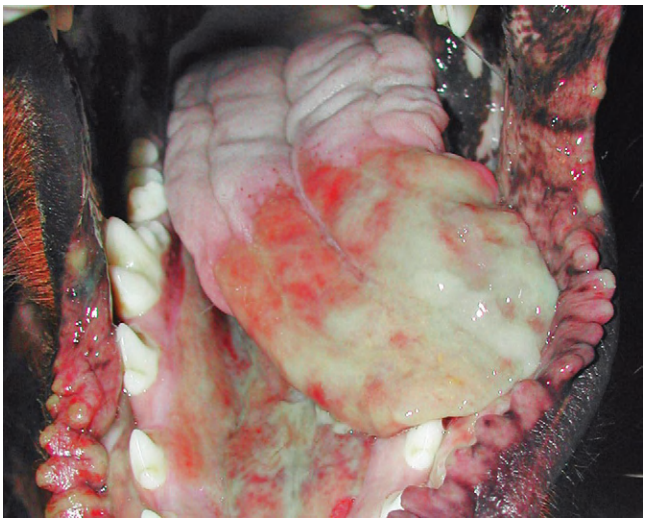

Figure 54-20 Alkaline chemical burn in the rostral oral cavity of a dog's mouth after chewing on a battery. Note the ulcerative buccal and lingual mucosa with sloughing of the epithelium. (Photograph courtesy of Gary Goldstein, DVM, FAVD, Dipl. AVDC, University of Minnesota.)

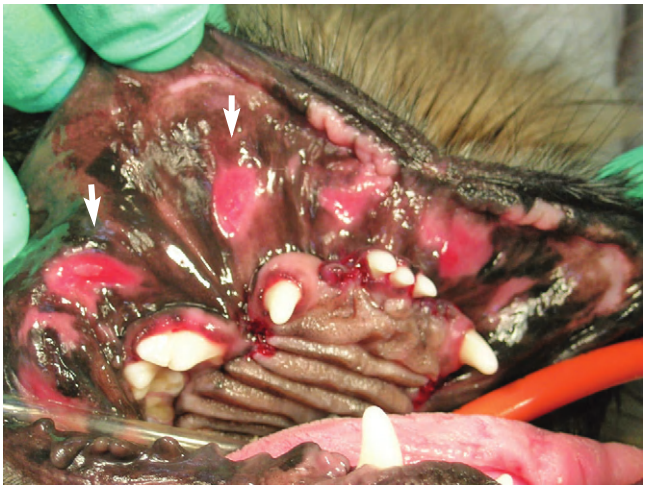

Figure 54-21 Chronic ulcerative paradental stomatitis (*white arrows*) where oral mucosa is ulcerated when contacting adjacent teeth. The plaque biofilm is the inciting cause.

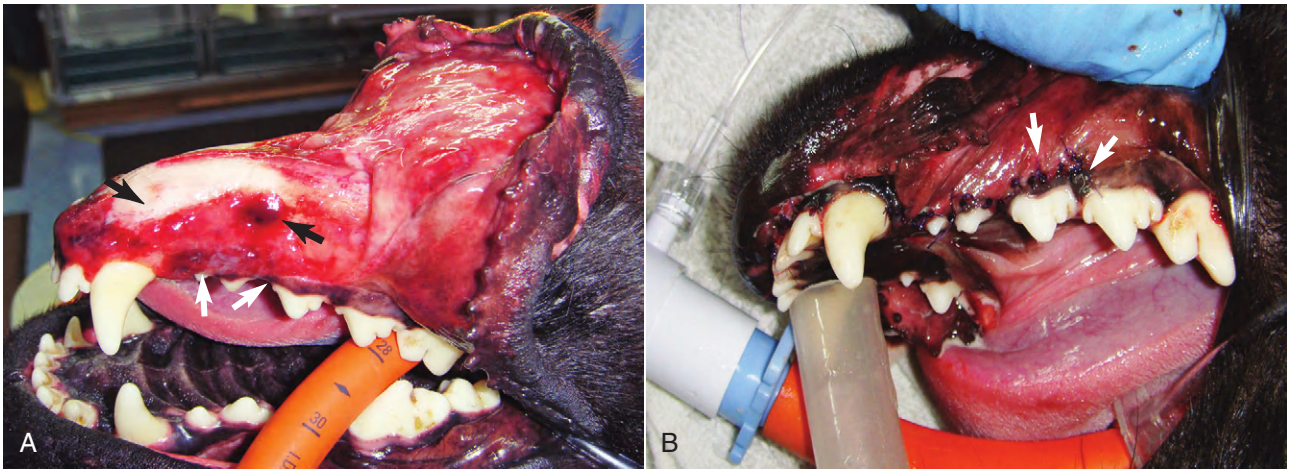

Figure 54-22 **A** and **B,** A mandibular lip avulsion injury in a dog after having its collar caught in a moving car tire. Mandibular mental foramen with avulsed neurovascular bundles are evident (*black arrows*). The tissue avulsed from the mucogingival junction. The mucosa was sutured to the gingiva at the mucogingival junction (*white arrows*).

Systemic chemotherapy and maxillofacial radiation damage soft and hard tissues. Mucositis, osteoradionecrosis, xerostomia, and radiation-induced caries result from oropharyngeal radiation damage. Unless the oral cavity is assessed as part of a comprehensive maxillofacial oncology plan, subsequent dental and oral surgery increases patient morbidity and regional sequelae.[13]

Mechanical and Electrical Trauma

Soft-tissue traumatic injuries (e.g., vehicular trauma, animal fights, and high-rise syndrome) are common and include avulsion of the oral mucosa/lips from the bone, the mucogingival junction, and associated teeth (Figure 54-22). Oral electrocution from chewing electrical cords can produce severe injury to the soft and hard tissues. Projectile ballistics (gunshot wounds) cause significant damage to soft and hard tissues. Thermal injuries from hot liquids and foods are much less common in animals than in humans. However, if food is warmed in a microwave to encourage pets to eat, uneven or over heating can result in thermal burns of the oral mucosa, only worsening the patient's anorexia.

Self-trauma ("gum chewer lesions") produces caudal oral buccal and sublingual granulomas. They are often incidental findings but may be problematic if they become large and secondarily infected. Separation anxiety and cage-biting patients self-inflict mucosal injury and gingival lacerations during behavioral episodes.[14]

Malocclusions[1] can lead to both soft-tissue and hard-tissue trauma. Linguoversed mandibular canine teeth damage the palatal mucosa leading to ulcerations, infections, pain, maxillofacial growth abnormalities, and behavioral changes such as head shyness and aggressive protection of the face and oral cavity (Figure 54-23). Alternatively, the patient may show no obvious clinical signs despite significant trauma. As the linguoversed teeth penetrate into the hard palate and nasal cavity, oronasal fistulation and rhinitis will result.

Brachycephalic cats have a shortened maxilla. Mandibular bowing during growth and development may occur in some cases. The maxillary fourth premolar cusps, occluding on the buccal aspects of the mandibular first molar, traumatize the gingiva and oral mucosa. Pain, infection, periodontal disease, inflammatory masses, and tooth loss result.

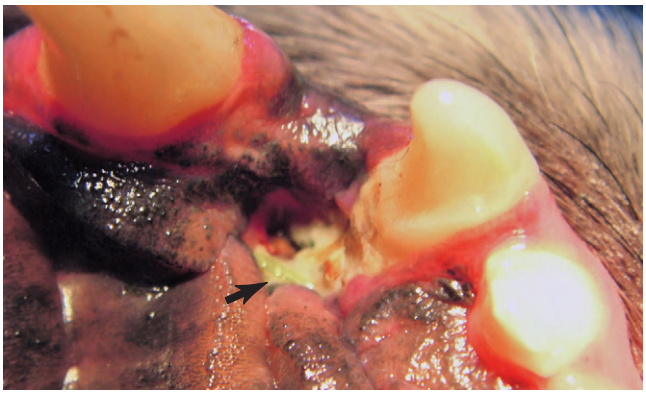

Figure 54-23 Palatal mucosal and bone trauma with a resulting oronasal fistula from a linguoversed mandibular canine tooth in a young standard poodle. The patient was head shy, aggressive, would not permit an oral examination, and was noncompliant with the owners and veterinarians. Following repair of the oronasal defect and crown reduction and direct pulp capping of the offending mandibular canine tooth, the patient's behavior dramatically improved.

Hard Tissue: Tooth Trauma

Dentition is often an overlooked aspect of the oropharyngeal cavity.[1] Approximately one in 10 cats and one in four dogs have dental fractures.[15,16] The most common injuries to the teeth are caused by hard objects (e.g., baseball bats, golf clubs, rocks), vehicles, falls, animal fights, and hard dental chews (e.g., cow hooves, bones, nylon bones). Physical forces from foreign objects can result in concussive pulpitis, dentin tubule exposure, fractured teeth with pulp exposure, and tooth luxation injuries (subluxated, luxated, and avulsed teeth). If a tooth fractures or luxates, endodontic inflammation, necrosis, and infection can result days, weeks, or months later as the patient suffers silently.

Abrasion of the teeth exposes porous dentin tubules and the pulp cavity. Trauma from tennis balls is frequent (Figure 54-24). Tennis balls, rocks, and other hard substances can quickly wear the teeth resulting in dentin tubule and pulp exposure and subsequent

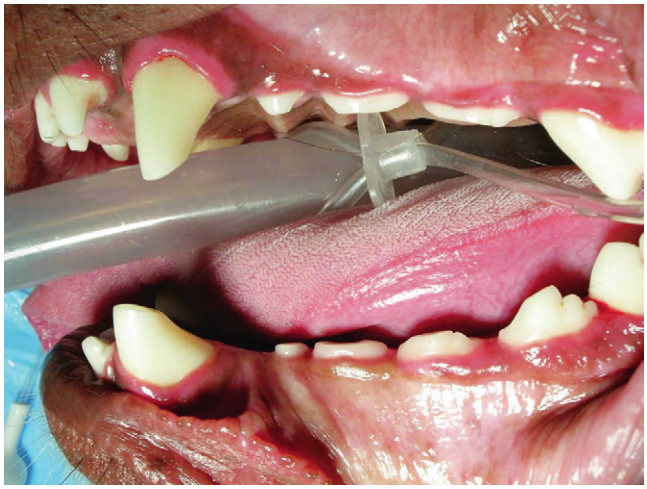

Figure 54-24 A young Labrador Retriever who routinely played with tennis balls. Maxillary and mandibular premolars have worn and the abrasion has resulted in pulp exposure in several of the teeth. Root canal therapy or surgical extraction is necessary to treat any tooth with pulp exposure.

infection. Similarly, separation anxiety and cage biting patients wear the distal aspects of the canine teeth and maxillary third and incisors.

Corrosive acid and alkalis can damage the teeth by dissolving the enamel and dentin mineral resulting in pulpal inflammation and infection. Iatrogenic thermal tooth trauma, from poorly performed ultrasonic dental cleanings, results in pulpitis, intrinsic staining (pulpal hemorrhage), and death of the tooth. Although uncommon, as compared with humans, dental caries do occur on the occlusal molar surfaces in dogs.[17]

Fibrous material such as string and dog hair can wrap around teeth and quickly induce gingival inflammation and periodontal disease. Small breeds with large and crowded teeth[18] and significant facial hair "beards" are overrepresented.

Hard Tissue: Skeletal Trauma

Significant force is required to fracture the maxillofacial skeletal (e.g., vehicular trauma, falls, baseball bats, golf clubs, and animal bites, and from poorly performed surgical extractions). If there is one mandibular or maxillary fracture following trauma, there are often more.[19,20] Trauma can cause a patient to have pain or difficulty opening or closing the mouth.

If the patient has difficulty closing the mouth, or pain in closing the mouth, the following pathologies should be considered: temporomandibular joint (TMJ) luxation with or without fracture, TMJ dysplasia with coronoid entrapment (open-mouth jaw locking),[21-24] zygomatic or coronoid neoplasia, mandibular neurapraxia, and masticatory muscle neurogenic atrophy.[25] If the patient has difficulty opening the mouth or pain in opening the mouth, other pathologies should be considered, including TMJ intracapsular or extracapsular ankylosis (previous trauma), zygomatic arch/coronoid fracture/healing, masticatory myositis, retrobulbar abscess/cellulitis, tetanus (*Clostridium tetani*), osteoarthritis of TMJ, craniomandibular osteopathy, severe otitis interna/media, and neoplasia.

Side effects of bisphosphonate therapy (bisphosphonate-related osteonecrosis of the jaws) are theoretically possible in veterinary patients. Although not yet documented in clinical canine patients, intravenous use of bisphosphonate compounds can lead to osteonecrosis of the jaws following dental extractions or trauma.[26,27] This may become a concern as bisphosphonate use in veterinary medicine increases over time.

Pathophysiology

Soft Tissue

Oropharyngeal Foreign Body

Foreign bodies lacerate, puncture, and penetrate oropharyngeal tissue resulting in hemorrhage, ulcers, and granulomas. Many cases of oropharyngeal cellulitis and retrobulbar abscesses are the result of foreign-body penetration.[28] Environmental pathogens may be easily inoculated into the soft tissue. *Actinomyces* and *Nocardia* cause chronic pyogranulomatous inflammation resulting in swellings and draining tracts of the head and neck.

Oral Mucosal Inflammation

Acute traumatic ulcerations are often associated with pain, have a yellow base and red halo, are associated with a traumatic event, and often in heal in 7 to 10 days after the inciting cause has been removed.[29] Chronic ulcers have little or no pain, are yellow-based with elevated and scarred margins, delayed healing, and may be easily confused with neoplastic conditions such as SCC.[29]

Mucositis may be secondary to periodontal disease, autoimmune conditions, or radiation therapy. Radiation induced mucositis results from damaged basal cell turnover of the oral mucosa and mucosal atrophy resulting in a thin, fetid, pseudomembrane that sloughs and leaves an ulcerated surface.[13] The flow, character, and protective properties of saliva are lost in these conditions.

Glossitis accounts for 33% of all lingual lesions in dogs.[30] The cause of glossitis includes plant material, suture, bone, hair, chemicals, medications, and electrical injuries, as well as systemic diseases such as uremia.[30] Trauma of the tongue and oral mucosa can result in amorphous, gritty, hard mineral deposits in the tissue (lingual calcinosis circumscripta).[4,30,31]

Ballistic characteristics, such as yaw, flight length, and blast effect, factor into the damage caused by gunshot wounds.[32] Ballistic projectiles cause laceration and crushing injuries of the soft tissues; fractured, thrombosed, and concussed teeth; and maxillofacial fractures. In addition to the direct effect of the ballistic, soft-tissue injuries secondary to the related shock wave and cavitation occur.[32]

Mechanical and Electrical Trauma

Obvious lacerations, crushing injuries, and avulsion injuries lead to major hemorrhage if the lingual, sublingual, maxillary, infraorbital, palatine, or mandibular vessels are damaged. Electrical trauma causes necrosis of tissue, fibrosis, and wound contracture that affect the function of the oral cavity. Developing tooth buds may be damaged. As pets chew on electrical cords, low-voltage (<1000 V) conduction and arcing currents, generating 2000°C to 4000°C, damage tissue and thrombose vessels.[6,33] The extent of injury to the lips, palate, gingival tissue, mucosa, tongue, and pharynx may take several weeks to demarcate; blanched, pale, gray, tan ulcerative mucosa with secondary infection results. Without corrective surgery the wounds contract and epithelialize from the margins. Oronasal fistulas, functional disfigurement, dysphagia, and severe morbidity result from electrocution injuries. Multiple organ failure is possible in severe cases.[33]

Hard Tissue: Tooth Trauma

Endodontic disease is a silent source of pain and infection in pets. Bacteria may enter the tooth via exposed pulp, exposed dentin

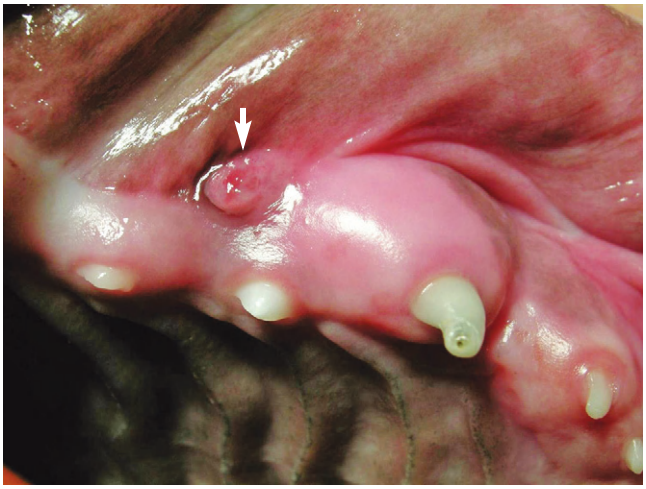

Figure 54-25 A complicated crown fracture (pulp exposure) in right maxillary deciduous canine tooth (note the black hole in the coronal aspect of the canine tooth). The patient is approximately 12 weeks old. The fracture likely occurred several weeks prior to the photograph. Note the sinus draining tract just apical to the mucogingival junction. The infection and inflammation is occurring in the region of the developing adult tooth buds of the canine and second premolar. The first premolar is erupted. Immediate extraction of the deciduous canine tooth is indicated.

tubules, or anachoresis (hematogenous distribution).[34] Complicated crown fractures result in irreversible pulpitis, pulp necrosis, and apical periodontitis that will not resolve unless the tooth is endodontically treated or surgically extracted. Complicated crown fractures[1] of deciduous teeth expose the pulp to bacteria (Figure 54-25). An apical infection results and the developing adult tooth bud can be damaged by the regional infection and inflammation. Malformed teeth, enamel defects, unerupted teeth, and associated dentigerous cysts can result.

Enamel fractures, uncomplicated crown fractures (no direct pulp exposure), and abrasions cause reversible and irreversible pulpitis from the concussive trauma and the ingress of bacteria through the porous dentin tubules. The odontoplastic process within the tubules transmit pain. If reversible pulpitis occurs, the odontoblasts will seal the dentin tubules by producing reparative dentin.

Concussive injuries to teeth lead to pulp hemorrhage and a pink-purple-gray intrinsic staining. It was reported that 92.2% of discolored dog teeth had partial or total pulp necrosis with 42.9% having no endodontic radiographic signs.[35] Thermal injury to the tooth results in pulp thrombosis and irreversible pulpitis. Lack of appropriate water coolant and/or prolonged periods of instrument to tooth contact while cleaning and polishing can overheat the pulp within the tooth.

Luxation injuries disrupt apical blood supply, the periodontal ligament, and alveolar bone resulting in a nonvital (endodontic) tooth and compromised periodontal tissues. Therefore, both the periodontal tissues and the endodontic system require treatment.[36,37]

Hard Tissue: Skeletal Trauma

Mandibular fractures are more common than maxillary fractures. However, without careful examination and the use of CT, maxillary fractures may be underrecognized and go unreported.[19] The mandibular molar region, particularly in the region of the first molar, and the maxillary bone are the most common regions for oral fractures in dogs.[38] Mandibular symphyseal separations are the most common maxillofacial fracture in the cat.

Feline high-rise syndrome is the result from falls higher than the second story.[39] The patients can fracture the hard palate and mandible, separate the mandibular symphysis, luxate the TMJ, avulse oropharyngeal soft tissue, and fracture teeth.[39,40] Concurrent injuries include skeletal fractures, pneumothorax, pulmonary contusions, hemothorax, urinary bladder ruptures, and diaphragmatic hernias.[39] Occasionally, the animal will show few clinical signs but may present with inability to open the mouth or eat several weeks after the injury.[39] The severity of the injuries increases linearly up to the height of the seventh floor, but the incidence of fractures decreases after the third floor as a consequence of the feline's vestibular mechanism and limb position.[39]

Bites to the face of the developing skeleton in dogs and cats may seem innocuous in some cases. However, damage to the growth plates and tooth buds may not manifest for several weeks or months. In such instances, there may be axillary–mandibular asymmetry malocclusions, unerupted teeth resulting in dentigerous cyst formation, malformed teeth, and malpositioned teeth.

Bisphosphonates target the osteoclasts and suppress osteoclast-mediated bone resorption.[41,42] The mandible and maxilla have increased skeletal remodeling rates and require proper functioning osteoclasts. Bisphosphonates accumulate in the bone and proper bone remodeling is impaired following tooth extraction and trauma.

Clinical Examination

Conscious Oropharyngeal Examination

Prior to oral examination, a complete history, including signalment, vaccination status, diet, previous dental and oral treatments, trauma, behavior, chew toys, infectious diseases, and oral home care, should be obtained. Dysphagia, anorexia, ptyalism, pawing at the face, chewing on one side, bruxism, and dropping food are indicators of oropharyngeal pain. However, many patients may not show any of these clinical signs.

The oral examination begins in the conscious patient. The oral examination should proceed slowly, methodically, and thoroughly so that subtle lesions are identified and patients remain compliant. Observations for facial symmetry, punctures, wounds, lacerations, masticatory muscle atrophy or swelling, alopecia, draining tracts, pyoderma, and moisture are noted.[43] Halitosis may be noted at this time. Halitosis may be the result of dental disease, oral ulcerations, respiratory disease, gastrointestinal disease, or dermatologic disease (e.g., lip-fold pyoderma).

The regional lymph nodes are palpated for size, symmetry, and mobility. The eyes are retropulsed for resistance. Resistance and pain suggests retrobulbar abscess or cellulitis, space-occupying lesions, or myositis. The maxillary and mandibular bones are palpated for irregularities, swellings, crepitation, and draining tracts. Each side of the mouth is separately evaluated by gently, and carefully, lifting the lips. Occlusion is evaluated to rule out traumatic occlusions as a cause of mucosal trauma. The oral examination should account for a complete dentition (42 and 30 teeth in an adult dog and cat, respectively). The distal dentition may be difficult to assess without opening the mouth. The mouth is opened and the TMJs are evaluated for pain, crepitation, and clicking. The mucosa of the hard palate and caudal oral pharynx is evaluated. However, patients with oropharyngeal trauma to the bones and soft tissue will resist opening or have pain upon opening the mouth. Mandibular fractures often are shifted toward the side of the

fracture whereas the mandible is more often shifted to the contralateral side of a luxated TMJ.

Lingual foreign bodies present with dysphagia and rapid tongue and jaw movements.[4] The base of the tongue should be closely evaluated for foreign bodies. This can be accomplished by pushing the tongue dorsally from the ventral aspect in the intermandibular space during examination. However, complete evaluation of the tongue requires general anesthesia.[44,45]

Anesthetized Oropharyngeal Examination

Physical forces that fracture the maxillofacial skeleton may cause trauma beyond the oral cavity. Therefore, the entire patient must be evaluated for pulmonary, neurologic, and systemic injuries prior to anesthesia. Anesthesia is required for a complete and thorough oral exam in addition to intraoral radiographs, biopsy, and advanced imaging techniques.

The oral mucosa of the tongue, palate, cheeks, and oropharynx are evaluated for ulcerations, erosions, lacerations, foreign bodies, sinus tracts, and vesicles. Sinus tracts apical to the mucogingival junction often indicate endodontic disease whereas those at, or coronal to, the mucogingival junction often indicates periodontal disease. Definitive diagnosis requires intraoral radiography. The sublingual and ventral regions of the tongue should be closely evaluated by moving the tongue laterally and dorsally. Sublingual edema needs to be differentiated from ranula.

Acute oropharyngeal penetrating injuries cause swelling, pain, and ptyalism with or without blood.[46,47] However, these signs are often missed and most cases present chronically with sinus tracts, swelling, dysphagia, and oral pain.[46,47] Oropharyngeal injuries resulting in retrobulbar cellulitis cause pain on opening the mouth, painful retropulsion of the eye, and possible swelling distal to the last maxillary molar. Exophthalmos, prolapse of the third eyelid, chemosis, and scleral injection may occur.[48-50]

The teeth are evaluated for fractures, mobility, gingival recession, and furcation exposure. The dental explorer will often stick in an exposed endodontic system whereas the explorer will slide across the smooth surface of worn teeth. If the dental explorer sticks to the tooth substance, endodontic disease should be thoroughly evaluated with intraoral radiography. Periodontal measurements with a dental probe should be made around each tooth (six surfaces of each tooth) and abnormal measurements recorded. The normal sulcus depth of the dog is 0 to 3 mm and of the cat 0 to 0.5 mm.[51]

Diagnosis

Diagnosis of oropharyngeal trauma requires history, clinical exam, an anesthetized oral exam, intraoral radiographs (when appropriate), and advanced imaging. Some dental pathology has sub-gingival manifestations therefore intraoral radiographs are *required* for complete assessment.[52,53] A complete blood count, chemistry panel, and urinalysis should be part of the systemic evaluation of the patient in preparation for anesthesia.

Skull and TMJ radiographs are reasonable screening tools. However, superimposition of maxillofacial skeletal anatomy, a requirement for heavy sedation or anesthesia to obtain diagnostically positioned films, and the related expense with a low diagnostic yield, make it less valuable compared with advanced imaging such as CT or MRI. CT improves both diagnosis and surgical planning for open-mouth mandibular and maxillofacial oropharyngeal trauma.[19,54,55]

Cytology from sinus tracts may aid in diagnosis but is often nonspecific. Cultures of oropharyngeal cavity and sinus tracts are also often unrewarding. The oral cavity contains hundreds of bacterial species in a mixed population. Additionally, it is difficult to culture anaerobic pathogens that are commonly involved in dental pathology. Special culture medium and consultation with the laboratory are necessary if trying to culture specific anaerobic pathogens.

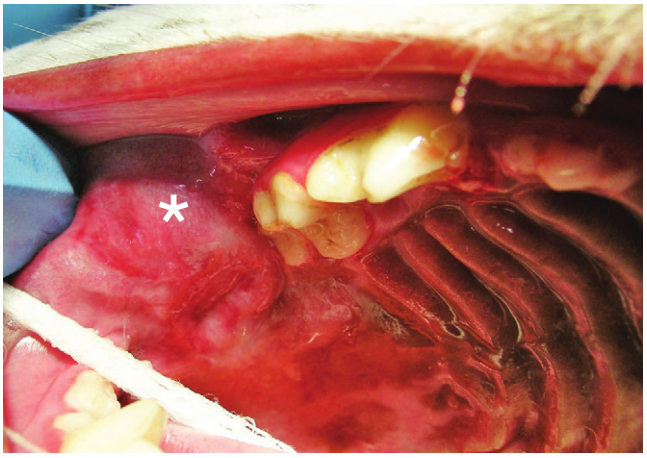

Figure 54-26 A caudal oropharyngeal puncture wound is present distal to the second right maxillary molar in the pterygopalatine fossa (*white asterisk*). The suborbital tissues and eye are present dorsal to the region. The patient was diagnosed with retrobulbar and caudal oropharyngeal cellulitis and responded well to treatment.

Exploration of the pterygopalatine fossa, retrobulbar tissue, and caudal oropharynx may be both diagnostic and therapeutic. The tissues are carefully explored to look for regions of abscess, sialocele, and cellulitis (Figure 54-26).[48] Vital maxillary arteries and their branches, maxillary and optic nerves, and the eye must be avoided.[56] Diagnosis of penetrating foreign bodies in the oropharyngeal regions includes CT, MRI, and ultrasound.[28,50,57]

Biopsies of oral mucosa are often nonspecific but are useful in the ruleout of autoimmune and neoplastic processes that may have clinical appearances similar to ulcers and granulomas. Experienced veterinary pathologists or human oral pathologists are necessary for challenging and atypical cases.

Additional testing, such as for type 2M antibody and muscle biopsies, are useful to rule out masticatory myositis as a cause of pain and difficulty in opening the mouth.[58] Proper diagnosis of oropharyngeal and retrobulbar infections is necessary as misdiagnosis and treatment may result in systemic and neurologic infection.[49]

Treatment

General Oropharyngeal Treatment

Treatment should be based on an accurate diagnosis. If antibiotics are necessary to treat oropharyngeal soft- and hard-tissue infections, the antibiotic spectrum should include drugs for anaerobic and facultative anaerobic infections (e.g., clindamycin, amoxicillin/clavulanic acid, tetracyclines, and metronidazole).[59,60]

Trauma often has an inflammatory component; therefore, nonsteroidal antiinflammatory drugs are needed to control inflammation and pain if there are no medical contraindications to their usage. Additional analgesia with regional nerve blocks, opioids, for example, for multimodal pain control, is always recommended.[61,62]

An often overlooked, but excellent treatment modality, is the use of an oral 0.12% chlorhexidine gluconate rinse.[63] The oral cavity can be rinsed every 8 to 12 hours to help control oral bacteria and secondary infection of oropharyngeal wounds, ulcers, and inflammation. Soft food (canned and/or moistened kibble) is necessary during the healing period of mucosal injuries, oral surgery, and skeletal repair.

Oropharyngeal Soft-Tissue Trauma Treatment

Ulcerative oropharyngeal trauma requires removal of the inciting cause and supportive analgesic, antibiotic, and nutritional care (e.g., feeding tubes if necessary) during the healing period. Retropharyngeal cellulitis and abscesses may be explored with blunt dissection. Whether or not a true pocket of purulent debris is found, the site is lavaged with sterile saline and surgically closed to prevent further bacterial contamination from the oral cavity. Deep and blind biopsy is contraindicated because of the vital regional anatomy.

Traumatic soft-tissue wounds can be treated intraorally with debridement, lavage, and surgical closure with poliglecaprone 25, chromic gut, or polyglactin 910 suture material. It may be difficult to identify a foreign body with penetrating injuries.[46] If cervical emphysema is present, exploration of the cervical region may be necessary.[47] If the presumptive diagnosis is *Actinomyces* or *Nocardia* infection, treatment involves surgical debridement and drainage, as indicated, and prolonged use of antibiotics. Removal of impaled oropharyngeal, cervical, and transoral foreign bodies should be done under general anesthesia as the removal of the object may unmask occluded major vessels that result in immediate and massive hemorrhage of the regional vasculature.

Soft-tissue avulsion injuries require the mucosa to be sutured back over the bone. It is crucial to return *gingiva* to surround each tooth, as it is required to protect the tooth and underlying periodontium. Small 5-0 suture should be used to suture the mucosa and gingiva (often at the mucogingival junction). Interdental sutures with 3-0 or 4-0 may be used to support the mucoperiosteal flap. Treatment of electrical wounds requires extensive client consultation and, potentially, multiple surgeries as the trauma demarcates over several weeks.

Soft-tissue and palatal trauma secondary to malocclusion dentition requires endodontic, orthodontic, and/or exodontic treatment.

Dental Trauma Treatment

Any tooth with pulp exposure *requires* endodontic treatment or surgical extraction. Endodontic treatment for a tooth fracture is not an emergency and the patient can be referred in a timely manner to veterinary dentists experienced in endodontic treatment. Even if the pulp is not exposed, sealing of the dentin tubules with a dental sealant or unfilled resin decreases tooth sensitivity and pain and stops the ingress of bacteria through the dentin tubules. Discolored teeth require endodontic treatment or surgical extraction as indicated. A root canal treatment involves accessing and mechanically and chemically cleaning and disinfecting the root canal(s), followed by obturation (sealing the root canal system), and, finally, restoring the tooth. The tooth is dead, but functional, and the periapical inflammation can heal. Freshly fractured immature adult teeth, without formed apices and minimal secondary dentin production, can often be treated with vital pulp procedures (partial coronal pulpectomy and direct pulp capping). Fractured deciduous teeth require careful and complete extraction at the time of diagnosis to prevent damage to the adult tooth buds.[64]

Tooth luxations are urgent and avulsion of the tooth is a true dental emergency. Tooth luxation injuries require gentle replacement *without* debridement of the microscopic periodontal ligament cells and cementum from the tooth surface. The tooth must be splinted in place with stainless steel wire and/or composite material and treated with a root canal therapy within a couple of weeks.[37,65,66] Avulsed teeth must be immediately placed in saliva or milk and a veterinary dentist should be contacted within the hour to reimplant the tooth, splint the tooth, and perform endodontic treatment.

Skeletal Trauma Treatment

Treatment of trauma patients includes stabilization of the patient, thoracic radiographs to evaluate for pneumothorax and pleural effusion, and treatment of concurrent injuries. Often maxillofacial repair can be delayed for 24 to 72 hours to allow the patient to be a more suitable anesthesia candidate. During that period, aggressive pain management protocols and nutritional support is provided. Placement of esophagostomy or gastrotomy tubes should be considered based on the extent of maxillofacial trauma and planned repair. Nasoesophageal tubes should perhaps be avoided as many of the patients have nasal fractures that may not be obvious. Placing a tube in the nasal cavity can be irritating and painful in these cases.

Noninvasive fracture repair with preservation of occlusion and rapid return to function is preferred.[67,68] During fracture repair it is crucial to not only focus on skeletal structures but the dentition as well. Repair with interdental wires and composite materials provide stabilization to achieve these goals.[20] The use of straight orthopedic plates on curved jaws often results in a traumatic malocclusion and damage to the tooth roots and neurovascular bundles. If external fixators or plates are used, tooth roots and neurovascular bundles must be avoided. Fractured teeth may require endodontic or exodontic treatment.

Treatment of Gunshot Wounds

Treatment for gunshot wounds includes patient stabilization, recognition of life-threatening injuries, clarifying the history (type and range of firearm), and performance of CT, intraoral radiographs, and other imaging modalities. Client preparation and meticulous medical record documentation, including photographs, is essential.[32] The client should be counseled that multiple surgeries may be necessary with both primary closure and delayed second intentional healing. Projectile ballistics can remain in the tissues if they are not threatening vital structures as retrieval may lead to excessive regional damage and increased morbidity. If they are removed, they should be saved for potential criminal investigations. Long-term followup and intraoral radiographs in 6 to 12 months is necessary to evaluate for hidden tooth damage.

Prognosis

With proper recognition, early diagnosis, and treatment many oropharyngeal injuries have a good to excellent prognosis. The oral mucosa has a tremendous capacity to heal after the inciting cause has been removed. The most frustrating condition, with a reasonably good prognosis if identified and treated correctly, is cervicofacial actinomycosis from a penetrating foreign body.

Dental injuries have a good to excellent prognosis if there is not a failure to recognize the injury or failure to evaluate the dentition with intraoral radiographs. Endodontic (root canal therapy) treatment for fractured teeth is 96% successful if carried out by a trained and experienced veterinary dentist.[69] Endodontic treatment is

preferred compared with surgical extraction of the tooth. Vital pulp procedures (e.g., partial coronal pulpectomy, direct pulp capping, and indirect pulp capping) can have a good prognosis that is dependent on the duration of injury and age of the patient.[70-72] There are increased morbidity and functional and cosmetic sequelae with the loss of some teeth. However, if the owner declines endodontic treatment each patient deserves the right to a comfortable and infection free oral cavity and affected teeth should be surgically extracted. Just because they are "eating" does not mean that there is not chronic inflammation, infection, dull pain, and possible systemic associations.

Maxillofacial fractures can have a good to excellent prognosis once the patient is systemically stabilized. Even when there appears to be a hopeless destruction of the oropharyngeal tissues and of the maxillofacial skeleton, the tissues can be rebuilt in skilled hands. Electrocution injuries are the most challenging and have a guarded to fair prognosis to return to normal. Scarring, oronasal fistulas, tooth injury, bone injury, and the need for multiple reconstructive surgeries makes these cases challenging surgically, and financially and emotionally challenging for the client.

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CHAPTER 55

Esophagus

STRUCTURE AND FUNCTION

Anjop Venker-van-Haagen

The esophagus conveys food from the pharynx to the stomach. This relatively narrow tube begins dorsal to the cricoid cartilage of the larynx and accompanies the trachea, at first inclining to the left but regaining a median position above the trachea before or shortly after entering the thorax. Within the thorax it runs in the mediastinum and, continuing beyond the tracheal bifurcation, it passes over the heart before penetrating the esophageal hiatus of the diaphragm to join the stomach at the gastroesophageal junction (the cardia).[1] The cardia is pulled caudally and may be found in the abdomen, but this is not a consistent finding in all canine breeds.[2]

Structure of the Esophagus

Macroscopic Structure

The structure of the esophagus conforms to a pattern that is common to the alimentary canal (see Chapter 1). The outer coat of loose connective tissue, the adventitia, is present in the cervical part but is largely replaced by serosa in the thorax. In dogs, the muscle of the esophagus is striated from the cricopharyngeus muscle to the junction with the stomach. In cats, the striated muscle is replaced by smooth muscle within the thorax, such that roughly the proximal one-third is striated muscle and the remainder is smooth muscle. The muscular layer of the esophagus is composed of two strata, both of which are spiral, and they wind in opposite directions in the first part of the esophagus. Closer to the stomach the outer stratum becomes more longitudinal and the inner more circular.[1,3] Two sphincters are suggested on the basis of functional studies; a cranial (upper) and a caudal (lower) sphincter, but these are less convincingly demonstrated morphologically. The cranial sphincter is provided by fibers of the cricopharyngeal muscle. In the cat the cricopharyngeal muscle and the esophageal muscle are not morphologically separate.[3] A thickening of the esophageal muscle mass at the junction of the esophagus with the stomach suggests a sphincter, but food is impeded slightly more cranial to this—just cranial to the diaphragm.[1] In dogs, the thickness of the circular striated muscle layer increases from the distal esophagus to the gastroesophageal junction and cardia.[3]

The inner part of the wall of the esophagus consists of submucosa and mucosa, divided by the fenestrated muscularis mucosae, which is more prominent in the thoracic part of the esophagus. The submucosa loosely connects the mucosa and the muscularis. This structure allows the relatively inelastic mucosa to be thrown into longitudinal folds when the esophagus is contracted. The submucosa contains blood vessels, nerves, and glands. Glands are found over the entire length of the mucosa in dogs, but only in the cranial one-third of the esophagus in cats.[3] In both dogs and cats, the muscularis mucosae is more prominent in the thoracic esophagus. The mucosa is composed of keratinized, stratified squamous epithelium, which contains the openings, at about 1-mm intervals, of the ducts of the esophageal glands. The cat has transverse folds in the mucosa in the caudal half of the esophagus. These folds are permanent and independent of the state of contraction of the esophagus.[3]

Microscopic Structure

The outer coat of the esophagus, the adventitia, consists of connective tissue with elastic fibers. In dogs the muscularis of the esophagus is entirely striated muscle, whereas in cats the striated muscle is replaced by smooth muscle within the thorax. Fiber type composition has been studied by histology and immunohistochemistry, and myosin type has been studied by electrophoretic peptide mapping and two-dimensional gel electrophoresis, respectively.[4]

In both dogs and the cats, the striated esophageal muscle was composed of a small percentage of type I and IIC fibers, but the predominant type was very different histochemically and immunohistochemically from all fiber types (I, IIA, IIB, IIC) present in skeletal muscles. This esophageal fiber type (IIoes) had an acid- and alkaline-stable m-adenosine triphosphatase (ATPase) activity and a moderate histochemical Ca-Mg actomyosin ATPase activity, and it reacted weakly with anti-IIA and anti-IIB myosin sera. Although the light chains of the IIoes were the same as the light chains of a mixture of IIA and IIB myosin, their respective heavy chains gave different peptide maps. Greater differences were observed between the heavy chains of IIoes and other striated muscle myosins.[4] It was concluded that this predominant fiber type in the dog and cat striated muscle is of the "fast" type, and contains a distinct isoform of myosin similar, but not identical, to the other fast-type myosins. Histochemically and immunohistochemically, the muscle of the canine esophagus was similar to that of cats.[4]

The histologic characteristics of the lower or gastroesophageal sphincter (LES) were compared with those of the smooth muscle of the distal esophagus in three cats. Numerous thin, annulospiral elastic fibers were found in the circular layer of the LES and the distal esophagus. These fibers were not observed in other areas.[5]

In dogs the esophageal glands were found over the entire length of the esophagus, whereas in cats they were found only in the cranial one-third of the esophagus.[3] Scanning electron microscopy (SEM), light microscopy, and morphometric analyses were used to study the morphology of the mucosa and submucosa of the cervical, thoracic, and abdominal esophagus in the dog.[6] Apart from the absence of a lamina muscularis mucosae in the cervical part of the canine esophagus, little regional variation was detected. There was, however, morphologic variation associated with age. The number and complexity of microplicae on surface epithelial cells observed by SEM increased with age, particularly between 1 and 21 days of age. Although SEM revealed typical duct openings from submucosal glands in 1-day-old dogs, light microscopy revealed few functional glands at that age. However, there was a marked increase in the volume fraction occupied by glands between 1 and 161 days of age, followed by some decrease between 161 and 337 days of age.

Ciliated cells were observed in the esophagus of 1-day-old dogs, being most abundant in the abdominal part, but by 21 days of age, groups of ciliated cells were no longer observed in any part of the esophagus.[6]

Vessels of the Esophagus

The arterial blood supply to the cervical part of the esophagus in dogs and cats is supplied by the thyroid arteries and esophageal branches of the carotid arteries.[7,8] The esophageal portion of the bronchoesophageal artery is the main supply to the cranial two-thirds of the esophagus and the remaining part is supplied by esophageal branches of the aorta.[7]

Venous drainage is via the external jugular and azygos veins; adjacent veins anastomose with each other on the esophagus.[7,8] Lymph vessels from the esophagus drain into the medial retropharyngeal, deep cervical, cranial mediastinal, bronchial, portal, splenic, and gastric lymph nodes.[7]

Nerves of the Esophagus

Innervation of the striated muscle of the esophagus in dogs and cats is provided by special visceral efferent neurons from the bilateral nucleus ambiguus in the medulla oblongata. Axons are carried in the vagus nerves and distributed with the pharyngoesophageal nerves, the recurrent laryngeal nerves, and the vagal trunks. In cats the smooth muscle innervation, via general visceral efferents, arises from the rostral parts of the bilateral nucleus ambiguus and is also distributed via the branches of the bilateral vagus nerves. Three major regions of innervation can be recognized in the esophagus of dogs: a cervical region, supplied by paired pararecurrent laryngeal nerves; a cranial thoracic region, supplied mainly by the left pararecurrent laryngeal nerve; and a caudal thoracic and abdominal region, supplied by the vagal trunks.[7,9]

Function of the Esophagus

The function of the esophagus is to transport food and liquid from the pharynx to the stomach. The esophageal stage is the last stage of the swallowing action and although linked to the pharyngeal stage, is under distinct neuronal control. Swallowing is a physiologic phenomenon that occurs many times daily. Although it may be initiated consciously as a voluntary act during eating, most swallowing occurs subconsciously between meals, without apparent cerebral participation. Swallowing irrespective of eating occurs about once a minute in conscious individuals and is driven by salivation, which stimulates the sensory receptors in the mouth and pharynx.[10] Studies in humans show that both salivation and swallowing virtually cease during sleep.

Swallowing is a complex and complicated function that can be divided into four overlapping stages: oral preparatory, oral, pharyngeal, and esophageal. The first two are voluntary and the last two are involuntary. In the oral preparatory stage, food is chewed and prepared for the oral stage (see also Chapter 54). In the oral stage the food bolus is moved from the front of the oral cavity to the faucial arch, where the pharyngeal stage is initiated. The pharyngeal stage has four defined components: palatopharyngeal closure, peristalsis of the pharyngeal constrictor muscles, airway protection, and cricopharyngeal relaxation. The larynx is elevated and closed, protecting the airway. These reflex movements occur in sequence and overlap one another. They are mediated by the reticular formation in the brainstem and follow a fixed pattern. The interneuronal network involved in this pattern is termed the central pattern generator (CPG) for swallowing. Interconnections between the left and right CPGs coordinate their activity (Figure 55-1). There is coordination with the respiratory center as well.

In the final stage of swallowing, the bolus is moved through the esophagus by the peristaltic contractions of the esophageal

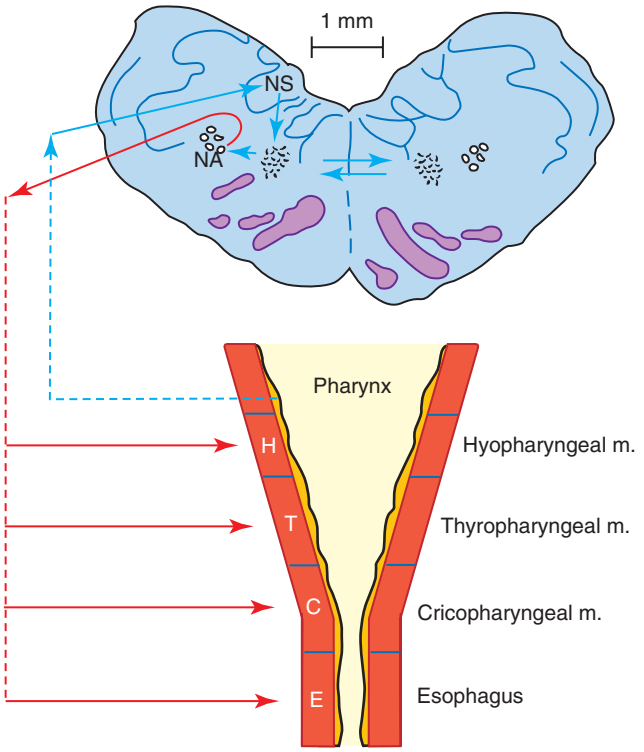

Figure 55-1 Swallowing occurs in sequential reflex of the pharyngeal and esophageal muscle contractions and in relation between these muscles and the brainstem. Afferent fibers in the glossopharyngeal nerve, the pharyngeal and esophageal branches of the vagus nerve and the cranial laryngeal nerve activate the solitary nucleus (NS). The sequential contractions are mediated by the reticular formation in the brainstem and follow a fixed pattern. The interneuronal network involved in this pattern is termed the *central pattern generator* (CPG) for swallowing. Via the CPG for swallowing the neurons in the nucleus ambiguus (NA), the motoneurons of the swallowing muscles, generate sequential swallowing activity. Interconnections between the left and right CPGs coordinate their activity. (From Venker-van Haagen AJ: Diseases of the throat. In Ettinger SJ, Feldman EC, editors: *Textbook of Veterinary Internal Medicine*, Philadelphia, 2000, Saunders.)

musculature.[11] The swallowing action during this stage is best illustrated by contrast videofluorography.[12] After the prehension of food by the stripping action of the tongue, a bolus is formed at the base of the tongue and is passed into the oropharynx. This is immediately followed by contractions of the pharyngeal muscles, lifting the food bolus up and passing it through the relaxed cranial esophageal (cricopharyngeal) sphincter into the cervical part of the esophagus. At the same time, the pharyngeal egresses (i.e., nasopharynx, oral cavity, and laryngeal opening) are closed, preventing regurgitation and leakage into the trachea. After entry of the bolus into the esophagus, the cranial esophageal sphincter immediately closes and the bolus is transported by one slow and regular peristaltic wave from the cervical region to the gastroesophageal junction, where it passed slowly through the relaxed sphincter into the stomach.

The passage of food through the cricopharyngeal sphincter is usually followed immediately by esophageal peristalsis. However, in some dogs, especially those that bolt their food, not every swallowed bolus is picked up immediately by esophageal peristalsis; sometimes, peristaltic activity starts only after a second or even a third bolus entered the esophagus. Another frequent phenomenon is the stopping of a bolus of food somewhere in the esophagus until it is carried along with the next bolus. Similarly, a bolus sometimes stops at the gastroesophageal sphincter and does not enter the stomach until it is carried in with the next bolus. Reflux of food from the stomach into the terminal portion of the esophagus occurs occasionally, but it is always followed by secondary peristalsis that clears the esophagus. The pharynx and esophagus are always completely cleared of food at the end of the meal.[12]

Neurophysiologic Control of the Esophageal Stage of Swallowing

Esophageal peristalsis initiated by the pharyngoesophageal action is termed *primary peristalsis*. Secondary peristalsis occurs when a bolus remains in the esophagus. It is initiated by receptive fields in the esophagus which are stimulated by the persistent bolus.[13]

The motor sequence of the esophageal stage depends, as does the pharyngeal stage, on the activity of medullary interneurons in the swallowing center. Through excitatory and inhibitory connections, these interneurons program the sequential excitation of motor neurons and vagal preganglionic neurons responsible for the entire motor sequence, in both striated and smooth muscles of the esophagus. The activity of the medullary swallowing neurons occurs without feedback phenomena, and is thus entirely dependent on a central network.[14]

Components of the Sensory Pathway in the Esophageal Stage of Swallowing

The esophageal stage of swallowing requires sensory feedback to control and modulate its function. The importance of sensory feedback is suggested by the finding that the peristaltic waves were slower, greater in amplitude, and longer in duration during swallowing of water than during dry swallowing.[14,15] The influence of stimulation of the afferent fibers of the esophagus was shown to increase the discharge of the vagal motor fibers supplying the esophagus.[15-17] The afferent fibers of the esophagus are in the glossopharyngeal and vagus nerves. The cell bodies of these cranial nerves lie in their associated sensory ganglia. Branches of these sensory nerves pass rostrally to innervate the nerve cells in the nucleus of the solitary tract in the medulla oblongata. The neurons of this nucleus connect with interneurons in the dorsal area around the nucleus tractus solitarius. This dorsal region contains the first synaptic sites for the sensory input that evokes swallowing and the interneurons that are excited switch on the specific timing during pharyngeal and esophageal swallowing. Once triggered, bursts of sequential activity in interneurons in the dorsal region may function without feedback. They are driven by central neurons, the "master" interneurons, which set up the sequential activation of specific motor neurons. These master neurons control in particular the pharyngeal swallowing pattern. They are linked to interneurons in the ventral region around the nucleus ambiguus, which control the esophageal stage of swallowing and activate the motor neurons in the nucleus ambiguus. The interneurons in the ventral region connect with the contralateral region involved in swallowing and thus unilateral activation of swallowing may activate nucleus ambiguus motor neurons bilaterally. It is not clear how the dorsal and ventral regions connect with the motor neurons of the dorsal motor nucleus of the vagus.[13]

Components of the Motor Pathway in the Esophageal Stage of Swallowing

The motor neurons for the esophageal stage of swallowing are in the left and right nucleus ambiguus in the brainstem. The motor neurons innervating both the striated and smooth muscles of the esophagus are located in the rostral part of the nucleus ambiguus. The dorsal motor nucleus of the vagus nerve, which would be expected to harbor preganglionic neurons innervating the smooth muscles of the distal esophagus, are apparently not of major importance to the swallowing action of the esophagus in the cat. The axons of the motor neurons in the nucleus ambiguus associated with esophageal swallowing proceed through the vagus nerve and directly innervate esophageal striated muscles, or they pass to ganglia near the esophagus from which postganglionic excitatory cells then innervate the smooth muscles.[13] As mentioned previously, the timing of esophageal swallowing is controlled by the CPG, a group of interneurons in the reticular formation and around the nucleus ambiguus, under influence of the sensory input that elicits swallowing.[13]

Peripheral Neural Control of Esophageal Peristalsis

Esophageal peristalsis is normally a smooth, uninterrupted contraction wave that traverses the esophagus. It consists of a rapid wave of relaxation followed by a slower wave of contraction. A rapidly descending wave of inhibition sequentially relaxes the upper esophageal sphincter, the body of the esophagus, and the LES, so that they are prepared for passage of an oncoming bolus. In recumbent subjects, transport of the bolus is exclusively the result of pharyngoesophageal peristalsis, while in upright subjects it is assisted by gravity.[10,18]

Neural control of esophageal peristalsis differs between dogs and cats in that the end organ in dogs is striated muscle and in cats it is both striated and smooth muscle. The striated muscle of the canine esophagus is a relatively slow-contracting muscle, as shown by direct electrical stimulation in vitro.[13,19] Electrical stimulation of the vagus nerve to the esophageal striated muscle caused contraction of the muscles,[13,20] and curare, which antagonizes the neurotransmitter acetylcholine, blocks the vagal excitation of the canine striated esophageal muscle. Curare blocks the peristaltic contractions of the entire esophagus in dogs.[13,21] Pharmacologic studies show that the striated esophageal muscle is under central neural control via motor fibers that release acetylcholine to stimulate nicotine receptors, the same receptors as in somatic muscles. In the same comparison with somatic muscles, inhibition of the striated esophageal muscles depends on a decrease in discharges from the vagal efferent fibers. No separate inhibitory mechanism for striated esophageal muscles

has been found.[13] Esophageal peristalsis in the dog is produced by a descending sequence of efferent neural discharges, generated by the central swallowing program.

In the cat, the esophageal striated muscles are innervated and function in the same way as in the dog. In the smooth muscles of the distal part of the esophagus in the cat, peristalsis can develop with or without central efferent signals via the vagus nerve.[13,22] As peristalsis reaches the distal part of the striated muscle segment, the central swallowing program stimulates the onset of peristalsis in the proximal part of the smooth muscle segment. Esophageal peristalsis is most likely initiated by neural excitation. This originates centrally in primary peristalsis and in cats it also does so in secondary peristalsis.[10] The organization of esophageal muscle peristalsis was shown to persist after experimental transection of the vagus, and the smooth muscle segment of the esophagus can also function without central control.

Acetylcholine is an important transmitter in the ganglia or at the neuromuscular junction of the esophageal smooth muscle.[13,23] It is postulated that the timing of sequential activation could depend on the amount and ratio of neural transmitters at each segmental level, the timing of their release, and the density of smooth muscle receptors.[13,24] It is probable that peristalsis in the smooth muscle segment of the esophagus in the cat functions via a neuronal network through the ganglia, with or without the smooth muscle providing control for a sequential contraction, and thus with or without sequential activity descending in the vagal efferent fibers.

Peripheral Neural Control of the Gastroesophageal Sphincter Function

During swallowing, the neural control of the LES in the dog and cat is similar to the neural control of peristalsis in the distal third of the esophagus. In dogs, relaxation and contraction of the LES follows the activity of the distal esophagus and is under control of the central pattern generator for primary peristalsis in the distal esophagus. Vagal nerve fibers directly innervate the striated muscle cells, their neurons being located in the nucleus ambiguus. In the cat, neural control of the sphincter is similar to control of peristalsis in the distal third of the esophagus and is under control of the central pattern generator. The smooth muscle of the sphincter is directly innervated by postganglionic cells and in part by mechanisms intrinsic to the esophagus itself.[10]

Other Influences on Gastroesophageal Sphincter Function

Also influencing LES function are the receptor responses to intrinsic or extrinsic pharmacologic agents. Most studies of these agents have been concerned with better understanding of the causes of reflux esophagitis in humans, but several of the studies have contributed to our understanding of the function of the LES in dogs and cats. In conscious dogs the LES response to a meal consists of tonic contractions of the sphincter. These appear to be mainly regulated by muscarinic receptors. Nitric oxide can inhibit postprandial contractions of the LES.[25]

In dogs, gastric distention induces transient relaxation of the LES. The basal LES pressure fell progressively during distention of the antrum but not during distention of the fundus alone. The antrum was considered to be primarily responsible for triggering transient relaxation of the LES induced by distention.[26] Radiofrequency energy applied to the LES in dogs inhibited the triggering of transient relaxations and this reduced the resulting gastroesophageal reflux. Basal LES pressure and LES relaxation during swallowing were unchanged.[27] In cats, swallowing and balloon distention of the esophagus both caused relaxation of the LES.[28] Microinjections of bicuculline (γ-aminobutyric acid [GABA] antagonist) in the dorsal motor nucleus of the vagus in the medulla oblongata in cats caused a decrease in the LES pressure. This effect was abolished by vagotomy. These results indicate that the dorsal motor nucleus of the vagus influences the functional regulation of the LES in cats.[29] It is to be expected that more detailed information about the function of the LES in relation to gastric motility will become available, since better understanding of the dysfunction of the LES in reflux disease is of high priority in human gastroenterology.

DIAGNOSTIC EVALUATION

Robert G. Sherding

Most esophageal diseases in dogs and cats are diagnosed by the signalment, history, physical examination, survey thoracic radiography, barium contrast esophagraphy ("barium swallow"), and esophagoscopy. Survey and static-image barium radiography and endoscopy are generally adequate for diagnosis of structural and intraluminal disorders of the esophagus; functional motility disorders are best evaluated by a dynamic contrast imaging procedure (three-phase barium videofluoroscopy). Ancillary laboratory tests are useful for identifying underlying causes of esophageal hypomotility and acquired megaesophagus. Specialized procedures for evaluating esophageal function include nuclear scintigraphy, manometry, pH monitoring, and electromyography, but these procedures have not been used routinely in dogs and cats because of limitations in availability and practicality.

History and Signalment

Clinical signs suggestive of esophageal disease include regurgitation, dysphagia, odynophagia, salivation, retching, gagging, and repeated swallowing. Other less-specific signs include weight loss, anorexia or ravenous appetite, and depression. Aspiration pneumonia, a frequent complication of esophageal disease, can cause fever, cough, tachypnea, and dyspnea.

Regurgitation

Regurgitation is the hallmark of esophageal disease and is defined as the passive evacuation of food or fluid from the esophagus into the environment. Regurgitation results primarily from local mechanical events within the esophagus and must be distinguished from *vomiting*, which is a centrally mediated reflex characterized by the active evacuation of gastroduodenal contents preceded by nausea, hypersalivation, retching, and abdominal contractions. The history should determine the age of onset of regurgitation, the duration of signs, the timing of regurgitation in relation to eating, and a description of the regurgitated material. Videorecordings of eating and drinking behavior are often very informative and may help to differentiate esophageal and upper airway signs. Chapter 21 has additional discussion of regurgitation and a diagnostic algorithm.

Breed predispositions for esophageal disease should be considered, especially in young puppies and kittens with persistent regurgitation of undigested food that begins shortly after weaning, which is suggestive of vascular ring anomaly, congenital idiopathic megaesophagus, or congenital esophageal stenosis.[1] The congenital form of megaesophagus is heritable in Wire-haired Fox Terriers and Miniature Schnauzers and an increased prevalence has been noted in Irish Setters, Great Danes, German Shepherds, Labrador Retrievers,

Newfoundlands, Chinese Shar-Peis, and Siamese cats.[2-4] In addition, acquired megaesophagus and oropharyngeal dysphagia may be associated with several types of myopathy (e.g., myasthenia gravis, muscular dystrophies, and polymyositis) that have increased incidence in many breeds of dogs and cats.[5,6] Vascular ring anomalies have been reported in many breeds of dogs and cats, but German Shepherds, Irish Setters, and Labrador Retrievers appear to be at increased risk.[7,8] Late-onset regurgitation can occasionally be seen with mildly obstructive vascular ring anomalies that have gone undetected until as old as 8 years of age.[9] Young Chinese Shar-Pei dogs are predisposed to congenital hiatal hernia resulting from malformation of the esophageal hiatus.[10,11] Bulldogs and other brachycephalic breeds with upper airway obstruction have a high prevalence of concurrent hiatal abnormalities, reflux esophagitis, esophageal deviation, gastroduodenal disease.[12]

An acute onset of signs of regurgitation, salivation, and dysphagia is suggestive of an esophageal foreign body, acute esophagitis, developing stricture, or gastroesophageal intussusception. A chronic history of regurgitation is more consistent with megaesophagus, vascular ring anomaly, diverticulum, hiatal hernia, chronic reflux esophagitis, mature stricture, or esophageal neoplasia. An intermittent pattern of regurgitation is most consistent with hiatal hernia and reflux esophagitis. Esophageal tumors usually develop in old-aged dogs and cats and the signs progressively worsen over time.

The timing of regurgitation in relation to feeding is determined by the location of the esophageal abnormality, the degree of luminal obstruction, and the reservoir effect of esophageal dilation. Regurgitation immediately after eating is most likely to occur with esophageal obstruction, especially involving the cranial esophagus, or gastroesophageal intussusception. Regurgitation may be delayed for minutes to hours with megaesophagus, diverticulum, and caudal obstructions because of the accommodation of the dilated esophagus.

The regurgitated material is usually composed of undigested food (often tubular in shape), water, and white to clear frothy liquid (mucus and saliva). In comparison, vomitus usually consists of partially digested food mixed with yellow bile-stained fluid. Dogs and cats with megaesophagus usually regurgitate both solids and liquids. Tolerance of liquids but not solid foods is more typical of obstructive esophageal diseases.[1] Fresh red blood is occasionally seen with severe mucosal trauma or erosions, especially from foreign bodies. Putrefaction of ingesta may occur after prolonged retention in a diverticulum or dilated esophagus, which can cause halitosis. Both regurgitation and vomiting can occur concurrently in animals with dysautonomia, hiatal hernia, gastroesophageal intussusception, or vomiting disorders complicated by secondary reflux esophagitis.

Dysphagia, Odynophagia, and Salivation

Dysphagia, or difficult swallowing, more often connotes oropharyngeal disease and cricopharyngeal dysfunction, but may be seen with cranial esophageal diseases such as foreign body, stricture, or esophagitis. Dysphagia is characterized by repeated, often unproductive attempts to swallow with extension of the head and neck during swallowing, and is often accompanied by gagging, retching, *odynophagia* (pain on swallowing), and *ptyalism* (excessive salivation). Anorexia and unexplained salivation may be the only clinical signs in some patients with painful esophageal disease, especially esophagitis. Esophageal dysphagia and salivation must be differentiated from oropharyngeal dysphagia and salivary gland diseases, such as sialadenitis and sialadenosis. Chapters 13 and 22 provide additional discussions of dysphagia and salivation, respectively, and diagnostic algorithms.

Historical Findings Indicative of Esophageal Injury

The history is important for identifying potential causes of esophageal injury that could culminate in severe esophagitis or esophageal stricture. These include esophageal foreign bodies, gastroesophageal reflux (secondary to general anesthesia, hiatal hernia, or malpositioned esophageal feeding tubes), acid or peptic injury from persistent vomiting, irritating oral medications (e.g., doxycycline, clindamycin), ingestion of corrosive chemicals, radiation injury, thermal injury from overheated (microwaved) food, and prior esophageal surgery.[1,13-17] Clinical signs of esophagitis usually develop within 1 to 3 days following injury and include regurgitation, dysphagia, salivation, odynophagia, retching, gagging, and repeated swallowing.[1,17] In mild esophagitis, clinical signs may be subtle or absent. Severe esophagitis or foreign-body impaction can lead to serious complications of esophageal necrosis, perforation, fibrosis, and stricture. The possibility of esophageal perforation may be suggested by a recent history of foreign body ingestion. Iatrogenic perforation can also occur after endoscopic removal of foreign bodies, dilation of esophageal strictures, laser ablation of tumors, and esophageal surgery. Penetrating injuries of the cervical esophagus can be caused by bite wounds or gunshot wounds.

Esophageal strictures result from deep circumferential injury of the esophagus that heals by intramural fibrosis, resulting in narrowing of the lumen and reduced distensibility.[1,14,17] Regurgitation (solids more than liquids) and other clinical signs attributable to esophageal obstruction usually begin within 1 to 4 weeks after the inciting esophageal injury.[14,18-22] Despite the severity of the inflammation, many animals will have preservation of appetite because of the caloric deprivation and worsening malnutrition.

Owners should be questioned about the likelihood of ingested foreign objects. Esophageal foreign bodies are common, especially in small dogs (weighing <10 kg), and include objects such as bones, chew toys, plastic, rubber, pins, needles, fishhooks, string, and trichobezoars. Trichobezoars are particularly important in cats.[23-29] In one report, 12% of dogs with moderate to severe foreign-body–induced esophagitis subsequently developed strictures.[25] Esophageal foreign-body obstruction caused by dental chew treats resulted in strictures in six of 25 dogs (24%) in another report.[24] Esophageal perforation and esophagobronchial fistula are also potential complications of foreign-body trauma.

Overall, 65% of esophageal strictures in dogs and cats occur following general anesthesia.[18-22,30,31] This is presumably a result of the reflux of gastric (H^+, pepsin) and/or intestinal (bicarbonate, bile salts, and pancreatic proteases) content associated with relaxation of the gastroesophageal sphincter (GES), and the delayed clearance of the refluxate from the esophagus in the anesthetized animal.[31,32] Clinical signs of esophagitis usually develop within 2 to 4 days of the anesthetic procedure, followed by progressive worsening of regurgitation if fibrosis takes place.

Hiatal hernia is a protrusion of a portion of the stomach through the esophageal hiatus of the diaphragm, which can be the result of congenital or acquired laxity in the hiatal opening.[1,13,33,34] Clinical signs in the acquired form are often intermittent and attributable to secondary reflux esophagitis caused by displacement of the GES into the thorax. Clinical signs in the congenital form are often more frequent and more severe due to extreme laxity at the esophageal hiatus. Reflux esophagitis can occur independently of hiatal hernia, is idiopathic in some dogs and cats, and presumably results from GES incompetence or dysmotility.

Corrosive injury to the esophagus can result from several oral medications and ingested chemicals. The severity of the injury depends on chemical concentration, pH, duration of contact with

the mucosa, and distribution of the lesion (e.g., focal vs. diffuse injury). Oral tablet and capsule medications with high acidity, especially doxycycline and clindamycin in cats, can cause severe focal esophagitis and strictures.[35-39] The corrosive effects of these medications are worse in cats because of the slower esophageal propagation velocity in this species (compared with the dog), and prolonged mucosal contact time when tablets or capsules are administered as a "dry swallow."[40,41] Ingested chemical irritants are usually concentrates that have highly acidic, alkaline, or oxidant properties. This should be suspected when esophagitis is accompanied by stomatitis and oropharyngeal ulcerations (mucositis). Examples include chlorine granules, button batteries, and undiluted quaternary ammonium disinfectants such as benzalkonium chloride that cats can lick from their paws and haircoat.[42,43]

Other Clinical Signs

Other clinical signs can be seen in dogs and cats with esophageal disease. Weight loss and poor body condition can occur secondary to persistent regurgitation and inability to retain ingested food. An otherwise healthy animal with persistent regurgitation may have a ravenous appetite. This is common in animals with megaesophagus, vascular ring anomaly, and some esophageal strictures. In contrast, anorexia can occur in animals that have painful and difficult swallowing associated with severe esophagitis, stricture, esophageal foreign body, or neoplasia. Anorexia can also occur in conjunction with cough, tachypnea, dyspnea, and fever in animals that have secondary aspiration pneumonia, esophageal perforation, mediastinitis, or bronchoesophageal fistula. The owner should also be questioned about signs of neurologic or neuromuscular dysfunction that could indicate an underlying cause of acquired megaesophagus.[1,2,4]

Laryngeal paralysis (stridor and change or loss of voice) can be associated with acquired megaesophagus in dogs.[4] Disorders of the esophageal hiatus (e.g., hiatal hernia, reflux esophagitis) can be associated with chronic obstructive airway conditions such as laryngeal paralysis and brachycephalic syndrome, presumably from enlargement of the esophageal hiatus and laxity of the surrounding support structures caused by abnormally high negative intrathoracic pressure.[12] Increased intraabdominal pressure associated with vomiting or blunt abdominal trauma can also cause hiatal hernia. Severe gastroesophageal reflux can cause signs of chronic laryngitis (stridor, change of bark) from exposure of the larynx to gastric refluxate. Mediastinal tumors (lymphoma, thymoma) that cause regurgitation from periesophageal compression of the esophagus can also cause dyspnea (pleural effusion) and Horner syndrome.

Geographic predispositions should always be considered, such as *Spirocerca lupi*–associated esophageal disease (granuloma or neoplasia) in dogs from the southern United States and many other endemic regions of the world, and *Pythium insidiosum*–induced necrotizing granulomatous esophagitis in the southeastern United States.

Physical Examination

When esophageal disease is suspected, the examination should include direct observation of the prehension and swallowing of food and water. A low body condition score is a frequent finding in animals that have lost weight from chronic regurgitation. Young dogs and cats with congenital megaesophagus or vascular ring anomaly may have poor weight gain and stunted growth.

The cervical esophagus should be palpated to detect masses, foreign bodies, or distention from mechanical obstruction or megaesophagus. Distention of the cervical esophagus can be accentuated in animals with megaesophagus by compressing the thorax while the nostrils are occluded. Perforation of the cervical esophagus can lead to local edema, cellulitis, abscess, or a draining fistula in the neck region. Enlargement of the mandibular salivary glands may indicate sialadenitis (see other sections in Chapter 55). A finding of oropharyngeal ulceration accompanied by signs of acute esophagitis may indicate ingestion of a corrosive substance.

Depression, fever, cough, tachypnea, dyspnea, mucopurulent nasal discharge, and abnormal pulmonary auscultation can indicate complicating aspiration pneumonia, or rarely, bronchoesophageal fistula. In animals with esophageal foreign body, a rigid stance with fever and depression can indicate mediastinitis secondary to esophageal perforation. Pleural effusion, Horner syndrome, and a noncompressible cranial thorax can be found in animals with periesophageal cranial mediastinal tumors (e.g., lymphoma or thymoma). Neurologic deficits or muscle weakness, atrophy, or pain may indicate an underlying neuromuscular disorder as a cause of esophageal hypomotility and secondary megaesophagus. A cranial nerve examination is also important in animals with abnormal oropharyngoesophageal motility. Dysautonomia, which is a generalized autonomic neuropathy that can cause megaesophagus, is suggested by mydriasis and loss of pupillary reflexes, decreased tear production, dry mucous membranes, bradycardia, dysuria, decreased anal tone, and diarrhea or constipation.[1,2]

Laboratory Evaluations

The results of routine laboratory evaluations are normal in most dogs and cats with esophageal disease. Nonetheless, a complete blood count (CBC) is indicated to detect neutrophilia and left shift that might suggest aspiration pneumonia or esophageal perforation, and a urinalysis and serum biochemical profile can help identify underlying disorders that have been associated with abnormal esophageal motility and megaesophagus. These include hyponatremia and hyperkalemia in hypoadrenocorticism; hypercholesterolemia in hypothyroidism; increased creatine kinase and aspartate aminotransferase in polymyositis. Fecal examination for *S. lupi* ova is indicated in endemic areas.

In dogs and cats with megaesophagus and motility dysfunction, additional laboratory evaluations should be considered to identify an underlying cause.[1-3,44] Primary megaesophagus can be either congenital or acquired. Acquired megaesophagus is often idiopathic, but this is a diagnosis of exclusion. Esophageal motility dysfunction and megaesophagus can also occur secondary to various underlying neuromuscular disorders that impair esophageal motility, including myasthenia gravis, polymyositis, muscular dystrophy, other polymyopathies, peripheral neuropathies, central nervous system disease, dysautonomia, botulism, tick paralysis, tetanus, anticholinesterase toxicity, lead toxicity, hypoadrenocorticism, and possibly hypothyroidism.[2-4,44] Measurement of serum acetylcholine receptor antibody for the diagnosis of acquired myasthenia gravis is especially important, even in the absence of generalized muscle weakness, because focal myasthenia can account for 25% of acquired canine megaesophagus cases.[5,45]

Radiography

Survey and contrast radiographic evaluations are useful for the diagnosis of many esophageal diseases (see Chapter 26 for techniques). Survey thoracic and cervical radiographs are obtained initially to evaluate the entire esophagus and to identify complications of esophageal disease, such as aspiration pneumonia (alveolar lung opacity) and esophageal perforation

(pneumothorax, pneumomediastinum, mediastinitis, pleural effusion). The esophagus is not normally visible unless it contains air, fluid, food, or foreign material, so survey radiographs can often identify radiopaque foreign bodies, megaesophagus, diverticula, esophageal masses, and esophageal dilation outlined by air, fluid, or ingesta cranial to an obstructive lesion.[46,47] A small amount of air in the esophagus from aerophagia can be an incidental finding caused by excitement, nausea, dyspnea, or anesthesia. Hiatal hernia and gastroesophageal intussusception are usually identified as a mass effect cranial to the hiatus in the dorsocaudal mediastinum if the stomach is displaced at the time of the radiograph.

Contrast radiography of the esophagus is indicated in animals with signs of esophageal disease that have normal or inconclusive survey radiographs.[46] Static image barium contrast radiography (i.e., without fluoroscopy) is useful for documenting radiolucent foreign bodies, megaesophagus, diverticula, and obstructive diseases (e.g., vascular ring anomalies, strictures, tumors, periesophageal masses). Hiatal hernia and gastroesophageal intussusception can be confirmed if the stomach is displaced at the time of the radiograph.

Potential complications of contrast esophagraphy are aspiration of contrast medium or leakage from an esophageal perforation. Perforation should be suspected when survey radiographs reveal cervical soft tissue emphysema, pneumomediastinum, pneumothorax, mediastinitis, or pleural effusion. In such cases a water-soluble, nonionic, iodinated contrast agent such as iohexol (Omnipaque; Amersham Health) is preferred over barium because it is less irritating to periesophageal tissues and more readily reabsorbed.[48] For demonstrating acquired esophagobronchial fistulas, which sometimes develop after foreign-body perforation of the caudal esophagus, a dilute barium mixture (20% to 30% w/v [weight per volume]) is preferred, as iohexol is hypertonic and can cause pulmonary edema if it enters the lung.[49]

Continuous videofluoroscopic recording of swallowing is required to characterize complex motility disorders of the esophagus, as exact timing of exposures is unlikely with static-image barium radiographs.[47,50] Contrast videofluoroscopy provides a dynamic evaluation of the oropharyngeal, esophageal (both primary and secondary peristalsis), and gastroesophageal phases of swallowing (see Chapter 26).[50] Sequential three-phase contrast videofluoroscopy can be performed in the unsedated animal using barium liquid, barium paste, and barium-soaked food (kibble, canned, or both).[51] Sternal positioning may be preferable to lateral positioning for videofluoroscopic evaluations of swallowing and esophageal transit.[52] Videofluoroscopy can be combined with esophageal manometry,[53] electromyography, and pH monitoring to provide additional information on pressure–time relationships, neuromuscular integrity, and gastroesophageal sphincter function, respectively (see "Esophageal Structure and Function" section).

Megaesophagus and Motility Disorders

Megaesophagus is characterized by severe diffuse esophageal hypomotility and flaccid dilation of the esophagus. Primary megaesophagus is usually idiopathic and can be either congenital or acquired.[2,3] Survey radiographs are usually diagnostic of a severely enlarged esophagus distended with air, fluid, or food.[2] If survey radiographs are inconclusive, a static-image barium contrast esophagram can be used to confirm esophageal dilation and reduced esophageal clearance. Contrast videofluoroscopy reveals aperistalsis and impaired esophageal transport of contrast medium in the absence of obstruction. Less severe esophageal motility dysfunction without overt megaesophagus usually requires barium swallow videofluoroscopy to assess the intensity and coordination of peristalsis and the coordinated functioning of the sphincters.[47,54] Diffuse or segmental esophageal hypomotility can also occur secondary to esophagitis, hiatal hernia, and obstructive esophageal lesions, such as strictures, vascular ring anomalies, and leiomyomas.[4,10,44]

Esophageal Diverticulum

Esophageal diverticula are large pouch-like sacculations of the esophageal wall that interfere with the orderly movement of ingesta through the esophagus. Diverticula can be identified by radiography or endoscopy.[55-57] Survey thoracic radiographs show an air-, fluid-, or food-filled esophageal sacculation or pouch, and contrast radiography demonstrates pooling of barium in the diverticulum. Most diverticula occur in the cranial mediastinal and epiphrenic regions of the esophagus.[55-57] Congenital diverticula are rare abnormalities of embryogenesis that permit herniation of the esophageal mucosa through a defect in the muscularis. Acquired diverticula can result from external traction and distortion of the esophagus caused by periesophageal inflammatory adhesions (traction diverticula), or most often from increased intraluminal pressure and food impaction (pulsion diverticula) associated with esophageal injury (esophagitis), hypomotility (megaesophagus), or obstruction (e.g., vascular ring anomaly, foreign body, stricture, and tumor). Radiographs should be evaluated carefully for underlying causes when an acquired diverticulum is identified. A redundant flexure or deviation of the esophagus at the thoracic inlet is a common incidental finding in clinically normal brachycephalic and Chinese Shar-Pei dogs and should not be mistaken for a diverticulum.[58] These false diverticula lack pooling of food and fluid and decrease or disappear with extension of the neck.

Vascular Ring Anomaly

Vascular ring anomalies are congenital malformations of the great vessels and their branches that entrap the intrathoracic esophagus and other intrathoracic structures, and cause clinical signs of esophageal obstruction.[1,7,59-62] Persistent right aortic arch accounts for 95% of vascular ring anomalies. In persistent right aortic arch, the ligamentum arteriosum continues to develop from the left side and forms a fibrous band that crosses over the esophagus to connect the main pulmonary artery and the anomalous aorta. The esophagus becomes entrapped and constricted circumferentially by the ligamentum, aorta, and base of the heart. Survey thoracic radiographs usually show a severe dilation of the esophagus with food and fluid cranial to the heart. A characteristic leftward deviation of the trachea near the cranial border of the heart is a consistent finding on ventrodorsal or dorsoventral views.[7] The normal shadow of the aortic arch to the left may be absent. Barium contrast esophagram will confirm obstruction of the esophagus at or just cranial to the base of the heart. Nonselective computed tomography (CT) angiography can be used to diagnose rare atypical vascular ring anomalies.[7,62]

Esophageal Foreign Body

Esophageal foreign bodies are common and lodge most often at the thoracic inlet, base of the heart, or gastroesophageal sphincter,[23-29] which are the least-distensible regions of the esophagus. Survey thoracic and cervical radiographs are usually diagnostic for radiopaque foreign bodies, such as bones or metal objects (pins, needles, fishhooks, etc.). Radiolucent objects can be identified if outlined by air, or they may require barium contrast radiography or esophagoscopy. Foreign bodies may injure the esophageal mucosa and cause complications such as esophagitis, perforation, or stricture. If

perforation is suspected, iohexol should be used as a contrast agent instead of barium.

Esophagitis and Stricture

Survey radiographs in esophagitis are usually unremarkable except for the occasional presence of small amounts of air in the esophagus. In some cases the underlying cause of esophagitis is identified (e.g., foreign body, hiatal hernia, or caudal esophageal mass with *S. lupi* infection). Contrast studies are normal in mild cases, but the mucosal surface may appear irregular with secondary hypomotility in severe cases. Segmental narrowing of the lumen can result from spasticity, intramural edema, and focal indistensibility caused by inflammation, which can be difficult to differentiate from a developing stricture. Contrast videofluoroscopy is helpful for identifying episodic gastroesophageal reflux or intermittent hiatal herniation that can cause esophagitis.

The diagnosis of esophageal stricture can be confirmed by barium contrast radiography of the esophagus or esophagoscopy. Survey radiographs are often normal unless the esophagus is distended cranial to the stricture with food, fluid, or air. Barium contrast radiography usually confirms the site of the stricture with dilation of the esophagus cranial to the stricture site. It is difficult to differentiate a fibrous stricture from severe inflammation or neoplasia radiographically, so endoscopic evaluation is usually needed. Moreover, the length of a stricture can be overestimated radiographically because of associated inflammation and esophageal spasm.

Hiatal Disorders

Hiatal hernia is a congenital or acquired protrusion of a portion of the stomach through the esophageal hiatus of the diaphragm.[1,10,11,13,33,34] In many cases the herniation and clinical signs are intermittent. A sliding hiatal hernia, which is most common, is a cranial displacement of the abdominal segment of the esophagus, gastroesophageal junction, and cardia region of the stomach through the esophageal hiatus of the diaphragm into the thorax. A paraesophageal hiatal hernia occurs when a portion of the stomach (usually the fundus) herniates through the hiatus into the caudal mediastinum alongside the caudal thoracic esophagus.[63]

Diseases of the hiatus can often be diagnosed radiographically, especially when the hernia is persistent. Survey thoracic radiographs may demonstrate a gas-filled soft-tissue mass (the stomach) in the dorsocaudal mediastinum. The normal gastric gas bubble that is usually seen in the cranial abdomen can be smaller and displaced. A contrast esophagram usually confirms the presence of hiatal hernia. The gastroesophageal junction and gastric rugae are visible cranial to the diaphragm, but the continuity of the esophagus and stomach is still obvious. Gastroesophageal reflux of barium is sometimes identified. Hiatal herniae that are small and reduce spontaneously are a diagnostic challenge because of their intermittent nature and unknown clinical significance. Applying pressure on the abdomen at the time of exposure may induce herniation at the hiatus. Fluoroscopy improves the chances of identifying an intermittent hernia and episodic reflux.

Gastroesophageal intussusception is an invagination of the stomach into the lumen of the caudal esophagus.[1,13,64-67] Gastroesophageal intussusception can be diagnosed by radiography or esophagoscopy. If needed to confirm the diagnosis, barium esophagram will identify gastric rugae within the lumen of the esophagus and severe esophageal obstruction. Like hiatal hernia, it can be a consequence of laxity of the esophageal hiatus and may occur intermittently. It is most often a complication of esophageal hypomotility or megaesophagus.[64,66,67]

Esophageal and Periesophageal Neoplasia

Primary esophageal tumors are rare.[1,13] Squamous cell carcinoma is the most common primary malignant tumor in cats.[68,69] In regions where *S. lupi* is an endemic parasite, dogs can develop fibrosarcomas and osteosarcomas from spirocercal granulomas.[70,71] Leiomyomas, which are the most common benign tumors of the esophagus, most often arise near the gastroesophageal junction of dogs and usually are incidental findings unless large enough to partially obstruct the lumen.[72] Leiomyosarcoma, lymphoma, and metastatic carcinoma are rare tumors of the esophagus. Survey thoracic radiography may be normal or may identify a soft-tissue mass in the region of the esophagus. The degree of luminal obstruction depends on the size and position of the mass, and the esophagus may be distended cranial to the tumor site. Barium esophagram may reveal stricture with irregular intraluminal filling defects, but endoscopic biopsy will be required for definitive diagnosis. Survey radiographs in dogs with *S. lupi*-induced sarcoma may reveal a dorsocaudal mediastinal mass, spondylitis of the caudal thoracic vertebrae, and hypertrophic osteopathy.[70,71]

Mass lesions arising from periesophageal tissues may cause extraluminal compression of the esophagus or may invade locally into the wall of the esophagus. Mediastinal lymphoma is most common, although any large tumor or abscess arising from cervical or mediastinal structures (e.g., thyroid, thymus, lymph node, lung, heart base) can cause secondary esophageal compression and occlusion. Survey thoracic radiography usually identifies an intrathoracic mass in the region of the esophagus. Barium esophagram, thoracic CT scan, or esophagoscopy can all be used to identify the location and extent of obstruction. Large mediastinal and pulmonary masses can be examined by ultrasound-guided fine-needle aspiration cytology. Thoracocentesis and cytology of pleural effusion may also be diagnostic.

Esophagoscopy

Esophagoscopy is indicated for the diagnostic evaluation of many dogs and cats with signs of esophageal disease, especially when radiography is inconclusive. Esophagoscopy enables thorough visual examination for diseases that disrupt the mucosa or obstruct the lumen, for example, foreign bodies, esophagitis, strictures, tumors, and gastroesophageal intussusception.[1,13,73] Esophagoscopy is less reliable for diagnosing megaesophagus and other functional motility disorders. Some diseases of the esophagus, stomach, and intestine cause overlapping signs or involve multiple regions of the digestive tract simultaneously; thus, most animals that undergo esophagoscopy should have a complete endoscopic examination of the entire upper gastrointestinal tract (*esophagogastroduodenoscopy*). It can be difficult to obtain good quality endoscopic biopsies of normal esophageal mucosa, but adequate biopsy specimens can usually be obtained from diseased mucosa with increased friability (esophagitis) and from neoplastic tissue. Endoscopic cytology specimens collected using a guarded (sheathed) cytology brush are sometimes useful for diagnosing esophageal neoplasia, unusual forms of esophagitis caused by infectious agents (pythiosis, candidiasis, and spirocercosis), and eosinophilic esophagitis. Esophagoscopy can also be used for therapeutic intervention to remove esophageal foreign bodies, guide balloon catheter placement with esophageal strictures, assist in the deployment of esophageal stents, place indwelling gastrostomy and esophagostomy feeding tubes, and ablate neoplastic tissue with lasers.[13,73] Chapter 27 describes the equipment and techniques for performing esophagoscopy.

Megaesophagus

Esophagoscopy is less reliable than radiography for confirming megaesophagus, but it can help rule out obstructive causes of esophageal dilation (GES abnormalities, vascular ring anomalies, strictures, tumors) and evaluate for the esophagitis that develops in many cases.[2,4] Esophageal motility and lumen size are difficult to assess with endoscopy because the normal esophagus becomes flaccid and dilated with general anesthesia and insufflation of air. The typical endoscopic appearance of megaesophagus is a markedly dilated, flaccid esophagus throughout its entire length, with variable amounts of saliva, fluid, and food residue in the lumen.[73] On initial insertion of the endoscope the normal esophagus in a fasted animal is usually empty, so a motility, hiatal, or obstructive disorder should be suspected when the esophagus contains a pool of fluid and ingesta. Megaesophagus must be differentiated from segmental dilations or sacculations that develop cranial to obstructions caused by vascular ring anomalies, strictures, tumors, or periesophageal masses. A diverticulum of the cranial thoracic esophagus sometimes develops as a complication of chronic megaesophagus.

Esophageal Diverticulum

In esophageal diverticulum, esophagoscopy reveals a saclike outpouching of the esophageal lumen, often with erosive esophagitis of the mucosa lining the diverticulum. Food, fluid, or hair may have to be removed from the diverticulum before it can be adequately visualized.[57] If a diverticulum is small, the only obvious finding may be a focal pooling of fluid. Because of the thin, weakened wall of the diverticular sac, caution must be used to avoid perforation.

Vascular Ring Anomaly

Esophagoscopy is useful for diagnosing vascular ring anomaly when radiography is inconclusive or unable to distinguish it from other causes of esophageal obstruction, such as stricture. Vascular ring anomaly causes entrapment and extraluminal compression of the esophagus, yielding a characteristic endoscopic appearance. Pulsations of the major vessels against the wall of the esophagus are seen at the level of the narrowed lumen, and the outline of the band-like ligamentum forms a distinct indentation that crosses over the left dorsolateral wall of the esophagus.[13,73] In some cases the obstructed lumen is only a tiny slit-like opening. The esophageal entrapment at the level of the heart base causes the cranial thoracic esophagus to be dilated, and often distended with ingesta and fluid at the time of endoscopy. In some cases vascular ring anomaly leads to sacculation of the cranial thoracic esophagus and secondary diverticulum formation.

Esophageal Foreign Body

Esophagoscopy is the definitive diagnostic procedure for esophageal foreign body. Most esophageal foreign bodies lodge at the thoracic inlet, base of the heart, or gastroesophageal sphincter, which are the least distensible regions of the esophagus. Depending on the type of object, its size and shape, and the length of time it is in contact with the mucosa, foreign bodies can injure the esophageal mucosa during passage or through impaction and pressure necrosis when they become entrapped.[23-29] Foreign bodies with sharp edges and points, especially bones, can become deeply embedded and lacerate or even perforate the esophagus, and with time tightly wedged objects can cause circumferential pressure necrosis.[23-25] In cats, large trichobezoars expelled from the stomach during vomiting may become lodged in the esophagus causing severe erosive esophagitis and stricture formation, presumably through the effects of pressure and prolonged mucosal contact with gastric acid and pepsin absorbed into the impacted hairball.[73] Chapter 27 describes techniques for the endoscopic retrieval of foreign bodies. After an esophageal foreign body has been removed, the mucosa should be examined for esophagitis, perforation, and esophagobronchial fistula.

Esophagitis

Esophagitis is an endoscopic diagnosis based on mucosal abnormalities that can include hyperemia, increased friability, ease of bleeding when rubbed by the endoscope tip, granular surface texture, accentuated folding, erosions, ulcers, focal necrosis, pseudomembranes, pale white areas of fibrosis with indistensibility, strictures, and GES abnormalities.[13-17,73] Inflammatory lesions in the caudal thoracic esophagus are indicative of reflux esophagitis, especially erythematous or erosive streaks radiating from the GES accompanied by a wide open sphincter and pooling of gastrointestinal contents (food, fluid, or bile) in the distal esophagus.[73] Reflux of gastric contents may be observed during endoscopy. In reflux esophagitis microscopic inflammation and epithelial changes may be evident before abnormalities can be seen with an endoscope, so if chronic reflux is suspected, mucosal biopsies should be taken adjacent to the GES for evaluation of hyperplastic, dysplastic, and metaplastic epithelial changes.[15,16,74]

Eosinophilic esophagitis is rare form of esophagitis diagnosed by endoscopic cytology and biopsy.[75] *P. insidiosum* is a waterborne fungus that can cause severe necrotizing pyogranulomatous esophagitis.[76] A presumptive diagnosis of pythiosis is based on finding characteristic broad, poorly septate hyphae with the Grocott methenamine silver stain in esophagoscopic biopsies. The diagnosis is supported by a positive serologic test for antibodies or by culture with polymerase chain reaction identification. *Candida albicans* causes white mucosal deposits of yeast, which develop secondary to retention of decomposing food residue in megaesophagus, diverticulum, or vascular ring anomaly. *S. lupi* is a nematode parasite that causes large granulomatous nodules in the caudal thoracic esophagus, which are transformed into fibrosarcoma or osteosarcoma.[70]

Esophageal Stricture

Esophagoscopy is the most reliable method for diagnosis of esophageal stricture and for determining the luminal diameter, stricture length, and presence of associated esophagitis. Diagnostic esophagoscopy is usually followed by endoscopic-guided mechanical dilation of the stricture using balloon catheter dilation or bougienage techniques. These procedures result in a favorable outcome in 70% to 88% of stricture patients.[18-22] Approximately 80% to 90% of strictures in dogs and cats are located in the intrathoracic esophagus, particularly between the heart base and gastroesophageal junction.[18-22] The degree of narrowing varies, but the luminal diameter averages 5 mm.[18,20,22] The stricture length averages 1 cm, but it can vary from a thin band, web, or ridge of fibrotic tissue to a segmental narrowing up to 10 to 15 cm in length.[18,20,31] In some cases diffuse esophagitis results in multiple strictures. Single strictures are found in 80% of cases and two or three strictures in the remaining 20%.[18-22]

Most strictures appear as focal circumferential narrowings formed by smooth, glistening-white, fibrotic rings or ridges.[18-22] Occasionally strictures form a web or imperforate membrane across the lumen. Concurrent esophagitis in 40% of cases causes the adjacent mucosa to be erythematous, hemorrhagic, friable, or ulcerated.[18-22] With chronicity, contraction of deep fibrotic tissue can distort the tubular axis of the esophagus so it appears to be angular or spiral shaped rather than straight. The degree of dilation of the esophagus cranial to the stricture depends on the duration and extent of obstruction. Benign strictures must be differentiated from other

causes of esophageal obstruction, such as neoplasia or extraluminal compression caused by a vascular ring anomaly or periesophageal mass. Mucosal biopsy is recommended to determine if an atypical appearing stricture is benign or malignant.

Esophageal Perforation and Fistula

Esophageal perforation is a rare complication of esophageal foreign bodies, especially objects with irregular or sharp edges such as bones, or chronically lodged foreign bodies that cause deep-pressure necrosis.[23,25,27-29] Iatrogenic esophageal perforation can also occur during endoscopic foreign-body extraction or stricture dilation, and as a complication of esophageal surgery or laser treatment. Esophageal perforation occurs in 4% to 9% of dogs and cats undergoing stricture ballooning or bougienage.[18-22] Penetrating injuries of the esophagus can result from bite wounds, gunshot injuries, and stick impalements. In general perforation of the intrathoracic esophagus has more serious consequences than perforation of the cervical esophagus because of the potential for tension pneumothorax and leakage of contaminated fluids into the thorax. During esophagoscopy, hemorrhagic fluid that bubbles from a deep defect in the thoracic esophagus in synchrony with respirations is indicative of acute perforation. If perforation occurs during endoscopic manipulation of a foreign body or stricture, life-threatening tension pneumothorax may occur that is accentuated by insufflation. This situation requires immediate thoracocentesis.

An esophageal fistula is a communication between the esophageal lumen and adjacent structures (e.g., mediastinum, trachea, bronchi). A fistula appears endoscopically as a small erythematous opening in the esophageal wall that drains purulent, bloody, or frothy fluid.[13,49] Esophagobronchial fistulas are the most common and often are accompanied by an esophageal diverticulum. Chronic perforations can also form fistulas that extend deep into the mediastinum.

Hiatal Disorders

Endoscopic findings consistent with hiatal hernia include pooling of fluid or ingesta in the caudal esophagus; enlargement of the esophageal hiatal opening; dilation and cranial displacement of the gastroesophageal sphincter into the thorax; rugal folds of the stomach protruding through the hiatus into the caudal thorax as viewed from the esophageal and gastric retroflex positions; and evidence of esophagitis in the caudal esophagus.[73] A pseudopouch can be seen if the stomach is herniated at the time of insertion of the endoscope.[73] This effect is created by narrowing of the lumen as the scope advances through the cranially displaced gastroesophageal junction followed by a dilated region of the lumen lined by rugal folds.

Gastroesophageal intussusception is diagnosed endoscopically when the rugal folds of the invaginated stomach form a bulging intraluminal mass that fills the caudal thoracic esophagus.[1,13,64-67] Concurrent findings can include esophagitis, esophageal obstruction, and megaesophagus. If intussusception is encountered, the endoscopist should maximally insufflate the esophagus and occlude it in the cervical region to retain the air. The combination of inflation pressure and advancement of the endoscope tip against the invaginated rugae may reduce small intussusceptions and allow entry into the repositioned stomach.

Esophageal and Periesophageal Neoplasia

Endoscopy and biopsy are indicated for the definitive diagnosis of esophageal neoplasia.[68,69,73] The intrathoracic esophagus is most often involved and the degree of luminal obstruction varies. Endoscopically, a carcinoma usually causes eccentric stenosis and appears as a proliferative mass with a friable, lobulated, or ulcerated surface. In dogs with *S. lupi*–associated esophageal granuloma or sarcoma, nematodes may be seen protruding from the nodular lesions and eggs may be identified by fecal examination.[70] Forceps biopsies should be obtained from all esophageal masses and proliferative lesions identified at endoscopy.

Endoscopy is useful for evaluating the extent of obstruction and determining whether masses are extramural or intramural. A stenotic region of esophagus with normal-appearing mucosa suggests extraluminal compression by a periesophageal mass rather than stricture or primary esophageal tumor.[73] Transmural endoscopic-guided fine-needle aspiration of periesophageal masses can be obtained for cytologic examination using a 21- to 23-gauge through-the-scope sclerotherapy needle.

Other Diagnostic Methods

Videofluoroscopy is the most clinically useful tool for evaluating all phases of swallowing in dogs and cats with esophageal motility dysfunction (see "Radiography" earlier in this chapter).[46,47] Other specialized procedures include nuclear scintigraphy, manometry, pH monitoring, and electromyography, but these studies are difficult and not routinely performed in dogs and cats.

Nuclear Scintigraphy

Scintigraphic evaluation of swallowing of a radioisotope such as technetium-99 m (^{99m}Tc) sulfur colloid or ^{99m}Tc-pertechnetate enables noninvasive quantitative assessment of esophageal transit time and clearance.[77] Nuclear scintigraphy can also be used to identify gastroesophageal reflux after intragastric instillation of the radioisotope via stomach tube. Scintigraphy can identify esophageal perforations and fistulas while avoiding the risks of extravasated contrast medium.

Esophageal Manometry

Continuous pull-through infusion manometry has been used extensively in people and research animals to record the pressure–time relationships during the cricopharyngeal, esophageal, and gastroesophageal phases of swallowing. Manometry techniques and normal values for dogs and cats have been described along with the effects of various drugs and neuroendocrine substances on gastroesophageal sphincter pressure.[78-84] Unfortunately, normal reference ranges in these studies have varied widely and individual dogs show considerable day-to-day variation, thus routine clinical application of manometry in animal patients has been limited. In addition manometry in dogs and cats may require anesthesia, which affects the measurements, except in some studies where research dogs have been trained to swallow manometric tubes while awake.[84,85] Esophageal manometry has been performed in dogs with idiopathic megaesophagus.[85] New high-resolution manometry catheters used in people have up to 128 circumferential pressure sensors that enable complex computer analysis of swallowing in new ways.

Esophageal pH Monitoring

Continuous ambulatory monitoring of the caudal esophageal pH and impedance with an intraluminal pH probe is the gold standard for verifying gastroesophageal reflux in people. Esophageal pH monitoring has not found clinical application yet in dogs and cats, but it has been used as a research tool to assess gastroesophageal reflux in anesthetized dogs.[86,87] A recent innovation in pH monitoring is a catheter-free pH sensor capsule (Bravo pH Monitoring System;

Medtronic) that is attached endoscopically to the esophageal mucosa where it transmits continuous pH data wirelessly (by telemetry) to a mobile receiver. The pH data are then downloaded to a computer for analysis. An esophageal acid clearance test was evaluated in healthy awake dogs using a pH probe in the caudal esophagus that recorded the number of swallows and time required for esophageal peristalsis to increase the pH to 4.0 following instillation of a 10-mL bolus of 0.1 N hydrochloric acid.[88] The mean clearance time was 5 minutes (range: 2.5 to 8) after eight swallows (range: 4 to 12).

Electromyography

Electromyography (EMG) can be used to evaluate striated muscle activity associated with swallowing, and it can be integrated with manometric and videoradiographic findings.[53] Abnormal EMG findings include fibrillation potentials, positive sharp waves, increased insertional activity, and complex repetitive discharges. In myopathic and neuropathic esophageal diseases, the EMG may reveal abnormalities in the muscles of the pharynx, cricopharyngeal sphincter, and cranial esophagus.[50,83] When esophageal disease is associated with polymyopathy, EMG of the masticatory and limb muscles may also be abnormal.[6]

INFLAMMATION

Robert J. Washabau

Esophagitis

Etiology

Esophagitis is an acute or chronic inflammatory disorder of the esophageal mucosa that occasionally involves the underlying submucosa and muscularis. It may result from ingestion of caustic or corrosive substances, injury from esophageal foreign bodies, gastroesophageal reflux, radiation injury, idiopathic generalized megaesophagus, and inflammation associated with malignancy.[1-5]

Pathophysiology

The esophageal mucosa has several important barrier properties to withstand caustic substances, including stratified squamous epithelium with tight intracellular junctions, mucus gel, and surface bicarbonate ions. Disruption of any of these barrier properties may result in inflammation, erosion, and/or ulceration of the underlying structures.[2,6-8] Clinical signs are related to the type of chemical injury, the severity of inflammation, and the involvement of structures underlying the esophageal mucosa, for example, the muscularis.[9] Although esophagitis may occur at any age, young animals with congenital esophageal hiatal hernia may be at increased risk for reflux esophagitis.[10,11] Cats appear to be particularly susceptible to doxycycline-associated esophagitis and esophageal stricture.[12-14] Anesthesia, poor patient preparation, and poor patient positioning during anesthesia places other animals at risk for gastroesophageal reflux and esophagitis.[15-19] Upper respiratory syndrome in brachycephalic breeds predisposes to reflux esophagitis.[20,21]

Esophagitis that is a consequence of gastroesophageal reflux may result from direct H^+ injury, or indirectly from inflammatory cytokines and chemokines (substance P [SP], interleukin-8 [IL-8], platelet-activating [PAF]) that induce neutrophil migration and activation (discussed in more detail in "Gastroesophageal Reflux" section).

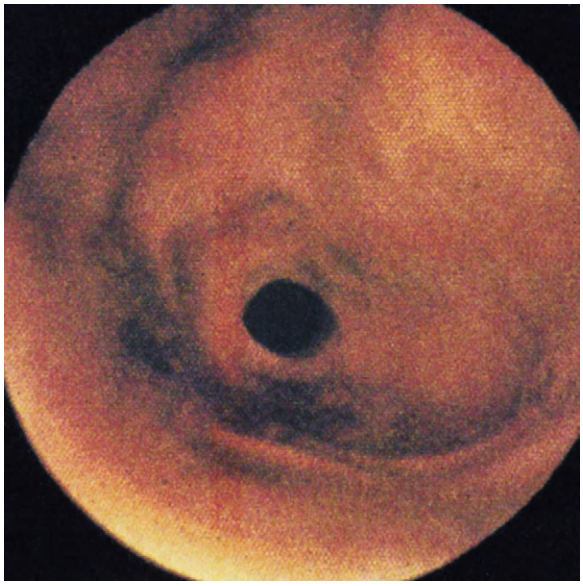

Figure 55-2 Endoscopic appearance of esophagitis and strieture in a 12-year old mixed breed dog.

Clinical Signs

Signs characteristic of esophagitis include regurgitation, salivation, odynophagia (inferred pain), extension of the head and neck during swallowing, and avoidance of food. Coughing may be observed in some animals with concurrent aspiration pneumonia. The physical examination is often nonremarkable in affected animals, although fever and salivation may be detected in animals affected with ulcerative esophagitis. Pulmonary wheezes and coughing occur with aspiration pneumonia.

Diagnosis

Leukocytosis and neutrophilia may be found in animals with severe esophagitis or aspiration pneumonia. Results of routine hematology, serum biochemistry, and urinalysis are otherwise nonremarkable. The esophagus often appears normal on survey thoracic radiographs unless there is some secondary dilation. Aspiration pneumonia may be evident in the dependent portions of the lung. Barium contrast radiographs include irregular mucosal surface, segmental narrowing, esophageal dilation, and/or diffuse esophageal hypomotility. Stricture formation may also be observed in chronic undiagnosed or untreated esophagitis. Endoscopy and biopsy are the most reliable means of diagnosing this disorder. In severe cases of esophagitis, the mucosa will appear hyperemic and edematous with areas of ulceration and active bleeding (Figure 55-2). Milder cases of esophagitis may appear endoscopically normal. Endoscopic biopsy of the esophageal mucosa is technically more difficult than other parts of the gastrointestinal tract,[22] but mucosal biopsy will be necessary to confirm the diagnosis in mild to moderate cases. Esophagitis will have several important differential diagnoses, including mechanical injury as a result of esophageal foreign body, esophageal stricture, hiatal hernia, megaesophagus, esophageal diverticulum, and vascular ring anomaly. Each of these disorders can be differentiated by survey or contrast radiography, or endoscopy.

Treatment

Animals with mild esophagitis may be managed on an outpatient basis. Oral food intake should be withheld for 2 to 3 days in cases of mild to moderate esophagitis. Animals with more severe esophagitis

Table 55-1 Components of Gastroesophageal Reflux and Therapy*

Pathogenesis	Components	Therapy
Esophagitis	Gastric acid	Acid suppression, e.g., H_2 histamine receptor antagonist; H^+,K^+-ATPase inhibitor
	Gastric pepsins	Chemical diffusion barrier, e.g., sucralfate
	Intestinal bicarbonate	Chemical diffusion barrier, e.g., sucralfate
	Pancreatic proteases	Chemical diffusion barrier, e.g., sucralfate
	Bile acids	Chemical diffusion barrier, e.g., sucralfate
Gastroesophageal reflux	Gastric secretions	Prokinetic agent, e.g., cisapride, metoclopramide, erythromycin
	Duodenal secretions	Prokinetic agent, e.g., cisapride, metoclopramide
Gastric secretion	Gastric acid	Acid suppression, e.g., H_2 histamine receptor antagonist; H^+,K^+-ATPase inhibitor
	Gastric pepsins	Chemical diffusion barrier, e.g., sucralfate
Delayed gastric emptying	Retention of gastric secretions	Prokinetic agent, e.g., cisapride, metoclopramide, erythromycin
Enterogastric reflux	Intestinal bicarbonate	Chemical diffusion barrier, e.g., sucralfate
	Pancreatic proteases	Chemical diffusion barrier, e.g., sucralfate
	Bile acids	Chemical diffusion barrier, e.g., sucralfate

*See also Figure 55-3.

may require hospitalization and enteral or total parenteral nutrition. Enteral feeding of half-solid nutrients (vs. liquids) reduces the frequency of gastroesophageal reflux in the dog.[23] Oral sucralfate suspensions (0.5 to 1.0 g PO, TID) are the most important and specific therapy for esophagitis.[24,25] Sucralfate suspensions are more therapeutic than intact sucralfate tablets because the liquid suspension will bind more readily to an erosive or ulcerative site. Gastric acid secretory inhibitors (e.g., cimetidine 5 to 10 mg/kg PO or IV, TID-QID; ranitidine 1 to 2 mg/kg PO or IV, BID-TID; famotidine 0.1 to 0.5 mg/kg PO or IV, BID; omeprazole 0.7 mg/kg PO, SID; esomeprazole, lansoprazole, or pantoprazole all at 1 mg/kg IV) should be useful in suspected cases of gastroesophageal reflux, but should be used in addition to, not in place of, sucralfate. Prokinetic agents should also be considered if there is concurrent gastroesophageal reflux (see "Gastroesophageal Reflux" later in this chapter). Broad-spectrum antibiotics may be needed in animals with aspiration pneumonia or severe esophagitis.

Prognosis

Animals with mild esophagitis generally have a favorable prognosis. Ulcerative esophagitis, on the other hand, warrants a more guarded prognosis. Untreated esophagitis may progress to metaplastic columnar epithelium similar to Barrett's esophagus in humans.[26] The most important complication of esophagitis in companion animals is progressive esophageal stricture.[17,18,27,28] Animals affected with esophageal stricture develop progressive regurgitation, weight loss, malnutrition, and aspiration pneumonia. A relationship between reflux esophagitis and idiopathic megaesophagus seems obvious,[4] but it is not yet clear whether this is cause or consequence (see Figure 55-11).

Gastroesophageal Reflux

Etiology

Gastroesophageal reflux is a disorder of the gastroesophageal sphincter permitting reflux of gastrointestinal fluids or ingesta into the esophagus. Varying degrees of esophagitis result from prolonged contact of gastric acid, pepsin, trypsin, bile salts, and duodenal bicarbonate with the esophageal mucosa.

Pathophysiology

The frequency of reflux and composition of the refluxed material determines the severity of the esophagitis.[29] Gastric acid alone produces a mild esophagitis, whereas combinations of acid and pepsin or trypsin, bicarbonate, and bile salts produce a severe esophagitis (Table 55-1 and Figure 55-3).[29] The risk of reflux esophagitis is also greater with multiple episodes than with a single long episode of acid exposure.[9] Gastroesophageal reflux has been poorly documented in dogs and cats, but it is undoubtedly more common than previously thought. Chronic vomiting, disorders of gastric emptying, hiatal hernia, upper airway obstruction, and anesthesia-induced reductions in gastroesophageal sphincter pressure have all been implicated in the pathogenesis of gastroesophageal reflux in dogs and cats.[2,15,16,19,21,30] Many of the preanesthetic agents currently in use are associated with reductions in gastroesophageal sphincter pressure as are all of the inhalant anesthetic agents.[15,19]

The pathophysiology of mucosal injury in gastroesophageal reflux remains to be completely elucidated, but prolonged contact of the mucosa with acid clearly contributes to the reflux injury. The central dogma has been that esophagitis develops from an acid (or other chemical) injury starting at the luminal surface of the squamous epithelium, progressing through the epithelium and lamina propria into the submucosa, and resulting in acid-induced necrosis of surface epithelial cells and stimulation of a proliferative response in the basal cells.[29] This dogma has been recently challenged by new experimental findings.[30] It has been proposed that refluxed gastric fluid does not directly damage the esophageal mucosa, but rather stimulates esophageal epithelial cells to secrete chemokines that attract and activate immune cells, causing damage to the esophageal squamous epithelial cells.[30] In this model, acid is believed to activate acid-sensitive transient receptor potential vanilloid 1 ($TRPV_1$) receptors, causing the production and release of PAF, SP, and IL-8, which attract and activate immune cells contributing to inflammation and injury of the esophageal mucosa (see Figure 55-4).[30] These data further suggest that inhibition of IL-8, SP, and PAF-induced neutrophil migration and activation may be the basis of future therapy in this disorder.[30]

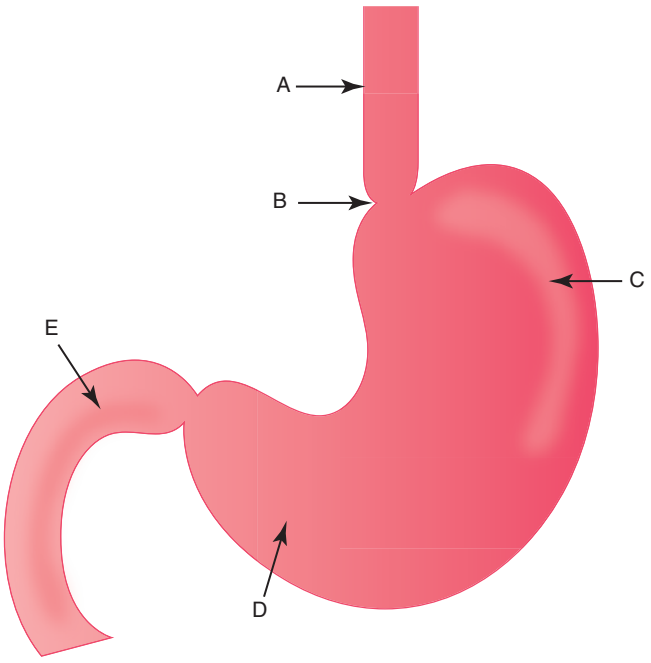

Figure 55-3 Mechanisms of esophageal inflammation with reflux esophagitis. Reflux esophagitis *(A)* results from gastroesophageal reflux *(B)*, continued gastric secretions *(C)*, delayed gastric emptying *(D)*, and enterogastric reflux *(E)*.

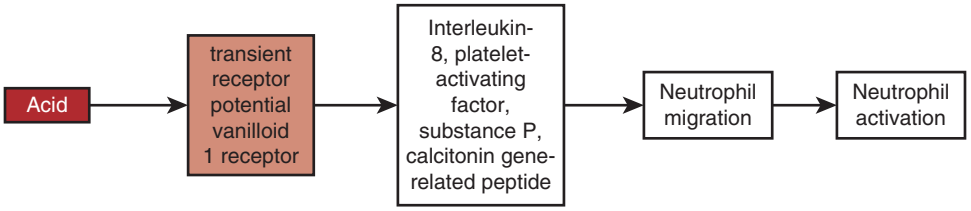

Figure 55-4 Activation of the inflammatory and immune response following acid injury in the esophageal mucosa.

Clinical Signs

The clinical signs of gastroesophageal reflux are similar to those of esophagitis. In severe cases, animals may develop regurgitation, salivation, odynophagia, extension of the head and neck during swallowing, and total avoidance of food. In milder cases, however, affected animals may have only an occasional episode of regurgitation, particularly in the early morning hours. The latter cases are physiologic and result from transient relaxations of the gastroesophageal sphincter during sleep.[31] The physical examination is usually unremarkable, but fever and excessive salivation may be detected in animals with severe concurrent esophagitis.

Diagnosis

The diagnosis of gastroesophageal reflux may be little more than clinical suspicion. Survey radiographs typically do not aid in the diagnosis. Videofluoroscopy may demonstrate intermittent gastroesophageal reflux, but this finding may also be observed in animals with normal esophageal function.[32,33] Endoscopy is the current best method for documenting mucosal inflammation consistent with reflux esophagitis (see Figure 55-2). Definitive diagnosis of gastroesophageal reflux requires continuous measurements of gastroesophageal sphincter pressure and 24-hour intraluminal pH, procedures for which most dogs and cats are not compliant. Hiatal hernia, esophagitis, and esophageal stricture are the most important differential diagnoses for gastroesophageal reflux.

Treatment

Because dietary fat delays gastric emptying and reduces gastroesophageal sphincter pressure, animals should be fed fat-restricted diets. Pet owners should also avoid late night feedings because this would tend to reduce gastroesophageal sphincter pressure during sleep. In addition to nutritional considerations, rational medical therapy for this disorder includes diffusion barriers (e.g., sucralfate), gastric acid secretory inhibitors (e.g., cimetidine, ranitidine, famotidine, or omeprazole), and prokinetic agents (e.g., cisapride or metoclopramide).[23-25] Diffusion barriers are perhaps the most important medical therapy in gastroesophageal reflux. Sucralfate (0.5 to 1.0 g PO, TID), for example, protects against mucosal damage from gastroesophageal reflux and promotes healing of existing esophagitis.[24,25] Refractory cases of gastroesophageal reflux should be concurrently medicated with acid secretory inhibitors and/or prokinetic agents. The H_2 histamine receptor antagonists, for example, cimetidine (5 to 10 mg/kg PO or IV, TID-QID), ranitidine (1 to 2 mg/kg PO or IV, BID-TID), and famotidine (0.1 to 0.5 mg/kg PO or IV, BID), inhibit gastric acid secretion and reduce the amount of

acid reflux. Omeprazole (0.7 mg/kg PO, SID); esomeprazole, lansoprazole, and pantoprazole (all 1.0 mg/kg IV, SID); and all H^+,K^+-ATPase inhibitors could be used to inhibit gastric acid secretion as an alternative to H_2 histamine receptor antagonism.[34] Metoclopramide (0.2 to 0.4 mg/kg PO, TID-QID)[35,36] and erythromycin (0.5-1.0 mg/kg PO, BID-TID)[37,38] may be useful in treating gastroesophageal reflux because they increase gastroesophageal sphincter pressure. 5-HT_4 agonists like cisapride and tegaserod also increase tone in the gastroesophageal sphincter,[39] and are likely superior to other prokinetic drug classifications. Both cisapride and tegaserod have been withdrawn from several international markets because of high-potency binding to ventricular 5-HT_4 receptors, inhibition of the delayed rectifying K^+ channel, delayed repolarization, and prolongation of the cardiac Q-T interval.[40] Cisapride has continued availability in many countries through compounding pharmacies. Recent studies show that GABA type B receptor agonists (e.g., baclofen),[41] cannabinoid receptor agonists (WIN 55,212-2),[42] and metabotropic glutamate (mGlu) receptor 5 antagonists (MPEP)[43] abolish transient gastroesophageal relaxations in the dog, and therefore may have future application in the treatment of gastroesophageal reflux.

Prognosis

The prognosis for most animals with gastroesophageal reflux is good with medical management. Anatomic correction of upper airway obstruction in brachycephalic breeds should ameliorate gastroesophageal reflux in affected patients.

Esophageal Fistula

Etiology

An esophageal fistula is an abnormal communication between the esophagus and adjacent structures. Most esophageal fistulae involve the lungs or airway structures, for example, esophagopulmonary, esophagobronchial, or esophagotracheal fistulae. Occasionally, esophageal fistulae expand into the pleural space or cervical tissues.

Pathophysiology

Both congenital and acquired fistulae have been described.[44] Congenital fistulae are rare and result from incomplete separation of the tracheobronchial tree from the digestive tract, from which it is formed embryologically. An increased incidence of congenital esophageal fistulae (and esophageal diverticula) has been reported in the Cairn Terrier.[1] Affected animals often have concurrent esophageal foreign bodies, presumably because of abnormalities in esophageal motility associated with the fistula.

Acquired esophageal fistulae typically result from foreign body ingestion, esophageal perforation, and extension of inflammation into adjacent tissues. Bones and grass awns are most commonly incriminated. A traction diverticulum often also develops because of the inflammatory reaction between the esophagus and bronchus. Secondary complications that may occur with esophagobronchial fistula are localized pneumonias, pulmonary abscessation, and pleuritis. The severity of the secondary complications usually depends on the duration and size of the fistula.

Clinical Signs

Animals with congenital esophageal fistula usually develop clinical signs shortly after weaning, whereas animals with acquired fistula develop signs much later in life. Clinical signs in nearly all cases are related to the respiratory system and include coughing and dyspnea. Other signs that may develop include regurgitation, lethargy, anorexia, fever, and weight loss. Regurgitation is usually reported in relation to an esophageal foreign body.

Diagnosis

The radiographic manifestations of esophagobronchial fistula consist of localized alveolar, bronchial, and/or interstitial lung patterns. The right caudal, right intermediate, and left caudal lung lobes are most often involved. The esophagus appears radiographically normal unless a radiopaque esophageal foreign body is observed. Definitive diagnosis of esophageal fistulae requires contrast radiography or endoscopy. An esophagram should be performed with a thin mixture of barium sulfate (30% w/v) to elucidate the fistula. Use of iodinated contrast agents should be avoided since they are hyperosmolar and chemically irritating to the lung. Endoscopy may also be useful in documenting an esophageal fistula although small fistulae are occasionally missed. Lobar pneumonia is the most important differential diagnosis for esophagobronchial fistula. Aspiration, bacterial, and foreign body pneumonias can all mimic esophagobronchial fistula.

Treatment

Surgical excision and repair provide the most successful outcomes in animals with esophagobronchial fistula.[45] The fistula is surgically excised, and the defect in the esophagus is closed. Resection of the affected lung lobe is also generally warranted. A postoperative course of broad spectrum antibiotics should be prescribed in all cases.

Prognosis

The prognosis is guarded if secondary complications, such as pneumonia, pulmonary abscesses, or large quantities of pleural fluid, are present. In the absence of such complications, the prognosis is generally good.

INFECTION

Remo Lobetti

The most important infection of the canine esophagus is by the helminth, *S. lupi*, with sporadic reports of bacterial, viral, and oomycetial infections in the dog. There are no documented reports of algal, protozoal, or fungal infections in either the dog or cat.

Spirocercosis

Spirocercosis is a disease caused by the nematode *S. lupi*, which has a variety of clinical presentations; is found worldwide, especially in tropical and subtropical regions; and affects mostly carnivores, especially canidae.[1-3] Clinical signs associated with spirocercosis are usually associated with larval migration and the persistence of adult worms within the host.

Distribution

S. lupi has a worldwide distribution with the majority of the clinical reports from Israel,[3] Greece,[4] India,[5] Pakistan,[6] southern United States,[7] Brazil,[8] Kenya,[9] and South Africa.[2] In Israel, spirocercosis is more prevalent in urban areas, whereas in the United States the disease is more common in rural areas.[3] In South Africa, there does not appear to be any obvious distinction in the distribution between urban and rural areas.[2] The most significant factor associated with

the prevalence of *S. lupi* infection is the proximity of dogs to the intermediate and paratenic (transport) hosts. There is no sex or age predilection for infection, although infected dogs younger than 6 months of age may not develop esophageal disease and the classic clinical signs.[10] There appears to be a breed predilection as there is a higher incidence of spirocercosis in Hound Dogs,[11] German Shepherds,[1,5] Poodles,[8] and Labrador Retrievers.[3] Spirocercosis has also been reported in the domestic cat[12] and wild felidae.[13]

Life Cycle

S. lupi eggs containing L1 larvae are passed from the esophagus through the gastrointestinal tract and into the feces but may also be shed in the vomitus. Eggs are then ingested by coprophagous beetles, the intermediate host, in which the larvae excyst and develop to L3 larvae within 2 months. The beetle is then ingested by either the final host or a paratenic host, which can be poultry, wild birds, lizards, rodents, hedgehogs, and rabbits. The L3 larvae form small nodules within the paratenic host.[10] The final host becomes infected by ingesting either the infected beetle or a paratenic host with the latter a more likely source of infection for carnivores.

In the final host, the L3 larvae excyst in the stomach, penetrate the gastric mucosa, and migrate within the walls of the gastric and gastroepiploic arteries, where hemorrhagic lesions are evident from the fourth day of infection. In the initial stages of infection, larval migration is nondirectional and thus they may be found within the veins and lymphatics of the gastric wall, which may result in aberrant migration to other organs. The stimulus for directional and aberrant migration is still not known. L3 larvae reach the caudal thoracic aorta via the celiac artery approximately 10 days after excysting and remain there from day 7 to day 109 where they mature to L4 larvae. After their final molt, which is approximately 3 months postinfection, they migrate as immature adults, from the caudal thoracic aorta to the caudal esophagus where they form nodules in the esophageal submucosa and adventitia. Mature adult worms develop by 3 to 9 months postinfection.[11] The adult is a large spiraled pink worm with males up to 54 mm, and females up to 80 mm in length. The adult worm can reside in the esophagus for up to 2 years, with the female producing up to 3 million eggs per day.[14]

Pathology

Adult worms form granulomatous nodules in the submucosa of the caudal esophagus, which vary from less than 1 to more than 4 cm in diameter. *Spirocerca* nodules bulge into the lumen of the esophagus and distort the esophageal wall while extending into the surrounding mediastinal tissue at the same time. The number of worms present in a nodule may vary from a few to more than 30, but typically there are between three and six worms.

Migrating larvae cause necrosis, hemorrhage, and neutrophil exudation within the blood vessel walls. Except for the thoracic aorta, most of these lesions usually completely heal. In the thoracic aorta the lesions form permanent intimal scars and aneurysms of varying size and number. Although spondylitis of the thoracic vertebrae is a common finding in spirocercosis, the exact pathogenesis has not been established,[5,11] but is likely associated with aberrant migration or severe periaortic inflammation secondary to aortic migration.

Aberrant migration of larvae is a fairly common occurrence in spirocercosis and may be responsible for some of the presenting clinical signs. Nodules containing worms have been found in the stomach and intestine, mediastinum, lumbar fascia, rectum, trachea, interdigital tissue, lung, thymus, diaphragm, heart, kidney, subcutis, urinary bladder, and spinal cord.

An important complication of chronic spirocercosis is esophageal neoplasia with osteosarcoma and fibrosarcoma commonly associated with *S. lupi* infection.[11] Fibrosarcoma generally develop in dogs younger than 2 years of age and osteosarcoma in dogs older than 5 years of age. In a recent study of 15 cases, nine were diagnosed with osteosarcoma, five with fibrosarcoma, and one with an undifferentiated sarcoma.[15]

Clinical Signs

The clinical signs of spirocercosis vary greatly, depending upon the stage of disease, presence of aberrant migrations, and clinical complications. A dog with uncomplicated infection may be subclinical, or show mild to moderate signs of vomiting, regurgitation, weight loss, polypnea, dysphagia, and head and neck extension.[3] Complicated cases more typically result from normal or aberrant nematode migration. The normal migration route along the gastroaortic arterial system may result in either rupture of the aorta, causing hemothorax and acute death, or of other major blood vessels, resulting in the development of large hematomas.[1,11] Migration through the wall of the aorta to the esophagus may result in mediastinitis, pneumomediastinum, pleuritis, or pyothorax.[1] Sialadenitis and hypertrophic osteopathy have also been reported in association with *S. lupi* nodules. Concurrent or secondary bacterial infection may lead to discospondylitis,[10,11] septic polyarthritis,[1] endocarditis, and interstitial nephritis.[16]

Other nonspecific clinical signs associated with *S. lupi* are fever and mild peripheral lymphadenopathy.[1,3] Aberrant migration may result in a spectrum of clinical signs but the most common presentations include respiratory, neurologic, and musculoskeletal signs.[1] Reported complications of spirocercosis include aortic thromboembolism, aberrant migration to the vertebral canal, secondary megaesophagus, hemopericardium, esophageal obstruction or perforation, and gastroesophageal intussusception.

Diagnosis

Diagnosis of spirocercosis is based on finding *Spirocerca* eggs on fecal flotation, and pertinent diagnostic imaging, esophageal endoscopic, and necropsy findings. One study showed a 100% sensitivity of endoscopy compared to 80% sensitivity for fecal flotation and 53% sensitivity of survey radiography in the diagnosis of spirocercosis.[3]

Fecal flotation

S. lupi eggs are small (35 × 15 μm), thick shelled, and larvated. There are several factors that can affect the results of fecal flotation, including egg passage occurs for a relatively short period in the lifespan of the worm and is thus unpredictable; eggs will be present in the feces only if the female has a patent passage to the esophageal lumen; and eggs are difficult to detect with routine flotation techniques using sugar and salt solutions. Results of fecal flotation can be improved by using either the modified Stoll or sugar flotation technique, and with sodium nitrate or zinc sulfate flotation solutions.[17] Diagnostic accuracy can also be improved with multiple fecal flotations.[3]

Diagnostic Imaging

Radiography should be the initial diagnostic test of choice and a caudal esophageal mass may be seen on survey thoracic radiographs.[1] *Spirocerca*-associated masses are best seen on ventrodorsal or dorsoventral views as a single midline soft-tissue opacity superimposed on the caudal cardiac border and diaphragmatic cupula. *Spirocerca*-associated masses are less frequently observed on lateral views where they are located dorsally to the caudal vena cava. A right lateral recumbent view is preferable as the normal esophagus is usually not

seen on this view.[18] Mineralized opacities within the mass are often an indication of neoplastic transformation.

On the lateral thoracic radiograph, spondylitis of the ventral borders of the caudal thoracic vertebra (T5 to T12) may be evident as a lamellar, thick, brush-like or solid periosteal reaction filling up the ventral surface of the vertebral body, giving it a rectangular or even bulging appearance. Aortic mineralization secondary to small aneurysms may occasionally be seen on the lateral view,[1,3] as mineralized streaks on the dorsal or ventral edge of the thoracic aorta.

The diagnostic accuracy of survey radiography can be improved by utilizing either positive contrast radiography or pneumoesophagography. Using barium contrast, a spirocercosis lesion appears as a dorsal esophageal mural filling defect. Disease complications detected on radiographs include tracheal or bronchial displacement or compression, pleural effusion, pulmonary metastases, mediastinitis, pneumothorax, pneumomediastinum, and hypertrophic osteopathy.[1]

Computed tomography may be helpful in delineating the esophageal mass; evaluating the extent of the lesion; identifying presence of vertebral, pleural, mediastinal and pulmonary pathology; and assessing lesions and aortic mineralization.

Esophageal Endoscopy

Endoscopic findings in *S. lupi* infection vary depending on the progression of the disease. In early infection, one or several smooth rounded nodules may be evident in the caudal esophagus. Over time, nodules become large and lobulated, cauliflower-like masses, which can obliterate the esophageal lumen. These masses are often ulcerated and friable and can bleed easily if traumatized by the endoscope. In advanced cases it is often difficult to determine the extent of the disease as the mass hampers complete visualization of the esophagus. In some cases the mass may be extraluminal (intramural or mediastinal) and the only abnormality visualized is a bulging from within the esophageal wall. In some cases, reflux esophagitis may be evident.

The results of endoscopically performed biopsies are usually unrewarding because either the intact stratified squamous epithelium of the esophageal mucosa resists biopsy efforts or with ulcerated lesions, the biopsy often does not often include diagnostic tissue.

Clinical Pathology

In early disease a normocytic normochromic anemia may be evident, whereas a microcytic hypochromic anemia is more likely in dogs with advanced disease and severe esophageal hemorrhage.[15] Mild anemia will be present in at least 50% of cases.[3,15] Leukocytosis and monocytosis are relatively common whereas eosinophilia is an uncommon finding.[3] There are no typical serum biochemical changes in dogs with early disease other than a mildly elevated serum creatine kinase. Increases in serum alkaline phosphatase, creatine kinase, amylase, and lactate dehydrogenase have been reported in cases with advanced disease.[15]

An immunofluorescence antibody test with 100% sensitivity and 80% specificity for *S. lupi* has been reported,[19] although further testing is needed.

Medical Therapy

Anthelmintic drugs that have been used for the treatment of spirocercosis include diethylcarbamazine, disophenol, ivermectin, and doramectin.

The only anthelmintic drug with proven efficacy against *S. lupi* is disophenol. The drug kills adult worms within the nodules but has no effect against juveniles. Unfortunately, the drug is no longer commercially unavailable. Diethylcarbamazine can be effective in ameliorating the clinical signs of vomiting and regurgitation in dogs with esophageal nodules. Although the drug results in a clinical improvement, it only suppresses egg shedding but has no effect on the adult worm.

A combination of nitroxynil (10 mg/kg) and ivermectin (1000 µg/kg) administered subcutaneously was reported to be successful in treating 81.6% infected dogs.[20] Mylonakis[21] reported that by using two doses of ivermectin at 600 µg/kg, administered subcutaneously, 2 weeks apart, in combination with oral prednisolone (0.5 mg/kg BID for 2 weeks followed by dose tapering) promoted nodular regression in five of eight animals with natural *S. lupi* infection.

Doramectin, a macrocyclic lactone, has good clinical efficacy against spirocercosis. Berry[22] reported that 200 µg/kg of doramectin injected subcutaneously at 14-day intervals for three treatments was effective in treating spirocercosis in five of seven infected animals. The two dogs with incomplete resolution were treated with doramectin at 500 µg/kg PO daily for an additional 6 weeks, which resulted in complete resolution. Lavy[23] reported a treatment protocol of 400 µg/kg of doramectin injected subcutaneously every 14 days for six treatments, followed by monthly dosing until resolution of the parasitic nodule. The author's current treatment regimen is 500 µg/kg doramectin given PO daily for 6 weeks and followed up with repeat esophagoscopy to ensure resolution of the nodules. Therapy is continued until there is endoscopic resolution of the nodules.

The use of doramectin to treat *S. lupi* in dogs is extralabel usage in most countries as it is only licensed for use in cattle, pigs, and sheep. However, in experimental studies, dogs given a daily dose of more than 500 µg/kg for 91 days showed only mild, transient, and reversible side effects. The drug is highly lipophilic with a half-life of approximately 3 days and a mean tissue residence time of approximately 5 days in the dog.[24] A breed-specific toxicity has been reported in certain Collies and other herding dog breeds following the use of both ivermectin and doramectin. Toxicities are likely a result of a mutation in the MDR1-1Δ gene and its ability to express the protective P-glycoprotein pump.

Surgical and Chemotherapeutic Therapy

Nonneoplastic nodules usually regress with medical treatment. Surgery is required only in cases of nodular neoplastic transformation. In a recent study,[15] 10 of 15 dogs with esophageal sarcomas underwent surgery, six of which had partial esophagectomies, two had esophageal resection, one had gastrostomy, and one had a lesion too extensive to for surgical resection. The survival times in the six dogs with the partial esophagectomy and medical treatment with doxorubicin and doramectin averaged 267 days. The outcome for the cases with resection was very poor with the dogs surviving only 3 and 4 days, respectively. Doxorubicin was used as adjuvant antineoplastic therapy in five cases, but conclusions could not be drawn regarding efficacy. Currently, there are no data available on the effectiveness of chemotherapy in the treatment of spirocercosis-associated esophageal sarcomas.

Prevention

Disease incidence can be reduced by disposal of feces, preventing dogs from hunting, scavenging and eating uncooked viscera, and decreasing egg shedding by infected animals. Control of intermediate and transport hosts is not a feasible form of control due to the variety and ubiquity of hosts in an endemic area. A study by Lavy[25]

to evaluate the prophylactic effect of doramectin showed that treatment with 400 µg/kg 30 days prior to exposure to infective larvae delayed the development of parasitic nodules in the esophagus, resulted in fewer nodules, and delayed egg shedding. Unfortunately this study did not address ongoing prophylaxis in endemic areas, as the dogs were not treated again during the trial period nor were they further exposed to infective larvae.

Oomycetes

P. insidiosum, a primary pathogen of plants and animals occurs in stagnant fresh water and dogs are infected when they come in contact with the zoospores. Chronic esophagitis caused by *P. insidiosum* has been reported in two dogs that showed clinical signs of hypersalivation, dysphagia, and weight loss.[26] Regional esophagitis was evident in both dogs on esophagoscopy but the diagnosis was only made on postmortem examination. *Lagenidium giganteum* has been reported to induce a hilar lymphadenitis with invasion of the distal esophagus in the dog.[27] The diagnosis was made on histopathology, with the lesions similar to those associated with pythiosis and zygomycosis. The organism was confirmed on both serology and culture.

Bacteria

Helicobacter pylori have been recovered from the esophagus of gnotobiotic Beagle pups that were infected with the bacteria. These Beagles developed gastritis and were positive for serum immunoglobulin G specific for *H. pylori*.[28] *Helicobacter*-induced gastritis is an established syndrome in dogs and cats (see Chapter 56), but esophagitis is probably subclinical.

Viral

Canine distemper virus inclusions can be identified in the cytoplasm of the esophageal epithelium,[29] which is part of the general systemic infection of the disease. Therefore, distemper can result in esophagitis following mucosal damage, which can contribute to the clinical signs of the disease.

Using immunofluorescence and histological techniques parvovirus inclusions have been found in the tunica muscularis of the esophagus with esophageal erosions and ulceration in both dogs and cats affected with the disease.[30] The esophagitis can thus contribute to the clinical signs of the disease.

OBSTRUCTION

Robert J. Washabau

Esophageal Stricture

Etiology

Esophageal stricture is a pathologic narrowing of the esophageal lumen. Congenital esophageal strictures have been reported,[1] but most strictures are acquired as a result of chemical injury from swallowed substances, traumatic injury from esophageal foreign bodies, gastroesophageal reflux and esophagitis following anesthetic procedures, complications of esophageal surgery, and intraluminal or extraluminal mass lesions (neoplasia or abscesses).[2]

Box 55-1 Poiseuille's Equation

$$\text{Flow} = \frac{\Delta P}{8} \cdot \frac{\pi}{\eta} \cdot \frac{r^4}{L}$$

ΔP = Change in pressure along the length of the tube; r = radius of the tube; η = viscosity of the fluid; L = length of the tube.

Pathophysiology

Anesthesia, poor patient preparation, and poor patient positioning during anesthesia place some animals at risk for gastroesophageal reflux, esophagitis, and subsequent stricture formation.[3-5] Cats appear to be particularly susceptible to doxycycline-associated esophagitis and esophageal stricture.[6-8] Fibrosis and mass compression are the most important pathogenetic mechanisms involved in stricture formation.

Laminar flow through a cylindrical tube, which is governed by the Poiseuille equation,[2] is directly related to the fourth power of the radius and the pressure change across the tube, and inversely related to the fluid viscosity and the length of the tube (Box 55-1). Because flow rates change exponentially with luminal radius, even small reductions in luminal diameter result in significant reductions in esophageal flow.

Clinical Signs

The clinical signs of progressive regurgitation and dysphagia are related to severity and extent of the stricture.[2,3] At the outset, the animal's appetite is unaffected. As the disease progresses, regurgitation occurs shortly after feeding, and the animal may attempt to reingest the regurgitated meal. An important clinical sign is that liquid meals are often better tolerated than solid meals. With progressive esophageal narrowing and inflammation, affected animals develop complete anorexia, weight loss, and malnutrition. Some animals also develop aspiration pneumonia. The physical examination is remarkable for salivation, cachexia, and malnutrition. Pulmonary signs (wheezes and cough) may be detected in animals affected with aspiration pneumonia.

Diagnosis

As with other esophageal disorders, the diagnosis is based on clinical history and radiographic and endoscopic findings (Figure 55-5). Intraluminal or extraluminal mass lesions may be evident on survey radiographs in animals with compressive esophageal stricture. Survey radiographs are usually unremarkable in animals with benign fibrosing strictures. Segmental or diffuse narrowing observed with barium contrast radiography is usually diagnostic of the disorder. There may also be some esophageal dilation proximal to the stricture site. Ultrasonography has not proved useful in diagnosing benign fibrosing strictures, but may be useful in diagnosing those caused by mass compression. Mediastinal and other periesophageal lesions have been successfully aspirated with ultrasound guidance. Endoscopy should be performed in all animals to confirm the site and severity of stricture, and to exclude the possibility of intraluminal malignancy and foreign body. Benign fibrosing strictures must be differentiated from vascular ring anomaly, esophagitis, intraluminal esophageal masses, and extraluminal periesophageal masses. These disorders can usually be differentiated with survey and contrast radiography, endoscopy, and/or thoracic ultrasonography.[9]

Treatment

Oral feedings should be withheld in cases of severe stricture. In such cases, a temporary gastrostomy tube may be placed at the time of esophageal dilation as a means of providing continuous nutritional support. Liquid meals should be used when reinstituting oral feedings. Animals may be discharged from the hospital after adequate rehydration, stabilization, dilation of the affected esophageal segment, nutritional intervention, and appropriate therapy for aspiration pneumonia. Esophageal strictures are best managed with mechanical dilation. Dilation may be achieved with balloon dilation catheters or bougienage tubes.[3,4,10,11] Esophageal tears have been reported with balloon dilation catheters, but the technology is still thought to be relatively safe in applying radial forces to the stricture site. A greater risk of perforation has been attributed to the use of bougienage tubes due to shearing forces applied by the instrument, although one report showed outcomes similar to those reported for balloon dilation.[12] Table 55-2 outlines the parameters needed for a successful balloon dilation. Multiple redilations at 1- to 2-week intervals may be necessary until the stricture is resolved.[3,4,13,14] Esophageal dilation is best performed with direct observation at the time of endoscopy, but it could be performed with videofluoroscopy.

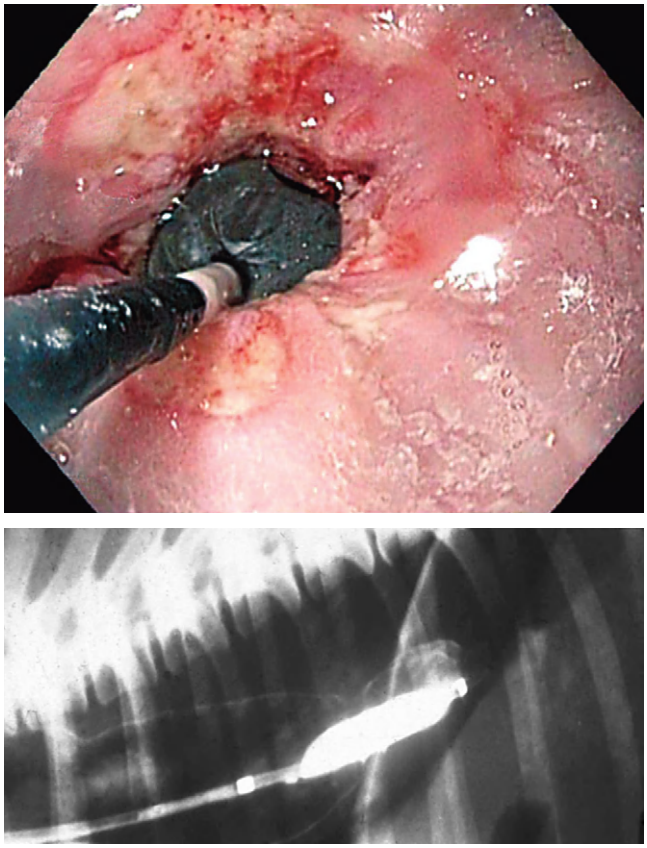

Figure 55-5 Inflammation, hemorrhage, and stricture of the esophagus in a 10-year-old dog undergoing balloon dilation.

Medical therapies aimed at treating the inflammatory component of this lesion are best used as adjunctive therapy to mechanical dilation.[2,9] Animals with concurrent esophagitis should be treated with oral sucralfate suspensions (0.5 to 1.0 g PO, TID) and gastric acid secretory inhibitors (cimetidine 5 to 10 mg/kg PO or IV, TID-QID; ranitidine 1 to 2 mg/kg PO or IV, BID-TID; famotidine 0.1 to 0.5 mg/kg PO or IV BID; or omeprazole 0.7 mg/kg PO, SID) or esomeprazole, lansoprazole, or pantoprazole at a dose of 1.0 mg/kg IV SID. Antiinflammatory doses of corticosteroids (e.g., prednisone 0.5 to 1.0 mg/kg PO or IM, BID) have been advocated to prevent fibrosis and restricture during the healing phase following esophageal dilation. It has been further suggested that intralesional steroid injections (e.g., 1 mg triamcinolone) administered at the time of stricture dilation may be beneficial in reducing the risk of recurrence.[4,15] Corticosteroid therapy should be used with caution if the esophageal mucosa is already ulcerative and/or devitalized as a consequence of the disease or of balloon dilation.

Surgical resection of esophageal stricture and reanastomosis has been reported, but resections may be complicated by inadequate surgical exposure, lengthy resections, tension on the anastomosis, and poor healing properties of the thoracic esophagus.[2] Omentopexy may improve vascularization and reduce stricture formation following esophageal anastomosis.[16] Surgical failures may subsequently be treated with intestinal interposition whereby a segment of the

Table 55-2 Strategies for Balloon Dilation Treatment of Esophageal Strictures

Intervention	Rationale	Implementation
Barium swallow	Determine location, length, and number of strictures	Barium suspension, 30% w/v
General anesthesia	High-pressure esophageal dilation stimulates visceral pain	Inhalant anesthesia, e.g., sevoflurane, isoflurane
Patient positioning	Inspection of esophagus and stomach poststricture dilation	Left lateral recumbency for maximal maneuverability
Endoscopes	Direct observation, balloon placement, postdilation trauma	7.5- to 8.5-mm insertion tube, 2.8-mm biopsy channel
Balloon dilation catheters	Multiple catheter lengths and balloon diameters	8 mm × 8 cm to 18 mm × 8 cm balloon catheters*
Procedure	Repeated balloon dilations to achieve increase in luminal diameter	1 to 3 cycles of balloon inflation and deflation/procedure
Manometry	Monitoring of inflation and deflation pressures	Vacuum to 160 psi pressure gauges
Gastrostomy tube placement	Nutritional maintenance during recovery phase with severe strictures	Low-profile gastrostomy tube systems
Recovery phase	Protect esophageal mucosa, inhibit acid secretion, promote healing	Sucralfate, H_2 histamine receptor antagonists
Recurrence/prevention	Most esophageal strictures require 2 to 4 successive balloon dilations	Repeat endoscopy at 13-day intervals as needed

*Sure-Flex esophageal balloon dilation catheters and Rigiflex esophageal balloon dilation catheters.

intestine is transposed to the esophageal body,[17] or by creation of a traction diverticulum.[18] Insufficient clinical experience with these techniques warrants caution before adopting them as best practice standards. Patients refractory or unresponsive to balloon dilation, may instead benefit from placement of a nitinol stent with or without drug elution (e.g., paclitaxel).[19,20] Although still relatively experimental, nitinol stents have been maintained for long periods of time with minimal tissue reactivity or worsening of esophageal compliance or biomechanics.[20] Future therapy may be based on principles of regenerative medicine[21-23] in which extracellular matrix scaffolds and autologous muscle tissue are used to prevent stricture recurrence.[21-23]

Prognosis

Strictures associated with foreign body ingestion or esophagitis have a fair to guarded prognosis. Multiple dilations are often required to achieve an adequate esophageal lumen (see Table 55-2).[14] Esophageal perforation is a potentially life-threatening complication of esophageal stricture dilation. Perforations usually occur at the time of esophageal dilation, although they have been observed several days to weeks afterward. Malignant strictures have a poor prognosis. Surgical resection is often the only possible recourse.

Hiatal Hernia

Etiology

Three types of hiatal hernia have been recognized in the dog and cat: (a) type I, which is the sliding hiatal hernia, in which the abdominal segment of the esophagus and parts of the stomach are displaced cranially through the esophageal hiatus, and (b) type II, which is the paraesophageal hiatal hernia, in which the abdominal segment of the esophagus and caudal esophageal sphincter remain in a fixed position but a portion of the stomach herniates into the mediastinum alongside the thoracic esophagus.[2,9,24] One case of a type IV esophageal hiatal hernia has been reported in which the liver, stomach, and small intestine were displaced into the thorax.[25]

Pathophysiology

Sliding hiatal hernia is the most common form and may occur as a congenital or acquired lesion in the dog and cat. Congenital sliding hiatal hernias have been reported in the Chinese Shar-Pei, Chow, English Bulldog, and French Bulldog breeds.[9] The hernia results from incomplete fusion of the diaphragm during early embryonic development. Affected animals develop clinical signs shortly after weaning.[24,26,27]

Acquired hiatal hernia may occur in any breed of dog or cat. The pathogenesis of acquired hiatal hernia is incompletely understood, but may result from chronic increases in intraabdominal pressure with chronic vomiting disorders, or from chronic increases in negative intrathoracic pressure in animals with intermittent airway obstruction.[2,28,29]

Clinical Signs

Regurgitation, vomiting, and hypersalivation are the most important clinical signs in congenital hiatal hernia. Regurgitation and hypersalivation result from the chemical effects of gastric fluid (e.g., H^+ and pepsins) on the esophageal mucosa, while vomiting may result from the obstructive effects of the hernia.[24] Dyspnea and coughing may also occur with severe obstruction and/or aspiration pneumonia. The physical examination findings are usually unremarkable but may include dehydration, pulmonary crackles or wheezes, and decreased body weight. Clinical findings are usually similar, but less severe, in animals with acquired hiatal hernia; these animals may have inspiratory stridor associated with laryngeal paralysis.

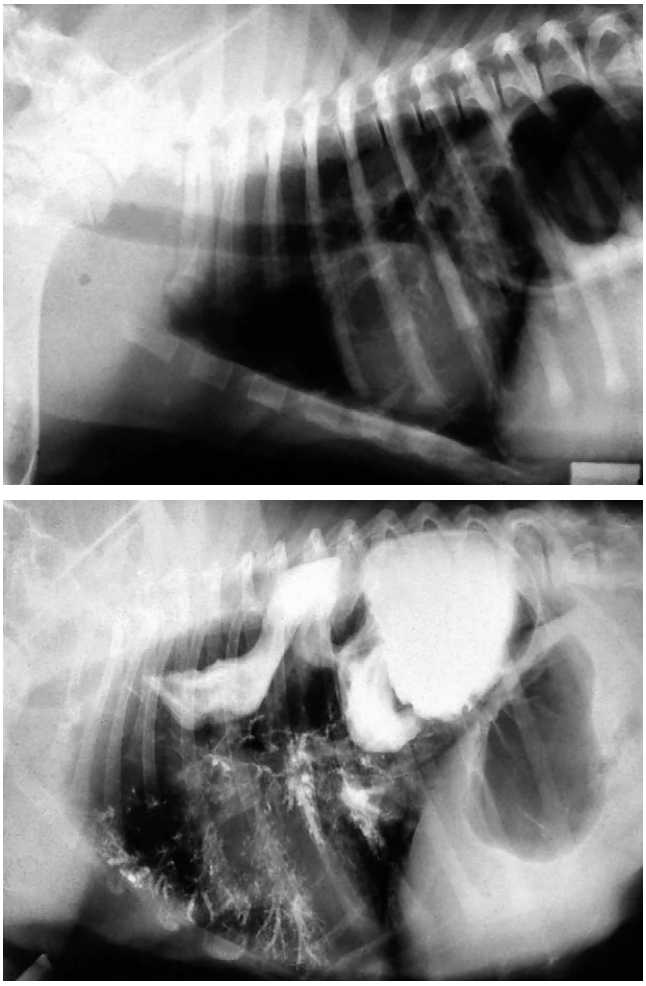

Figure 55-6 Congenital esophageal hiatal hernia in a 3-month-old Chinese Shar-Pei puppy.

Diagnosis

The survey radiographic finding of a caudodorsal gas-filled intrathoracic soft-tissue opacity is consistent with the diagnosis of hiatal hernia (Figure 55-6).[24] Affected animals may have concurrent esophageal dilation and dependent alveolar consolidation consistent with aspiration pneumonia. Barium contrast studies will confirm the diagnosis and further delineate esophageal dilation and hypomotility. Videofluoroscopy should always be performed if a hiatal hernia is suspected but not proved by survey radiographs. Endoscopic findings consistent with the diagnosis include cranial displacement of the caudal esophageal sphincter and a large esophageal hiatus. Because young animals with congenital hiatal hernia have varying degrees of esophageal dilation, a misdiagnosis of congenital idiopathic megaesophagus could be made if herniation at the hiatus is not readily apparent. Therefore, the finding of esophageal dilation in a young Shar-Pei or other breed should raise a high index of suspicion of an underlying hiatal hernia.[24,26] Gastroesophageal reflux, gastroesophageal intussusception, epiphrenic diverticulum, and diaphragmatic hernia are the other major differential diagnoses for hiatal hernia.

Treatment

A sliding hiatal hernia (type I) is not always associated with clinical signs, particularly the acquired form of the disease.[2,9] When animals develop clinical signs, medical therapy should be attempted first. Medical therapy is similar to that for gastroesophageal reflux and should be directed at reducing gastric acid secretion (e.g., H_2 receptor antagonism, H^+,K^+-ATPase inhibition), restoring the health of the esophageal mucosa (e.g., sucralfate), and increasing the tone of the gastroesophageal sphincter (e.g., metoclopramide, erythromycin, or cisapride). Many acquired sliding hiatal hernias will respond to conservative medical therapy alone,[27] although laryngeal surgery (e.g., partial laryngectomy or lateralization of the vocal folds) should be considered if laryngeal paralysis has contributed to the pathogenesis of the hernia. Congenital hiatal herniae often require surgical correction. Diaphragmatic crural apposition, esophagopexy, and gastropexy are usually sufficient to restore normal hiatus anatomy.[24,30] Fundoplication procedures may be performed but are generally not necessary.[24,30-32]

Prognosis

The prognosis for surgical correction is generally favorable. Animals have few if any clinical signs following restoration of the normal anatomy.

Esophageal Foreign Bodies

Etiology

Esophageal foreign bodies are a frequent clinical problem in dogs and cats. The most common esophageal foreign bodies found in dogs are bones, bone fragments, and coins, whereas play objects are more commonly found in cats.

Pathophysiology

Many foreign bodies are regurgitated or transported into the distal gastrointestinal tract, but others remain lodged in the esophageal body. Those that are too large to pass through the esophagus cause mechanical obstruction. The severity of esophageal damage is dependent upon foreign body size, angularity or sharp points, and the duration of obstruction.[2,33-36]

Clinical Signs

In many cases there is a history of foreign-body ingestion. Some cases go unnoticed, however, particularly those associated with garbage ingestion. The onset of clinical signs will depend upon the severity of esophageal obstruction. Animals with complete esophageal obstruction are often presented with acute signs, whereas animals with incomplete obstruction may be presented with clinical signs persisting for days or weeks. Relevant clinical signs include regurgitation, excessive salivation, odynophagia, anorexia, dysphagia, and retching. In severe cases, hematemesis and respiratory distress may predominate.

Diagnosis

Bone foreign bodies can occasionally be palpated if they become lodged in the cervical esophagus, but definitive diagnosis usually requires radiographic studies. Radiodense foreign bodies can be detected with survey radiography (Figure 55-7), but confirmation of radiolucent foreign bodies will require administration of contrast agents. Iodine contrast agents should be used instead of barium to avoid barium pleuritis if esophageal perforation is suspected. Foreign bodies may subsequently be confirmed and removed during endoscopy. A tentative diagnosis of esophageal foreign body may be made in animals presented with esophageal signs following a history of foreign-body ingestion. Without a compatible history, the most important differential diagnoses would include esophageal stricture, neoplasia, hiatal hernia, and gastroesophageal intussusception. Each of these conditions can be differentiated with radiography and/or endoscopy.

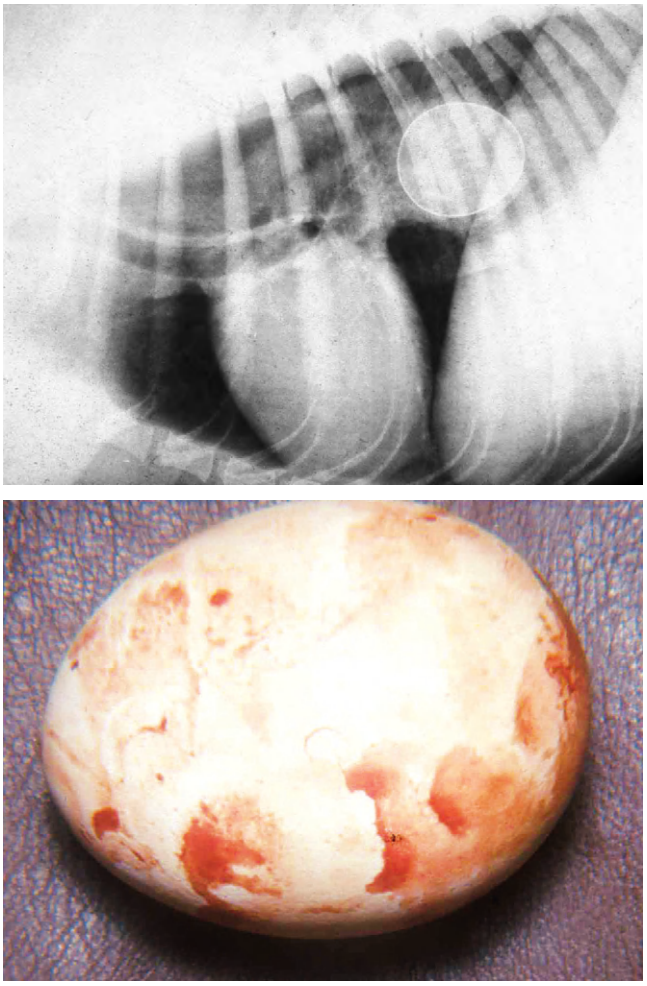

Figure 55-7 Esophageal foreign body in a 9-year-old dog.

Treatment

Esophageal foreign bodies should be removed promptly. Prolonged retention increases the likelihood of esophageal mucosal damage, ulceration, and perforation. Rigid or flexible fiberoptic endoscopic retrieval should be the initial approach to treating an esophageal foreign body although fluoroscopic-guided retrieval is also possible.[36] A rigid endoscope is most useful in retrieving large foreign bodies, particularly bones or bone fragments.[33] Large grasping forceps are passed through the rigid endoscope to retrieve the foreign body, and in many cases, the foreign body can be pulled into the endoscope for safe removal. Large foreign bodies that cannot be safely removed through the mouth can occasionally be pushed into the stomach and removed by gastrotomy. Smaller foreign bodies are best managed with a flexible fiberoptic endoscope and basket, tripod, or snare retrieval forceps.[34] Flexible endoscopes are particularly useful in retrieving fish hooks.[35]

Affected animals should be fasted for 24 to 48 hours after foreign-body removal. Longer periods of fasting may be required if the esophagus is necrotic or ulcerative. In the latter circumstance, animals may instead be fed through a gastrostomy tube placed at the time of endoscopy. Specific therapy for esophagitis should include oral sucralfate suspensions (0.5 to 1.0 g PO, TID).[37] Suspensions of sucralfate are more therapeutic than intact tablets. Antiinflammatory doses of glucocorticoids (e.g., prednisone 0.25 to 0.5 mg/kg PO, BID) should also be considered in those animals at risk for esophageal stricture. The risk of esophageal stricture is greatest in animals with 180-degree or greater transmucosal ulceration. Finally, broad-spectrum antibiotics should be considered in animals with severe ulceration and/or small perforations.

Surgery is indicated if endoscopy fails or if there is evidence of esophageal perforation. Gastrotomy is preferred to esophagotomy for distal esophageal foreign bodies because of the poorer healing properties of the esophagus and the potential for stricture formation. However, esophagotomy would certainly be indicated in those cases where the foreign body could not be removed through gastrotomy. Surgery is also indicated to repair esophageal perforation.

Prognosis

The prognosis for most esophageal foreign bodies is generally good, especially if they are removed immediately. A worse prognosis is associated with foreign bodies that are large, have sharp points, or are retained for a prolonged period of time. Immediate complications include complete obstruction or laceration, whereas late complications include perforation, hemothorax, fistulation, and diverticula or stricture formation.[9,38]

Vascular Ring Anomalies

Etiology

Vascular ring anomalies are congenital malformations of the major arteries of the heart that, because of altered anatomic relationships, entrap the esophagus and trachea. Persistent right aortic arch, persistent right or left subclavian arteries, persistent right dorsal aorta, double aortic arch, left aortic arch and right ligamentum arteriosum, and aberrant intercostal arteries have been described in both dogs and cats.[39,40]

Pathophysiology

Persistent right aortic arch is the most common vascular ring anomaly found in dogs and cats. Circular compression of the esophagus by the right fourth aortic arch results in physical obstruction of the esophagus and/or trachea. The anomaly is considered to be a familial disease with evidence of a hereditary basis in German Shepherds.[41] Aberrant subclavian arteries are the second most common vascular ring anomaly.[9] The latter anomalies result in significant esophageal compression from the left subclavian artery and brachycephalic artery.

Clinical Signs

Affected puppies and kittens are presented at a young age with the major complaints of regurgitation and failure to thrive. Animals usually do well until weaning. With the transition to solid food, progressive regurgitation ensues. Aspiration pneumonia develops in some animals as a result of constant regurgitation, but signs of tracheal compression are uncommon. Physical examination most often reveals a thin, stunted animal that is apparently malnourished but normal in other respects. Occasionally, a dilated esophagus can be observed or palpated in the cervical region.

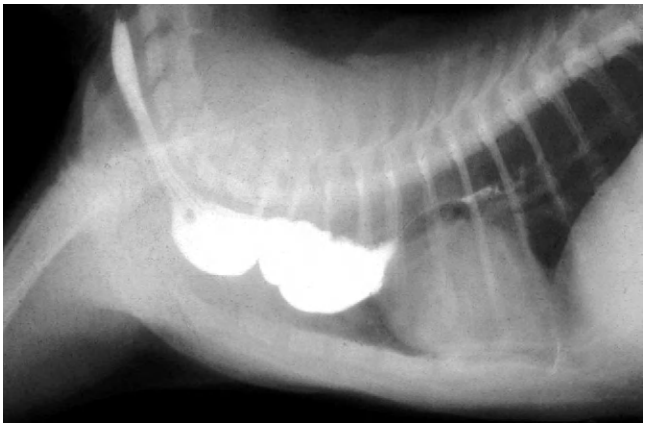

Figure 55-8 Persistent right aortic arch in a 3-month-old Persian kitten.

Diagnosis

Laboratory findings are usually normal. As with other esophageal disorders, regenerative neutrophilia may be associated with aspiration pneumonia, and hypoproteinemia may be associated with malnutrition. The diagnosis of a vascular ring anomaly is based upon a compatible history and the barium contrast radiographic finding of esophageal body dilation cranial to the base of the heart (Figure 55-8); a proximal diverticulum occasionally forms with longstanding untreated vascular ring anomalies. The caudal esophagus usually appears normal but there might be a mild dilation with reduced motility. Angiography is occasionally performed to clarify complex or atypical vascular ring anomalies, or to determine the best surgical approach. Endoscopy can be performed to differentiate intraluminal stricture from extraluminal compression. With vascular ring anomaly, pulsations of the major arteries can be observed in the region of esophageal narrowing. Furthermore, vascular ring anomalies occur at the base of the heart, whereas intraluminal strictures can occur in any segment of the esophageal body. The most important differential diagnosis for vascular ring anomaly is intraluminal stricture. Strictures resulting from ingestion of foreign bodies or chemical irritants, or from malignancy, are more common in adult animals.

Treatment

Vascular ring anomalies are best treated by conventional thoracotomy or interventional thoracoscopy.[42,43] Persistent right ductus arteriosus, aberrant right subclavian artery, and double aortic arch are all best managed by right intercostal approach, whereas persistent right aortic arch is best managed by a left intercostal approach. Ligation and division of the ligamentum arteriosum is the recommended therapy in cases of persistent right aortic arch.[42,43] If possible, periesophageal fibrosis should be reduced, and the stricture site should be dilated intraluminally with a balloon dilation catheter.[9] Other techniques to resect, reduce, or replace the redundant esophagus have not proven beneficial.

Some animals may have persistent esophageal hypomotility and clinical signs following corrective surgery. These animals may benefit from elevated feedings. Metoclopramide may be of some benefit in cats with esophageal motility disorders, but only those confined to the smooth muscle of the distal esophageal body.[9,44]

Prognosis

The best outcomes are obtained with early diagnosis and early surgical intervention. In undiagnosed cases, progressive esophageal

dilation causes irreversible myenteric nerve degeneration and esophageal hypomotility, but at least one study suggests that a 90% or greater recovery rate can be expected.[42] Clients should be informed that, although surgical correction is the preferred treatment, clinical signs may persist after surgery.

Gastroesophageal Intussusception

Etiology

Gastroesophageal intussusception is a rare condition of young dogs (most younger than 3 months of age) resulting from invagination of the stomach into the esophagus, with or without other abdominal organs, for example, spleen, duodenum, pancreas, and omentum.[45] The disorder is more common in males than in females, with a higher incidence reported in the German Shepherd breed.

Pathophysiology

Many affected animals have preexisting esophageal disease, most importantly idiopathic generalized megaesophagus. The role of idiopathic megaesophagus in the pathogenesis of gastroesophageal intussusception is incompletely understood, but it's likely that the greatly enlarged capacity of a dilated esophagus accommodates the invagination of the stomach through the diaphragmatic hiatus. Some gastroesophageal intussusceptions have been reported in association with hiatal hernia in young puppies.[46] Gastroesophageal intussusception is a true gastrointestinal emergency that may culminate in the death of the animal if untreated.

Clinical Signs

The initial clinical signs are vomiting or regurgitation, dyspnea, hematemesis, and abdominal discomfort. If diagnosis and therapy are delayed, these clinical signs are rapidly followed by marked deterioration in condition, shock, respiratory and cardiac arrest, and death.

Diagnosis

Survey radiographs will reveal proximal esophageal dilation, consolidation or mass effect between the cardiac silhouette and the diaphragm, and gastric rugal folds within the intrathoracic esophagus (Figure 55-9). Contrast radiographic studies usually reveal that the column of barium traverses the proximal esophageal body, but does not enter the distal esophagus or stomach. Endoscopy will confirm an intra-esophageal mass that completely obstructs the lumen of the esophagus. The major differential diagnoses are hiatal hernia, epiphrenic diverticulum, and diaphragmatic hernia. It is sometimes difficult to distinguish these entities from gastroesophageal intussusception. Because the defining characteristic of a gastroesophageal intussusception is the invagination of the stomach into the esophagus, gastric rugal folds are often readily identified within the lumen of the esophagus on survey or contrast radiographs.

Treatment

The recommended therapy is a brief period of stabilization followed by definitive endoscopic or surgical reduction.[45-47] After reduction of the intussusception, a gastropexy should be performed to prevent recurrence. If disease of the esophageal hiatus is involved in the pathogenesis of the intussusception, restorative surgery (e.g., diaphragmatic crural apposition) should also be performed.

Prognosis

The prognosis is poor unless the disorder is quickly recognized and treated. Mortality rates have been reported in excess of 95%.[45]

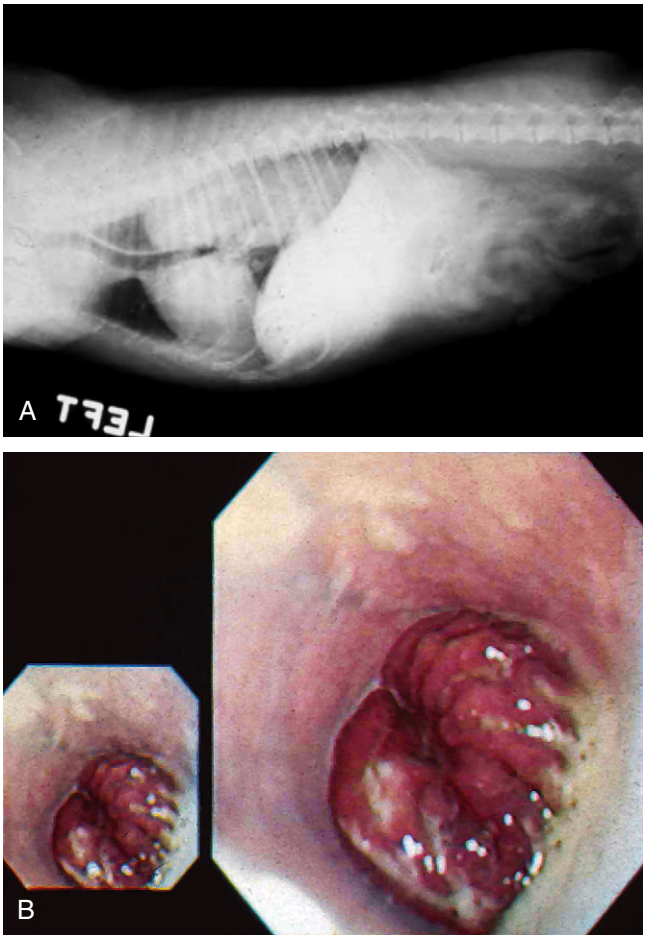

Figure 55-9 **A,** Radiographic appearance of a gastroesophageal intussusception in a 12-month old mixed-breed dog. **B,** Endoscopic appearance of a gastroesophageal intussusception in a 12-month old mixed-breed dog. (Courtesy of Dr. Kenneth Simpson, Cornell University, Ithaca, NY.)

DYSMOTILITY

Robert J. Washabau

Esophageal dysmotility is a primary motility disorder of the esophagus characterized by reduced esophageal peristalsis, food retention, and regurgitation. It is not necessarily accompanied by esophageal dilation or permanent megaesophagus, and therefore is not referred to as idiopathic megaesophagus. Esophageal dysmotility has been reported in young dogs as a consequence of delayed maturation,[1-7] muscular dystrophy,[8,9] myasthenia gravis,[10] inflammatory myopathy,[11,12] transient dysfunction following anesthetic episodes,[13] and breed-specific abnormalities.[14]

Therapy is primarily supportive and follows therapy outlined for idiopathic megaesophagus (Table 55-3). The prognosis for esophageal dysmotility is generally more favorable than it is for idiopathic megaesophagus.

Idiopathic Megaesophagus

Etiology

The term idiopathic megaesophagus refers to concurrent esophageal dysmotility and dilation of unknown etiology, and is the most common cause of regurgitation in the dog.[15,16] Aside from

dysautonomia, megaesophagus is an uncommon finding in the cat. The canine disorder is characterized by progressive regurgitation, aspiration pneumonia, and loss of body condition. Several forms of the syndrome have been described, including congenital, acquired secondary, and acquired idiopathic megaesophagus (Table 55-4).[16]

Pathophysiology

Congenital idiopathic megaesophagus is a generalized hypomotility and dilation of the esophagus causing regurgitation and failure to thrive in puppies shortly after weaning. An increased breed incidence has been reported in the German Shepherd, Great Dane, Irish Setter, Labrador Retriever, Chinese Shar-Pei, and Newfoundland breeds, and autosomal dominant inheritance has been demonstrated in the Miniature Schnauzer and Fox Terrier breeds.[16] The pathogenesis of the congenital form is incompletely understood, although several studies have pointed to a defect in the vagal afferent innervation of the esophagus.[2-6,17] Primary, but not secondary, esophageal peristalsis appears to be intact in this disorder (Figure 55-10). Congenital idiopathic megaesophagus has been reported in several cats[18] and in one group of cats secondary to pyloric dysfunction.[19]

Acquired secondary megaesophagus may develop in association with a number of other conditions. Myasthenia gravis accounts for 25% to 30% of the secondary cases.[10,20,21] In some cases of myasthenia gravis, regurgitation and weight loss may be the only presenting signs of the disease, whereas in most other cases of acquired secondary megaesophagus regurgitation is but one of many clinical signs including peripheral muscle weakness. Acquired secondary megaesophagus has also been associated with hypoadrenocorticism, lead poisoning, lupus myositis, and severe forms of esophagitis.[16] Hypothyroidism has been suggested as a secondary cause of idiopathic megaesophagus but retrospective risk factor analysis has not identified it as an important cause.[15]

Acquired-idiopathic megaesophagus usually has no known underlying etiology and occurs spontaneously in adult dogs between 7 and 15 years of age with no sex or breed predilection. The disorder has been compared erroneously to gastroesophageal achalasia in humans. Achalasia is a hypertensive sphincteric disorder characterized by failure of relaxation of the LES and ineffective peristalsis of the esophageal body.[1] A similar disorder has never been rigorously documented in the dog although putative case reports are occasionally reported.[22] Several important differences between idiopathic megaesophagus in the dog and achalasia in humans have been documented.[1,2,17] Although the precise etiology has not yet been identified, some studies have suggested a defect in the afferent neural response to esophageal distention similar to what has been reported in congenital megaesophagus (see Figure 55-9).[23]

Clinical Examination

Regurgitation is the most frequent clinical sign associated with megaesophagus. The frequency of regurgitation varies from intermittent irregular episodes to multiple episodes per day. As with other esophageal disorders, affected animals suffer from malnutrition and aspiration pneumonia. Physical examination may reveal excessive salivation, mild to moderate cachexia, coughing, and pulmonary crackles or wheezes.

Table 55-3 Therapy for Canine Idiopathic Megaesophagus

Problem	Therapy
Regurgitation of food	Elevated feedings, liquid to semiliquid density
Malnutrition	High-biologic, high-energy feedings
Pulmonary infections	Broad-spectrum antibiotics
Esophageal dysmotility	Bethanechol
Esophagitis	Oral sucralfate (liquid suspension)

Table 55-4 Medical Investigation and Treatment of Canine Idiopathic Megaesophagus

Etiology	Medical Investigation	Treatment
Congenital Megaesophagus		
Myasthenia gravis	Edrophonium response ± electrophysiology	Pyridostigmine (1 to 3 mg/kg PO, BID)
Neuropathy	Esophageal manometry ± electrophysiology	Elevated, small frequent feedings; bethanechol (5 to 15 mg/dog PO TID)
Acquired Idiopathic Megaesophagus		
Neuropathy	Esophageal manometry ± electrophysiology	Elevated, small frequent feedings, bethanechol (5 to 15 mg/dog PO TID), sucralfate (0.5 to 1.0 g PO, TID), antibiotics as needed
Acquired Secondary Megaesophagus		
Myasthenia gravis	Nicotinic acetylcholine receptor antibody, edrophonium response, ± electrophysiology	Pyridostigmine (1 to 3 mg/kg PO, BID) ± prednisone (1 to 2 mg/kg PO or SC, BID)
Hypoadrenocorticism	Adrenocorticotropic hormone (ACTH) stimulation	Prednisone (0.1 mg/kg PO, BID)
Lead toxicity	Hematology, blood lead concentrations	Chelation with calcium ethylenediaminetetraacetic acid (EDTA)
Esophagitis	Esophageal endoscopy	Sucralfate (0.5 to 1.0 g PO, TID), cimetidine (5 to 10 mg/kg PO, TID), omeprazole (0.7 mg/kg PO, SID)
Hypothyroidism	Thyroid function tests	Levothyroxine (22 µg/kg PO, BID)
Dysautonomia	Clinical diagnosis	Supportive care
Polymyositis/polymyopathy	Serum creatine phosphokinase, muscle biopsy ± electrophysiology	Prednisone (1 to 2 mg/kg PO or SC, BID)
Systemic lupus erythematosus	Antinuclear antibody	Prednisone (1 to 2 mg/kg PO or SC, BID)

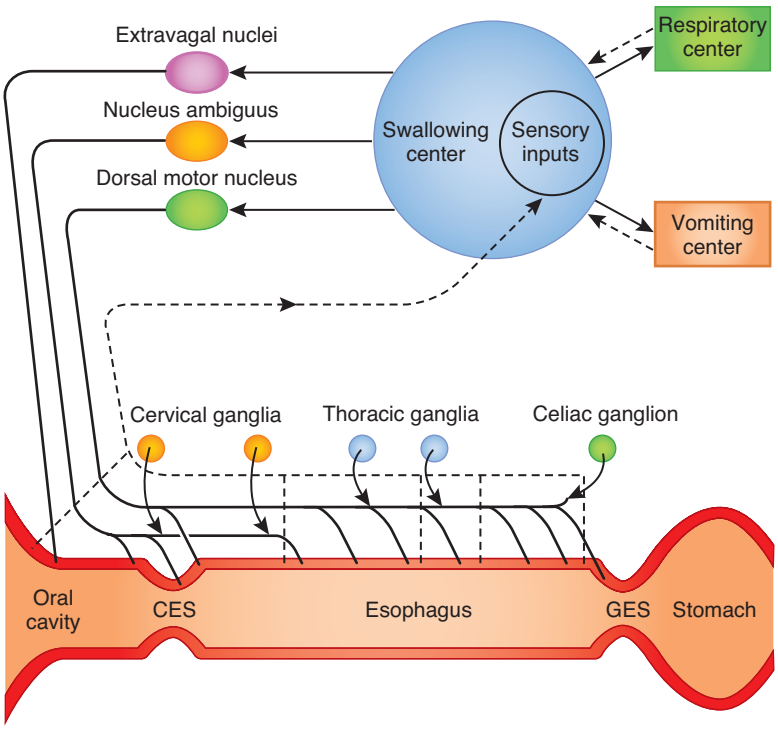

Figure 55-10 Neural regulation of swallowing in the dog and cat. Potential sites of esophageal hypomotility and megaesophagus: afferent sensory neurons, brainstem swallowing center, brainstem nuclei (dorsal motor nucleus of the vagus, nucleus ambiguus), efferent motor neurons, neuromuscular junction. The afferent neural pathway (from esophageal mucosa to brainstem) appears to be the site of involvement in both congenital and acquired idiopathic megaesophagus. *CES*, cricoesophageal sphincter; *GES*, gastroesophageal sphincter. (Reprinted with permission from Washabau RJ, Holt DE: Pathophysiology of gastrointestinal disease. In Slatter D, editor: *Textbook of Veterinary Surgery*, ed 3, Philadelphia, 2003, WB Saunders, p 532.)

Diagnosis

Routine hematology, serum biochemistry, and urinalysis should be performed in all cases to investigate possible secondary causes of megaesophagus. Survey radiographs will be diagnostic for most cases of megaesophagus (Figure 55-11), but generally do not differentiate one cause versus another.[24] Contrast radiographs may be necessary in some cases to confirm the diagnosis, evaluate motility, and exclude foreign bodies or obstruction as the cause of the megaesophagus. Endoscopy will confirm the diagnosis and may further reveal esophagitis, a frequent finding in canine idiopathic megaesophagus.[15,16] Risk factor analysis suggests that esophagitis markedly increases the risk for the development of megaesophagus.[15,16] Esophagitis could be cause or consequence of esophageal dysmotility and megaesophagus (Figure 55-12).

If acquired secondary megaesophagus is suspected (see Table 55-4), additional diagnostic tests should be considered, including serology for nicotinic acetylcholine receptor antibody, pre- and postadrenocorticotropic hormone (cortisol), serum creatine phosphokinase activity, electromyography and nerve conduction velocity, and muscle and nerve biopsy.[16] Additional medical investigation will be dependent upon the individual case presentation. Hypothyroidism has been cited as an important cause of idiopathic megaesophagus in the dog, although risk factor analysis has not revealed a clear association.[15] Thyroid function testing (e.g., thyroid-stimulating hormone [TSH] assay, TSH stimulation, free and total thyroid hormones) should be performed only in individual suspected cases.

Treatment

Table 55-4 provides an overview of therapy for canine idiopathic megaesophagus.

Animals with secondary acquired megaesophagus should be appropriately differentiated from other esophageal disorders (see Table 55-4). Dogs affected with myasthenia gravis should be treated with pyridostigmine (1 to 3 mg/kg PO BID), corticosteroids (prednisone 1 to 2 mg/kg PO or SC BID), or azathioprine (2 mg/kg PO SID initially, 0.5 to 1.0 mg/kg PO every other day). Mycophenolate has been recommended in the treatment of myasthenia gravis, but a recent report suggests that mycophenolate does not improve outcome over pyridostigmine alone.[25] Dogs affected with hypothyroidism should be treated with levothyroxine (22 μg/kg PO BID), and dogs affected with polymyositis should be treated with prednisone (1 to 2 mg/kg PO BID). If secondary disease can be excluded, therapy for the congenital or acquired idiopathic megaesophagus patient should be directed at nutritional management and treatment of aspiration pneumonia.

Affected animals should be fed a high-calorie diet, in small frequent feedings, from an elevated or upright position to take advantage of gravity drainage through a hypomotile esophagus. Dietary consistency should be formulated to produce the fewest clinical signs. Some animals handle liquid diets quite well, while others do better with solid meals. Animals that cannot maintain adequate nutritional balance with oral intake should be fed by temporary or permanent tube gastrostomy. Gastrostomy tubes can be placed surgically or percutaneously with endoscopic guidance.

Pulmonary infections should be identified by culture and sensitivity, and an appropriate antibiotic selected for the offending organism(s). This may be accomplished by trans- or endotracheal wash or by bronchoalveolar lavage at the time of endoscopy.

Smooth muscle prokinetic (e.g., metoclopramide or cisapride) therapy has been advocated for stimulating esophageal peristalsis in

affected animals, however metoclopramide and cisapride will not have much of an effect on the striated muscle of the canine esophageal body.[26-28] Esophageal 5-HT_4 receptors are present in many animal species, but are apparently absent in canine esophageal striated muscle.[26] Bethanechol (5 to 15 mg/dog PO TID) has been shown to stimulate esophageal propagating contractions in some affected dogs and is therefore a more appropriate prokinetic agent for the therapy of this disorder.[17] Because of the high incidence of esophagitis in canine idiopathic megaesophagus,[15] affected animals should also be medicated with oral sucralfate suspensions (1 g TID for large dogs, 0.5 g TID for smaller dogs, and 0.25 to 0.5 g BID-TID for cats).

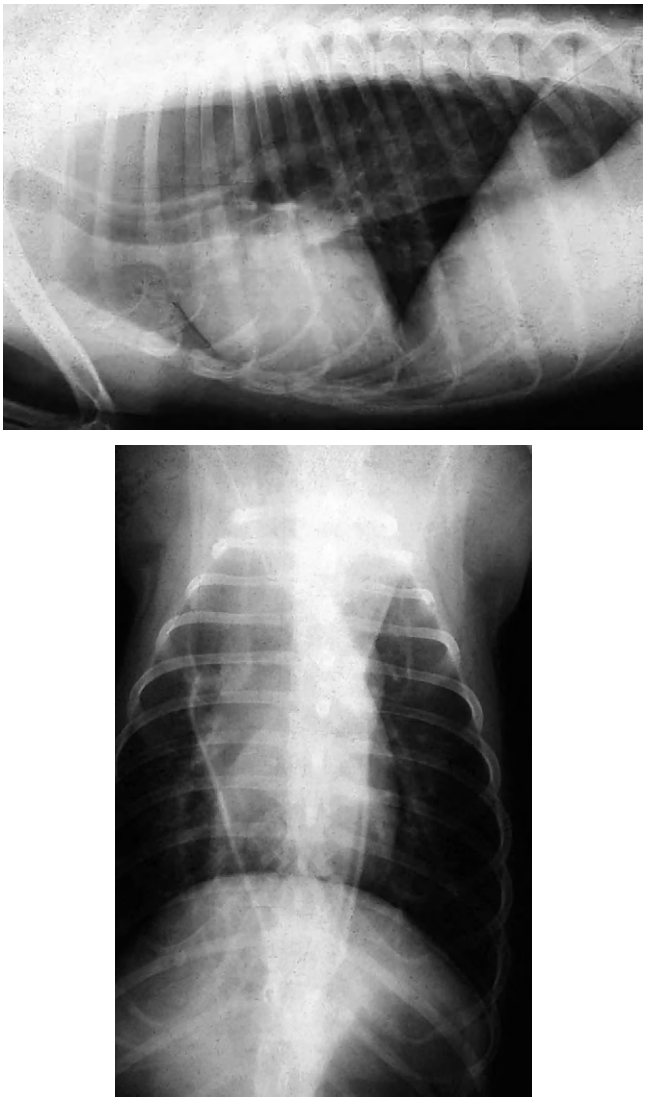

Figure 55-11 Idiopathic megaesophagus in an 8-year-old mixed-breed dog.

Surgical cardiomyotomy (myotomy of the gastroesophageal sphincter) has been recommended in the past as a therapeutic measure in the belief that canine megaesophagus is similar to human achalasia. Because most studies have reported normal gastroesophageal sphincter tone and appropriate relaxation with swallowing,[23] cardiomyotomy cannot be recommended for the treatment of this disorder. Indeed, animals treated with myotomy generally have had poorer outcomes than untreated animals.

Prognosis

Animals with *congenital* idiopathic megaesophagus have a fair prognosis. With adequate attention to caloric needs and recognition of episodes of aspiration pneumonia, many animals will develop improved esophageal motility over several months. Pet owners must be committed to months of physical therapy and nutritional support.

The morbidity and mortality of acquired idiopathic megaesophagus remain unacceptably high. Many animals eventually succumb to the effects of chronic malnutrition and repeated episodes of aspiration pneumonia. A poor prognosis must be given in such cases.

Animals with acquired secondary megaesophagus have a more favorable prognosis if the underlying disease can be promptly identified and successfully managed. Refractory cases result from chronic esophageal distention, myenteric nerve degeneration, and muscle atrophy.

Dysautonomia

Etiology

Dysautonomia is a generalized autonomic neuropathy that was originally reported in cats in the United Kingdom, but that has now been documented in dogs and cats throughout Western Europe and the United States.[29-35] The clinical signs reflect a generalized autonomic dysfunction but megaesophagus, esophageal hypomotility, and regurgitation are fairly consistent findings.[29,31]

Pathophysiology

Degenerative lesions are found in autonomic ganglia, intermediate gray columns of the spinal cord, and some sympathetic axons.[31,33,34] Despite an intensive search for genetic, toxic, nutritional, and infectious etiologic agents, no definitive etiology has ever been established.

Clinical Signs

The most frequently reported clinical signs are depression, anorexia, constipation, and regurgitation or vomiting. Fecal and urinary incontinence have been reported less commonly. Physical examination findings consistent with dysautonomia include dry mucous membranes, pupillary dilation, prolapsed nictitating membranes, reduced or absent pupillary light reflex, bradycardia, and areflexic anus. Paresis and conscious proprioceptive deficits have been reported in a small number of cases.[33]

Cause

Gastroesophageal reflux → Reflux esophagitis → Esophageal dysmotility → Idiopathic megaesophagus

Consequence

Esophageal dysmotility → Idiopathic megaesophagus → Gastroesophageal reflux → Reflux esophagitis

Figure 55-12 Interrelationships between gastroesophageal reflux, esophagitis, esophageal dysmotility, and idiopathic megaesophagus.

Diagnosis

A clinical diagnosis is made in most cases based on historical and physical examination findings. Additional findings consistent with the diagnosis would include (a) esophageal dilation and hypomotility on survey or barium-contrast radiographs; (b) delayed gastric emptying on barium-contrast radiographs; (c) reduced tear production in Schirmer tear tests; (d) atropine-insensitive bradycardia; and (e) bladder and colonic distention on survey radiographs. There are few differential diagnoses to consider in a dog or cat presenting with the myriad manifestations of the syndrome. Early in the course of the illness, however, other differential diagnoses to consider are colonic or intestinal obstruction, other causes of megaesophagus, and lower urinary tract disease.

Treatment

Supportive care (e.g., artificial tears, elevated feedings, expressing the urinary bladder, antibiotics, etc.) is still the basis of therapy in this disorder, although some dogs and cats are reported to show mild improvement with parasympathomimetic drugs (e.g., bethanechol or metoclopramide). Gastrostomy tube feedings or total parenteral nutrition may sustain some animals until they regain neurologic function.

Prognosis

In general, dysautonomia carries a guarded to poor prognosis for long-term survival in both the dog and the cat. Of affected cats, 20% to 40% are likely to recover, although cats may take 2 to 12 months to do so.[33-35] Recovery rates are lower still in the dog.[31,33] Complete recovery is uncommon and many cats and dogs are left with residual impairment, for example, intermittent regurgitation, dilated pupils, and fecal or urinary incontinence.

Esophageal Diverticula

Etiology

Esophageal diverticula are circumscribed sacculations in the wall of the esophagus that interfere with the normal esophageal motility patterns. Both congenital and acquired forms have been described.[36]

Pathophysiology

Congenital diverticula have been attributed to abnormalities in embryologic development that permit herniation of the mucosa through a defect in the muscularis. Acquired diverticula are subdivided into either traction or pulsion forms, depending upon the pathogenesis. Traction diverticula tend to develop in the cranial and midesophageal body and result from periesophageal inflammation and fibrosis. Adhesions to adjacent tissue (e.g., lung, bronchus, lymph node) distort the esophageal lumen and create sacculations. Abscess development from grass awn migration is a common cause of traction diverticula in the western United States. Pulsion diverticula develop in association with increases in intraluminal esophageal pressure, abnormal regional esophageal motility, or when normal peristalsis is obstructed by a stenotic lesion.[16] Pulsion diverticula may develop as a consequence of vascular ring anomalies in the cranial esophagus, or from foreign bodies that become lodged in the distal esophagus, in which case they are referred to as epiphrenic diverticula.

Clinical Signs

The clinical signs of esophageal diverticula are typical of many other esophageal disorders, and include regurgitation, odynophagia (painful swallowing), and retching. Signs usually result from impaction of food and/or fluid in the sacculated segment. On rare occasions, weakening of the muscularis results in perforation of the diverticulum, leakage of food and fluid into the mediastinum, and signs of sepsis.

Diagnosis

Survey radiographs may reveal an air-filled or tissue-density mass adjacent to or involving the esophagus. Contrast radiographs are necessary, however, because it may be impossible to differentiate an esophageal diverticulum from a periesophageal, mediastinal, or pulmonary mass. An epiphrenic diverticulum could also easily be confused with a hiatal hernia or gastroesophageal intussusception on survey radiographs. Contrast radiographs will demonstrate a focal dilated segment of esophageal lumen that fills partially or completely with contrast media. Videofluoroscopy might also demonstrate an underlying esophageal motility disorder associated with the diverticulum. Endoscopy will confirm the diagnosis, although it may be necessary to suction food and fluid to visualize the diverticulum. The differential diagnoses for cranial and mid-esophageal diverticula should include esophageal or periesophageal abscess, necrotic tumor, and pulmonary mass. Hiatal hernia and gastroesophageal intussusception are the major differential diagnoses for epiphrenic diverticula. The normal redundancy of the canine esophagus frequently seen in the brachycephalic breeds should not be confused with the sacculation of an esophageal diverticulum.

Treatment

Small diverticula may be managed by feeding liquid or semiliquid diets to minimize impaction of solid food in the diverticulum. Surgical excision and reconstruction of the esophageal wall are required for larger diverticula. Even small pulsion diverticula should probably be treated surgically as food impaction might cause them to enlarge.

Prognosis

Most cases warrant a guarded prognosis as segmental esophageal hypomotility may persist after surgery. Animals are also at some risk for esophageal stricture following corrective surgery. In cases of traction diverticula, the prognosis will also be somewhat dependent upon the pathogenesis and resolution of the periesophageal inflammation.

NEOPLASIA

Michael D. Willard

Etiology

Esophageal tumors are rare. Squamous cell carcinomas, fibrosarcomas, osteosarcomas, and leiomyomas are the more common types of primary esophageal tumor. Melanomas occasionally occur in dogs with black mucous membranes (e.g., Chows, Shar-Pei, Scottish Terrier), the same breeds that develop oral melanomas. Fibrosarcomas, osteosarcomas, and undifferentiated sarcomas are classically attributed to infection with *S. lupi*.[1] The cause of other esophageal tumors in dogs and cats is unknown. Gastric metaplasia caused by chronic gastroesophageal reflux (Barrett esophagus) is an important cause of human esophageal carcinoma, but it has only been reported in three cats,[2] none of which developed cancer. However, it is interesting to note that squamous cell carcinoma is the most common feline esophageal tumor.[3] Lymphoma, various carcinomas

(especially thyroid carcinomas[4]), and melanomas may secondarily invade the esophagus, which is probably as common as primary esophageal neoplasia.[5]

Pathophysiology

Esophageal tumors typically cause clinical signs as a result of mechanical obstruction. Poor esophageal motility might also occur in the region of the tumor, compounding the problem. Leiomyomas classically occur at or near the lower esophageal sphincter,[6] whereas most other esophageal malignancies more commonly occur in the caudal thoracic esophagus. Feline esophageal squamous cell carcinomas tend to occur in the middle third of the esophagus.[3,7] Esophageal tumors typically are locally invasive and occasionally metastasize to local lymph nodes.

Clinical Examination

Esophageal tumors tend to occur in older patients; breed-associations are largely unrecognized except for leiomyomas having a higher incidence in older Beagles.[6] *Spirocerca*-associated sarcomas are not as clearly age-associated since infection with the parasite is the initiating cause. Regurgitation is the "classic" clinical sign; however, this may occur late, not being seen until there is near complete esophageal obstruction (Figure 55-13). Odynophagia, excessive salivation, fever, anorexia, and lethargy[1,8] have been reported. Aspiration secondary to regurgitation may cause coughing, dyspnea, and/or fever. Hypertrophic osteodystrophy occasionally occurs (especially with *Spirocerca*-induced sarcomas), resulting in noticeably thickened extremities. In the later stages, patients may be lethargic, depressed, and/or emaciated.

Physical examination tends to be unrevealing unless there is evidence of aspiration pneumonia (e.g., pulmonary crackles, fever, dyspnea), a mass in the cervical esophagus, a dilated cervical esophagus (e.g., seen in the cervical region as an intermittent "puffing" out that coincides with respiration), or weight loss because of lack of nutrition (as a consequence of regurgitation) or cancer cachexia.

Sometimes a microcytic, hypochromic anemia and/or a neutrophilic leukocytosis may be found in dogs with *Spirocerca*-induced sarcomas, but these findings are nonspecific.[8]

Diagnosis

Diagnosis usually begins with thoracic radiographic findings. Esophageal masses produce soft-tissue densities that cannot always be distinguished from pulmonary or mediastinal masses unless they are partially surrounded by air, demonstrating that they are in the esophageal lumen. Sometimes these masses are noted fortuitously when thoracic radiographs are taken for other reasons (e.g., to evaluate the heart) (Figure 55-14). It may be necessary to perform a barium-contrast esophagram to distinguish pulmonary masses and esophageal masses. Dogs with *Spirocerca*-induced neoplasia often

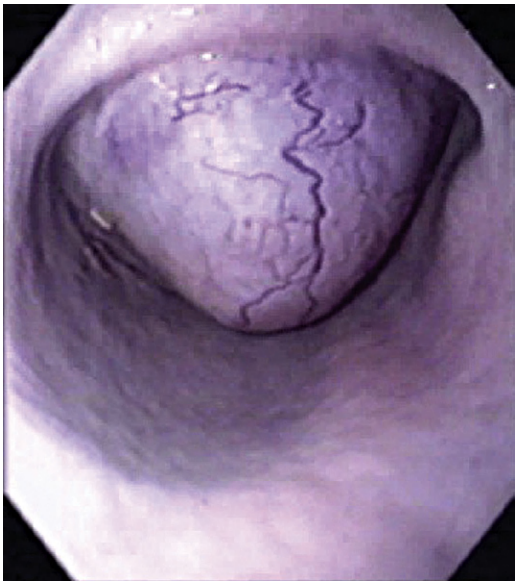

Figure 55-13 An endoscopic view of a large myxosarcoma occluding the distal lumen of the esophagus of a dog. Despite the large size of the mass, clinical signs were only reported 2 to 3 weeks before this image was taken.

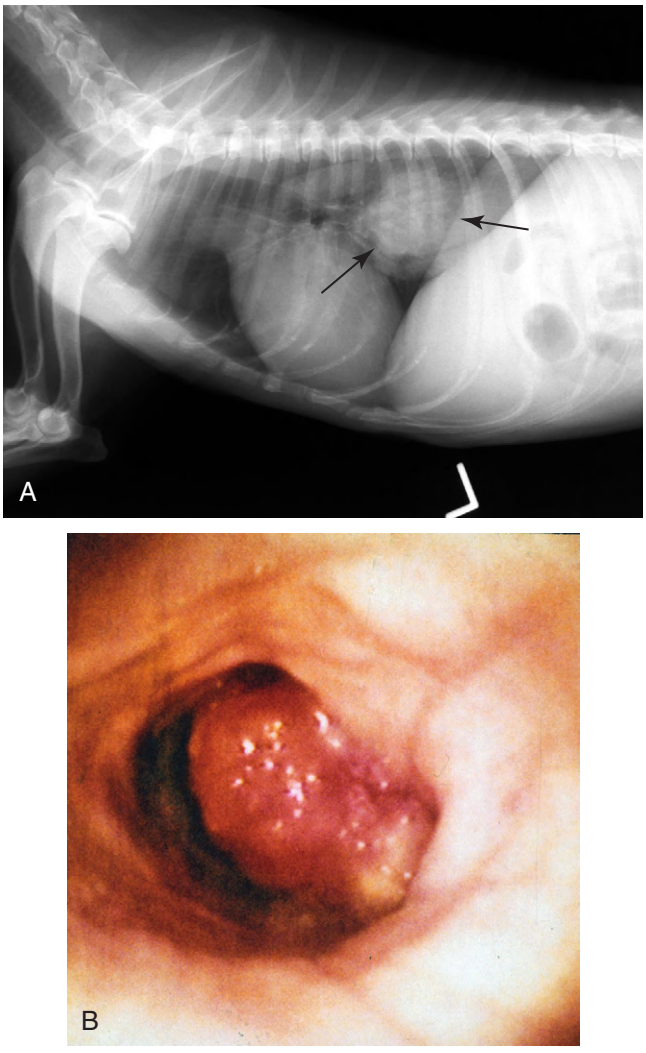

Figure 55-14 **A,** A radiograph of the chest of a Poodle with a heart murmur. There were no other clinical signs besides halitosis caused by dental disease. There is a mass in the caudal thorax (*arrows*), but it cannot be determined from this radiograph whether the mass is pulmonary, mediastinal, or esophageal. **B,** An endoscopic view of the esophagus of the dog in (**A**). There is a large carcinoma (*the red mass*) seen protruding into the esophageal lumen. (From Small Animal Surgery, ed 3, St. Louis, 2007, Mosby.)

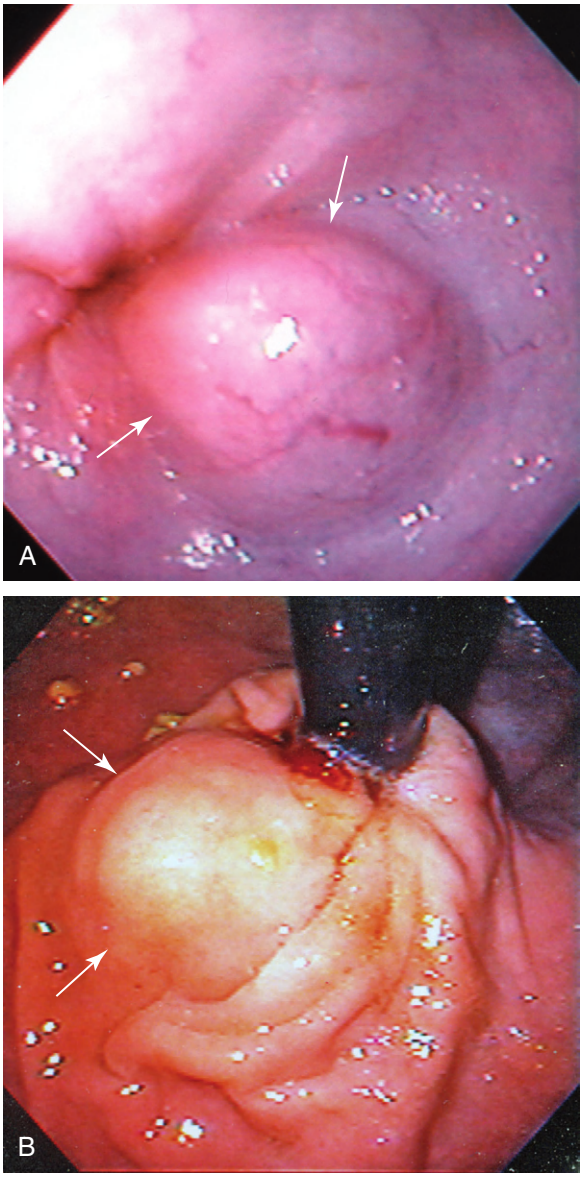

Figure 55-15 **A,** An endoscopic view of the lower esophageal sphincter of a dog, taken from inside the esophagus. There is a mass (*arrows*) seen near the sphincter. This is a submucosal leiomyosarcoma. **B,** An endoscopic view of the lower esophageal sphincter of a dog, taken from inside the stomach. The tip of the endoscope has been maximally retroflexed. A mass (*arrows*) is seen in the sphincter; this is a leiomyoma. The black tube is the insertion tube of the endoscope, entering the stomach.

have thoracic spondylosis.[5] Periosteal new bone proliferation of the limbs may be found in dogs with hypertrophic osteodystrophy secondary to esophageal neoplasms, but this is very nonspecific for esophageal disease.

Endoscopically, esophageal tumors can be seen as masses (Figure 55-15) or strictures (Figure 55-16).[5] Carcinomas and *Spirocerca*-induced sarcomas can typically be adequately sampled with flexible endoscopes; it helps to have an endoscope with a 2.8-mm biopsy channel as these biopsy forceps allow much larger tissues samples to be taken. Neoplastic and nonneoplastic lesions at the lower esophageal sphincter can resemble each other, making adequate biopsy of the lesion crucial (Figure 55-17). Leiomyomas usually

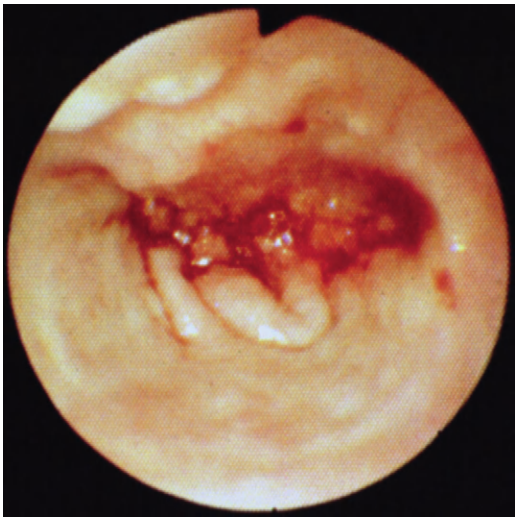

Figure 55-16 An endoscopic view of the esophagus of a cat. There is an irregular mass causing a stricture. This is a primary esophageal carcinoma.

occur close to the lower esophageal sphincter (see Figure 55-14, *A*)[6,9] and typically have a smooth appearance, covered by normal mucosa. If they are on the gastric side, one must maximally retroflex the endoscope tip after entering the stomach (see Figure 55-14, *B*). Their location and appearance are suggestive of the diagnosis. Leiomyomas typically cannot be successfully biopsied with flexible endoscopes because they are submucosal and covered with relatively normal esophageal mucosa (which is tough and cannot be readily penetrated by flexible biopsy forceps). Definitive diagnosis often requires surgical biopsy.

Malignancies that secondarily invade the esophagus (e.g., lymphoma, thyroid carcinoma) can be diagnosed by sampling the primary mass. Benign esophageal polyps are very rare in dogs and cats[5]; if a polypoid or adenomatous growth is diagnosed, an underlying carcinoma might be responsible for the overlying benign proliferation (Figure 55-18). Very rarely other causes of esophageal masses occur (e.g., pythiosis, ectopic esophageal tissue).

Spirocercosis before malignant transformation is typically seen as a large mass with a nodule or "nipple" (Figure 55-19). Occasionally, one may diagnose spirocercosis by fecal examination or by endoscopically seeing the parasite protruding from the esophageal granuloma, but these are not sensitive ways to diagnose this problem.[1,8]

Treatment

Surgery can cure benign masses (e.g., leiomyomas)[9,10]; however, it is extremely rare to cure esophageal malignancies with surgery. Tumors tend to be so locally invasive that complete resection is impossible by the time the patient shows clinical signs. If a patient is fortuitously diagnosed when the tumor is very small, cure might be possible, but even then a guarded to poor prognosis is appropriate. Aggressive resections can result in dehiscence as a result of excessive tension on the incision line. A surgical technique in which the esophagus is opened on the side opposite the mass has been reported.[11] This technique has the advantage of allowing the surgeon to determine more accurately the extent of the base of the tumor, aiding in deciding where to make the incision. Radiation, photodynamic therapy,[12] and chemotherapy[11] may be palliative in some

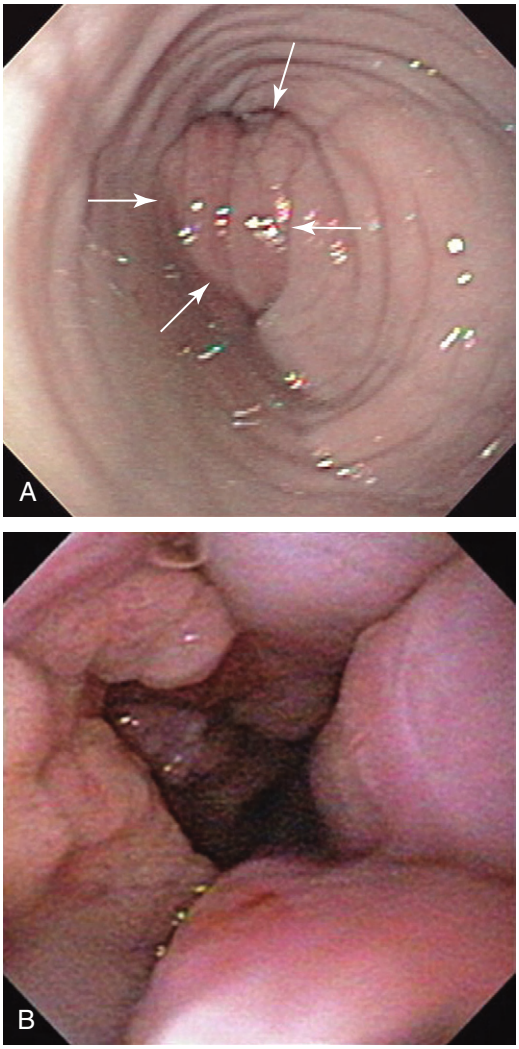

Figure 55-17 **A,** An endoscopic view of the lower esophageal sphincter of a dog. There is a mass of tissue protruding from the sphincter (*arrows*), which is nonneoplastic gastric mucosa that could be mistaken for a tumor. This must be biopsied because some carcinomas have a similar appearance. **B,** An endoscopic view of the lower esophageal sphincter of a Bulldog with a gastric carcinoma that has spread up through the lower esophageal sphincter and into the distal esophagus. The distal esophageal mucosa is irregular, especially from the 9 o'clock to the 12 o'clock position.

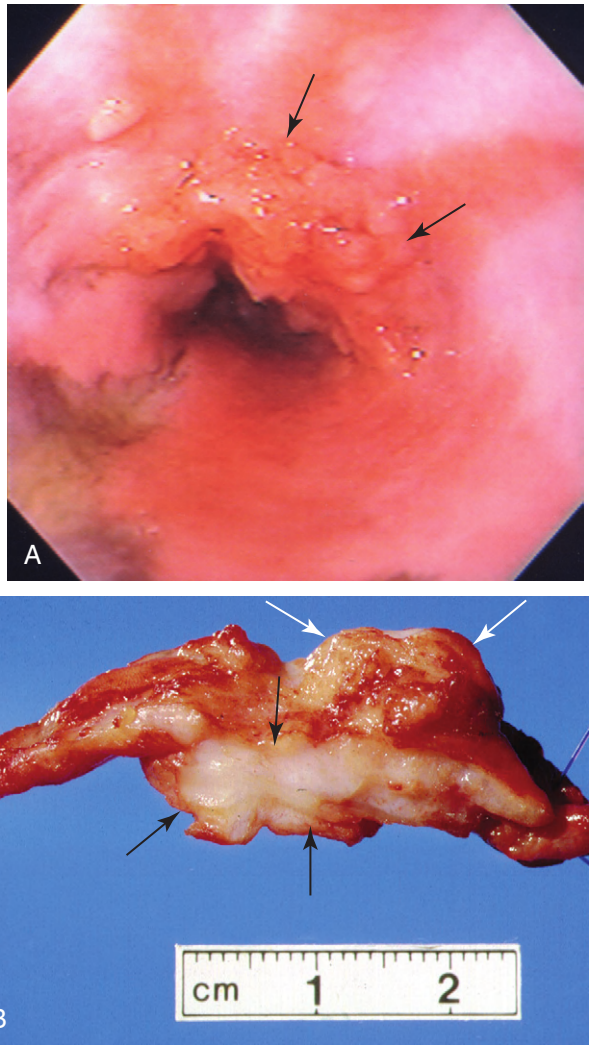

Figure 55-18 **A,** An endoscopic view of the esophagus of a dog showing an area in which the mucosa is roughened and irregular (*arrows*). Endoscopic biopsies revealed a benign, adenomatous growth. **B,** The same lesion seen in (**A**). Under the polypoid growth (*white arrows*) there is a thickening of the esophageal wall that is a carcinoma (*black arrows*).

cases; however, radiation-induced esophagitis and damage to surrounding structures is a significant concern. Spirocercosis can be treated successfully with doramectin (200 to 400 mg/kg given SC every 3 weeks for three treatments); however, resolving spirocercosis once malignant transformation has occurred will not resolve the malignancy.

Prognosis

The prognosis for patients with esophageal malignancies is poor with the exception of leiomyomas, which may be cured. One recent report gave survival times of 2 to 16 months in five dogs in which esophageal sarcomas, ostensibly caused by spirocercosis, were resected.[11]

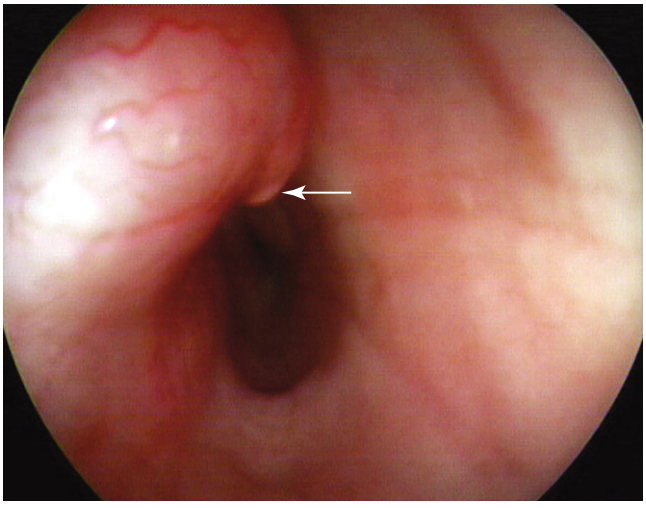

Figure 55-19 An endoscopic view of a canine esophagus with a mass caused by *Spirocerca lupi*. A small "nipple" is seen (*arrow*).

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CHAPTER 56

Stomach

STRUCTURE AND FUNCTION

Kenneth W. Simpson

Functional Anatomy

The stomach acts as a reservoir to control the size and rate of passage of ingesta into the small intestine, to initiate the digestion of protein and fat, and to facilitate the absorption of vitamins and minerals (see Chapter 1)

The stomach is composed of five anatomic regions: cardia, fundus, corpus, antrum, and pylorus (Figure 56-1). The fundus and body expand greatly to accommodate ingesta and to regulate the emptying of liquids. The antrum grinds food into smaller particles (<2 mm) that are sieved into the duodenum. The gastroesophageal sphincter prevents reflux of gastric fluid into the esophagus, and the pyloric sphincter controls emptying into the small intestine.

The gastric wall contains a mucosa, submucosa, muscularis externa, and serosa (see Figures 56-2 and 1-3, *B*). The mucosa has a superficial epithelium, gastric glands, and an innermost layer of smooth muscle (the muscularis mucosa), with fine structure and function varying depending on the gastric region. The mucosa in the cardia and pylorus is thinner and less glandular than in the fundus and body. The mucosa of the body contains mucous neck cells (producing mucous, pepsinogen A, and gastric lipase), parietal cells (producing H^+, pepsinogen A, and intrinsic factor), and chief cells (producing pepsinogen A) (Figure 56-2).[1-4] A variety of neuroendocrine cells are involved in the regulation of acid secretion and are interspersed between the glands. The predominant cells are enterochromaffin-like and somatostatin-producing cells in the fundus, and gastrin and somatostatin-producing cells in the antrum (see Figure 56-2). Localized small aggregates of lymphoid tissues are frequently observed at the base of the gastric glands. A rich network of blood vessels, lymphatics, and nerves weaves between the gastric glands. Beneath the submucosa are two layers of smooth muscle (circular and longitudinal) that run perpendicular to one another. The serosa is the outermost layer.

Regulation of Acid Secretion

Physiologically, luminal peptides and gastric distention are the primary stimuli for H^+ secretion from parietal cells. Pharmacologically, parietal cell acid secretion is regulated by endocrine (gastrin), neurocrine (acetylcholine), and paracrine (histamine) mechanisms.[4,5] Somatostatin released in response to gastric pH levels below 3 provides negative feedback and decreases gastrin, histamine, and acid secretion.

Luminal peptides and gastric distention stimulate gastrin secretion from G cells and effect histamine release from enterochromaffin-like cells. Gastrin-releasing peptide and acetylcholine are the primary enteric neurotransmitters regulating gastrin release from antral G cells (Figure 56-3).

Unstimulated acid secretion in dogs and cats is minimal[6-8] (e.g., dogs <0.04 mmol/kg$^{0.75}$/h) and the unstimulated H^+/K^+-adenosine triphosphatase (ATPase), "the proton pump," is localized within tubulovesicles in the cytoplasm of parietal cells.[4,9] The stimulated H^+/K^+-ATPase and KCl transporters are incorporated into the parietal cell canalicular membrane and hydrogen ions (derived from the ionization of water within the parietal cells) are transported into the gastric lumen in exchange for K^+ by H^+/K^+-ATPase. Potassium and chloride transporters in the canalicular membrane enable luminal transfer of potassium (for recycling via H^+/K^+-ATPase) and chloride. Hydroxide combines with CO_2, catalyzed by carbonic anhydrase, to form HCO_3^-, which diffuses into the blood giving rise to the "alkaline tide" phenomenon. Recent studies have expanded our knowledge of ion transport in the parietal cell by identifying KCNQ1 as the primary channel responsible for K^+ recycling and establishing the contribution of CFTR (cystic fibrosis transmembrane regulator) and SLC26A9 to the process of chloride secretion.[5] Figure 56-4 shows a schematic of ion transport in the parietal cell incorporating these findings. Stimulation results in a rapid increase in fluid and hydrogen ion secretion, with pH rapidly declining to around pH 1. The concentrations of K^+ (10 to 20 mmol/L) and Cl^- (approximately 120 to 160 mmol/L) in gastric juice are higher than in plasma.

The stomach is protected from gastric acid injury by a functional unit known as the gastric mucosal barrier.[10,11] The gastric mucosal barrier comprises tightly opposed epithelial cells coated with a layer of bicarbonate-rich mucus and an abundant mucosal blood supply that delivers bicarbonate, oxygen, and nutrients. Local production of prostaglandin (PGE_2) is important in modulating blood flow, bicarbonate secretion, and epithelial cell renewal. When damage occurs, epithelial cells rapidly migrate over superficial mucosal defects aided by the local production of growth factors such as epidermal growth factor.

Evaluating Gastric Secretory Function

Gastric secretory testing is primarily performed in patients with esophagitis, gastrointestinal (GI) ulceration, mucosal hypertrophy, and in patients suspected of having acid hypersecretion.

As a starting point, fasting gastric pH and serum gastrin can be measured to determine if acid hypersecretion is likely. Ideally, antisecretory therapy should be discontinued for 7 days prior to testing,[12] and renal and hepatic function should be monitored as these may

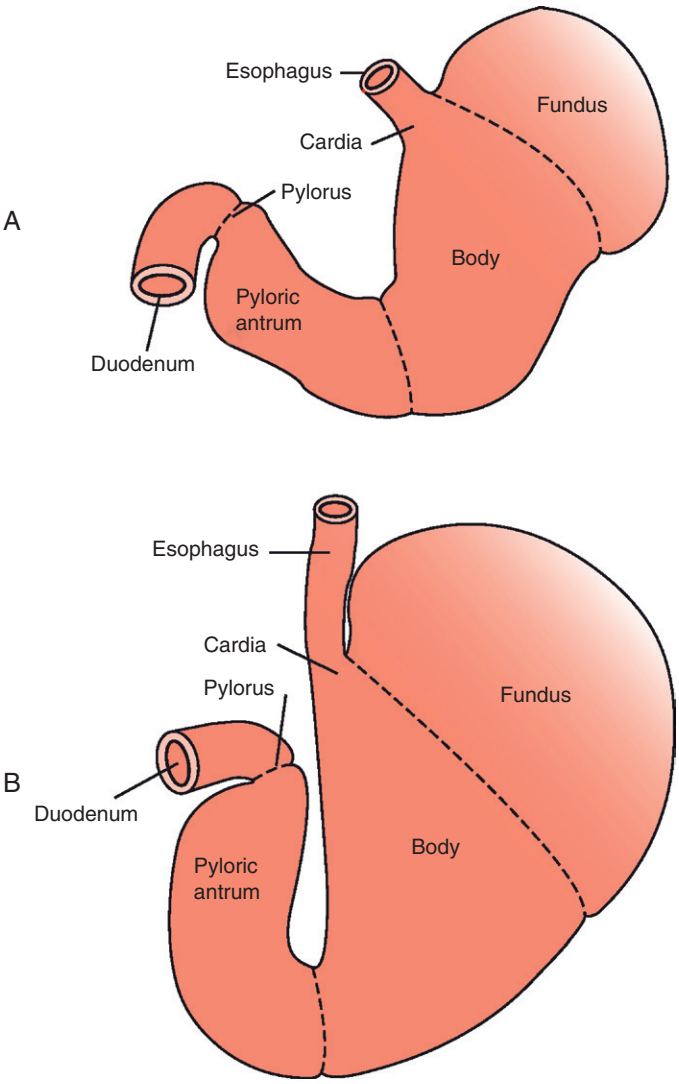

Figure 56-1 Gastric anatomy of the empty **(A)** and full **(B)** stomach. (From Guilford and Strombeck: *Strombeck's Small Animal Gastroenterology*, St. Louis, Saunders, 1996, p 239.)

be associated with decreased serum gastrin clearance and hypergastrinemia. The broad range of unstimulated (fasting) gastric pH in dogs and cats (from pH 1 to 8) makes definitive statements regarding basal acid production difficult. However, the presence of a gastric pH of less than 3 in the face of a high serum gastrin rules out the possibility of achlorhydria, or mast cell tumor, and raises the possibility of gastrinoma.[13,14] Dogs with mast cell tumors and hyperhistaminemia-induced acid hypersecretion have low serum gastrin concentrations,[15] whereas dogs with achlorhydria likely have a high gastrin, but a gastric pH greater than 3.

Measurement of serum gastrin following the intravenous infusion of secretin or calcium is used to further investigate the possibility of exogenous gastrin production by pancreatic gastrinomas (Zollinger-Ellison syndrome).[12-14] Basenji dogs with gastroenteropathy and diarrhea are reported to have elevated gastrin release in response to secretin stimulation, without evidence of gastrinoma.[16] Provocative testing of gastric acid secretion with pentagastrin or bombesin stimulation may be performed to detect achlorhydria in patients with atrophic gastritis, or elevated serum gastrin and gastric pH levels higher than 3, and in those with putative idiopathic small intestinal bacterial overgrowth to determine if achlorhydria is a contributing factor. Pentagastrin-stimulated acid secretion in dogs reaches a peak of 28 mL/kg$^{0.75}$/h, 4.1 mmol HCl/kg$^{0.75}$/h, 0.34 mmol K^+/kg$^{0.75}$/h, and 0.09 Na^+ mmol/kg$^{0.75}$/h.[6] Sedation with oxymorphone and acepromazine may be a suitable alternative to anesthesia for secretion studies in dogs.[16] In cats, acid output (mean ± standard deviation) in response to pentagastrin (8 µg/kg/h) ranges from pH 0.9 to 1.1, with secretion rates (median values) of 1.2 mmol/15 min to 1.4 ± 0.5 mmol/15 min in conscious cats and 1.2 (0.6 to 2.7) mmol/kg$^{0.75}$/h in anesthetized cats.[7]

Gastric Motility

Normal gastric motility is the result of the organized interaction of smooth muscle with neural and hormonal stimuli.[17,18] The rate of gastric emptying is directly proportional to the difference in pressure between the stomach and the duodenum, and inversely proportional to the resistance to flow across the pylorus. Liquids are emptied more rapidly than solids and the rate of emptying of liquids increases with volume. The emptying rate for digestible solids depends on caloric density. In dogs, digestible solids smaller than 2 mm are emptied into the duodenum, and gastric emptying is modulated via intestinal osmo-, chemo-, and tryptophan receptors. Lipids particularly retard gastric emptying. The release of cholecystokinin in response to fatty and amino acids such as tryptophan, is one factor that slows gastric emptying. Large, undigestible solids are expelled from the stomach in the fasted state by phase III of the migrating motility complex (MMC) in response to the release of motilin.

There is wide variation in the rate of gastric emptying reported in healthy dogs and cats that is largely a function of the method used to evaluate it (Table 56-1; see also Table 26-2),[19] and in clinical practice delayed gastric emptying is usually suspected when food is retained in the stomach for more than 8 hours. The advent of noninvasive, nonradioactive methods of measuring gastric emptying, such as telemetry capsules,[18,20,21] holds the promise of improving our basic understanding of gastric motility in health and disease.

Digestion and Assimilation of Nutrients

The stomach has a limited role in the digestion of proteins, fats, and micronutrients. Pepsin, which hydrolyzes peptide bonds, is secreted as pepsinogen in response to acetylcholine and histamine in parallel with gastric acid secretion. Dog gastric lipase, which digests fat, is secreted in response to gastrin, histamine, prostaglandin E_2, and secretin, and lipase secretion parallels the secretion of gastric mucus. Although pepsin is active only at acidic pH, dog gastric lipase remains active in the small intestine and constitutes up to 30% of total lipase secreted over a 3-hour period.[22] Although gastric lipase and pepsin are not essential for the assimilation of dietary fat and protein, the entry of peptides and fatty acids into the small intestine likely helps to coordinate gastric emptying and pancreatic secretion.

Intrinsic factor, which is necessary for cobalamin (vitamin B_{12}) absorption, is produced by parietal cells and cells at the base of antral glands in the dog but not the cat.[1,23] The importance of gastric intrinsic factor secretion in dogs is questionable as the pancreas is the major site of secretion in both dogs and cats. Gastric acidity may also have an effect on the availability of minerals such as iron and calcium.

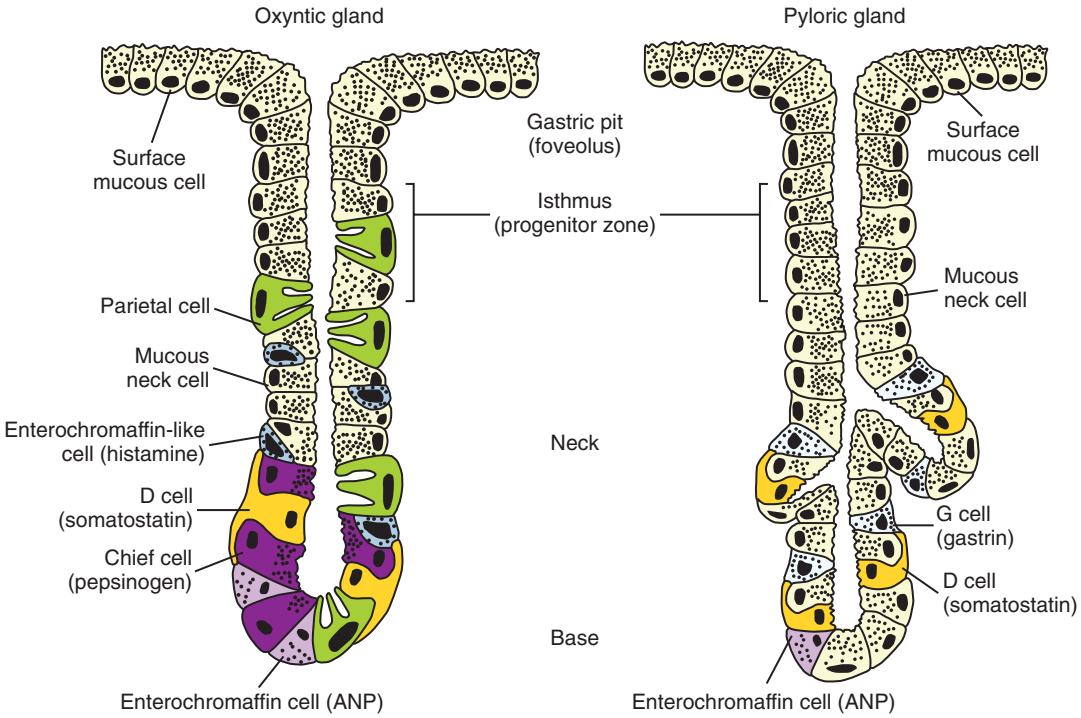

Figure 56-2 Functional mucosal anatomy. Somatostatin-containing D cells contain cytoplasmic processes that terminate in the vicinity of acid-secreting parietal and histamine-secreting enterochromaffin-like cells in the oxyntic gland area (fundus and corpus), and gastrin-secreting G cells in the pyloric gland area (antrum). The functional correlate of this anatomic coupling is a tonic paracrine restraint exerted by somatostatin on acid secretion that is exerted directly on the parietal cell as well as indirectly by inhibiting histamine and gastrin secretion. (From Schubert ML, Peura DA: Control of gastric acid secretion in health and disease. *Gastroenterology* 134:1842–1860, 2008.)

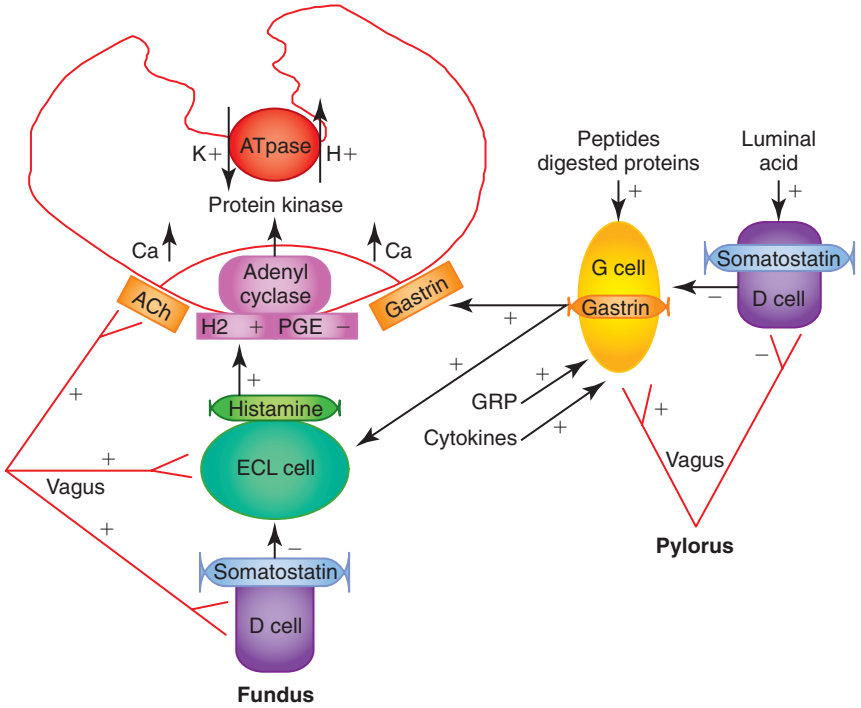

Figure 56-3 Regulation of acid secretion. *Ach*, Acetylcholine receptor; *ECL*, enterochromaffin-like cell; *GRP*, gastrin-releasing peptide; H_2, histamine H_2 receptor; *PGE*, prostaglandin E_2 receptor. (From Simpson KW: Fluid and electrolyte disturbances in gastrointestinal, pancreatic, and liver disease. In: *Dibartola Fluid Therapy in Small Animal Practice*, ed 2, Saunders, 2006.)

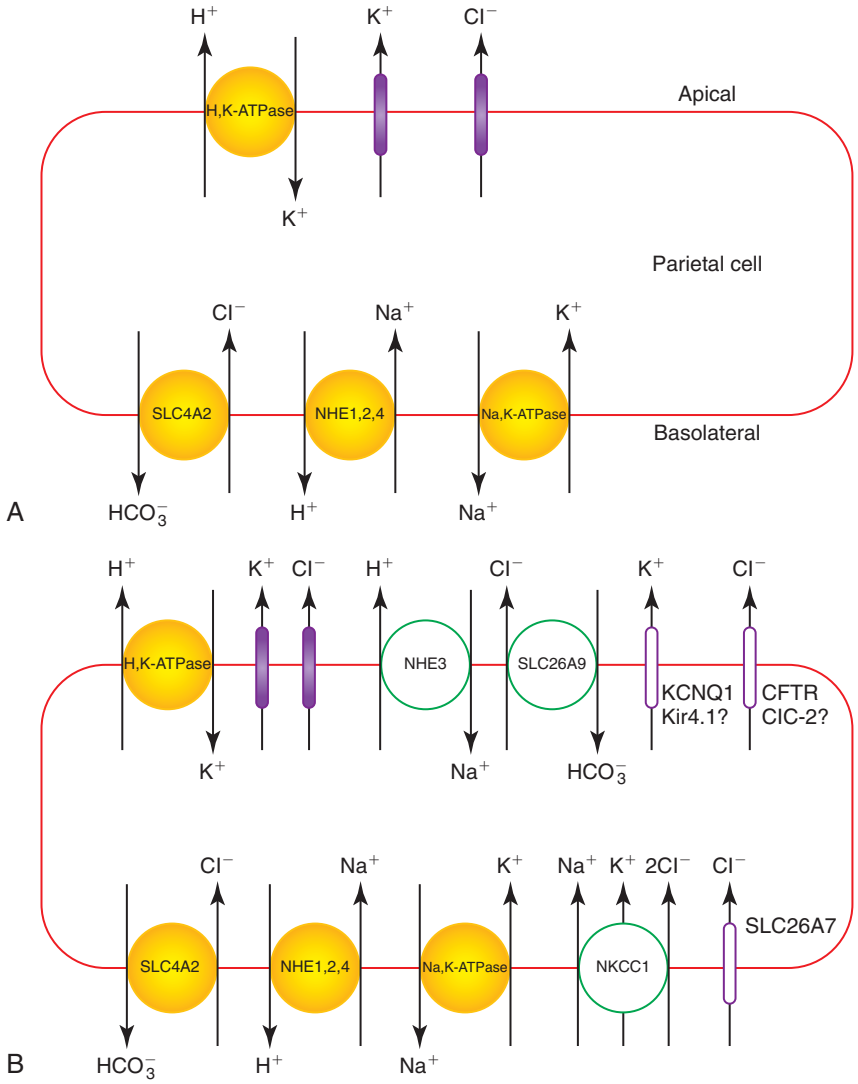

Figure 56-4 Ion transport in the parietal cell. Recent studies have expanded our understanding of ion transport in the parietal cell by identifying KCNQ1 as the primary channel responsible for K^+ recycling and establishing the contribution of CFTR (cystic fibrosis transmembrane regulator) and SLC26A9 to the process of chloride secretion. **A**, Standard model of ion transport in the parietal cell. **B**, Revised model that incorporates additional ion channels. (From Kopic S, Murek M, Geibel J: Revisiting the parietal cell. *Am J Physiol Cell Physiol* 298:C1–C10, 2010.)

Gastric Flora and Immune Surveillance

The concept of the stomach as a sterile place was completely dispelled by the isolation of the gastric bacterium *Helicobacter pylori* from people in 1983.[24] A mixed flora of aerobes and anaerobes (approximately 10^6 to 10^7 cfu/mL) is rapidly established soon after birth in dogs,[25] and colonization with *Helicobacter* spp., which are likely acquired from the dam, has been documented as early as 6 weeks of age. The stomach of healthy dogs and cats harbors a diverse spectrum of large, spiral, acid-tolerant *Helicobacter* species[26] that stimulate local and systemic immune responses characterized by lymphoid follicular hyperplasia and seroconversion,[27-29] and may play a role in the development of gastritis[30,31] and cancer. These host–bacterial interactions are discussed further in Chapter 2 and in "Inflammation" section of Chapter 56. *Helicobacter* spp. are adapted to life in an acid environment and produce urease, which catalyzes the formation of ammonia from urea to buffer gastric acidity. Other bacterial species, such as *Proteus*, *Streptococcus*, and *Lactobacillus*, cultured from the canine stomach, may transiently increase after a meal or coprophagia. Acid secretion and gastric emptying likely regulate much of this transient flora and bacteria may proliferate in the event of gastric acid hyposecretion because of glandular atrophy or pharmacologic inhibition. From a diagnostic standpoint it is important to recognize that bacteria such as *Escherichia coli* and *Proteus* spp. produce urease that can lead to a false-positive test result for *Helicobacter* spp.

DIAGNOSTIC EVALUATION

Anette Spohr

Inflammation, ulceration, neoplasia, dysmotility, and obstruction are the primary gastric pathologies. The clinical signs of gastric disease range from mild anorexia and vomiting to hypersalivation, retching, weight loss, hematemesis, melena, abdominal distention, and abdominal pain. The clinical approach to these patients should

Table 56-1 Measurements of Gastric Emptying

Method	Species	Test Meal	Number (N)	Gastric Half-Emptying Time ($t_{1/2}$)
Radioscintigraphy	Dog	Eggs, starch + glucose	27	66 min (median); 45 to 227 min (95% CI)
		Beef baby food + kibble	6	4.9 ± 1.96 h (mean ± SD)
		Liver	4	Approximately 2 h
		Canned dog food + egg	6 (18 tests)	172 ± 17 min (mean ± SE)
		Canned dog food + egg	7 (14 tests)	285 ± 34 min (mean ± SD); 294 ± 39 min (mean ± SD)
		Canned dog food	6	77 min (mean)
	Cat	Dry cat food	10	2.47 ± 0.71 h (mean ± SD)
		Liver + cream	6 (15 tests)	163 ± 11 min (mean±se)
		Canned cat food	20	2.69 ± 0.25 h (mean ± SD)
		Dry cat food	20	3.86 ± 0.24 h (mean ± SD)
		Eggs	10	330 min (median); 210 to 769 min (range)
Radiography	Dog	Dry dog food + radiopaque solids	10	3.5 h (median); 1 to 6 h (range)
		Canned dog food + egg + BIPS	6 (18 tests)	Small BIPS = 416 ± 81 min (mean ± SE)
		Canned dog food + BIPS	20	Small BIPS = 6.05 ± 2.99 h (mean ± SD) Large BIPS = 7.11 ± 3.60 h (mean ± SD)
		Kibble + BIPS	8	Small BIPS = 8.29 ± 1.62 h (70% of dogs ± SE) Large BIPS = 29.21 ± 18.31 h (70% of dogs ± SE)
		Kibble + liquid barium	9 (27 tests)	Total gastric emptying time = 7 to 15 h (range)
		Kibble + liquid barium	4	Total gastric emptying time = 7.6 ± 1.98 h (mean ± SE)
	Cat	Canned cat food + BIPS	10	Small BIPS = 6.43 ± 2.59 h (mean ± SD) Large BIPS = 7.49 ± 4.09 h (mean ± SD)
		Canned cat food + BIPS	6	Small BIPS = 7.7 h (median), 3.5 to 10.9 h (range) Large BIPS = 8.1 h (median), 5 to 19.6 h (range)
		Canned cat food + BIPS	10	Small BIPS = 5.36 h (median) Large BIPS = 6.31 h (median)
		Cat food + liquid barium	8	Gastric emptying time = 11.6 ± 0.9 h (mean ± SD)
Gastric emptying breath test	Cat	Canned cat food	6	Peak ^{13}C excretion = 56.7 ± 9.8 min (mean ± SD)
	Dog	Bread, egg + margarine	6 (18 tests)	3.43 ± 0.50 h (mean ± SD)

BIPS, Barium-impregnated polyethylene spheres; CI, confidence interval; SD, standard deviation; SE, standard error. Small BIPS = 1.5 mm BIPS; Large BIPS = 5.0 mm BIPS.
From Wyse CA, McLellan J, Dickie AM, et al: A review of methods for assessment of the rate of gastric emptying in the dog and cat: 1898-2002. *J Vet Intern Med* 17:609-621, 2003.

be systematic as large numbers of nongastric diseases can demonstrate similar clinical signs.

History and Physical Examination

The diagnosis of diseases of the stomach starts with a thorough history and physical examination. The history should include consideration of signalment (age, gender, breed), description and duration of clinical signs, frequency and severity of vomiting, vaccination status, diet, past medical history, anthelmintic usage, travel history, and previous or current medications.

Special attention should be made if the vomiting animal has been treated with nonsteroidal antiinflammatory drugs (NSAIDs), as serious GI ulceration is a well-known side effect of this treatment.[1,2] Concurrent weight loss could indicate a low calorie intake, small intestinal involvement (e.g., inflammatory bowel disease [IBD]), or neoplasia. Access to garbage, plants, and cleaners all may be important causes of vomiting. The age and breed is important as young animals are more likely to ingest foreign bodies and older animals more frequently experience gastric cancer. Gastric cancer is more frequently seen in the Belgian Shepherd, Rough Collie, Staffordshire Bull Terrier, Beagle, and Lundehund breeds. The large and giant breeds with deep chest conformation, such as the Great Dane, are at increased risk for gastric dilation volvulus syndrome.

Vomiting is one of the major clinical signs of gastric disorders (see Chapter 23). Descriptions of the vomitus should include the amount, color, consistency, odor, and presence of bile or blood. The relationship of vomiting to food and water consumption should also be noted. Vomiting should also be differentiated from gagging, coughing, dysphagia, and regurgitation, all of which may appear the same for the pet owner, before beginning a medical workup for gastric disease. Nonproductive retching and vomiting in deep-chested dogs may require immediate medical attention for gastric dilation or gastric dilation and volvulus (GDV) syndrome. Persistent vomiting of large volumes of fluid is highly suggestive of GI obstruction, whereas vomiting of digested food 12 hours after feeding suggests delayed gastric emptying because of gastric outflow obstruction or a gastric motility disorder. Associated clinical signs, such as anorexia (nausea caused by gastritis), diarrhea (intestinal involvement), and melena (gastric bleeding), may occur in animals with gastric disease. Box 56-1 lists the most common causes of vomiting, and Table 56-2 lists the diagnostic procedures that are used in the differentiation of the vomiting disorders.

Complete physical examination is needed with special attention to abdominal palpation for distention and tympany (e.g., gastric dilation), masses or organomegaly (e.g., neoplasia, intussusception, and foreign body), pain (e.g., perforation, peritonitis, pancreatitis,

Box 56-1 Common Causes of Vomiting

Disorders of the Stomach
- Gastritis
- *Helicobacter* infection?
- Parasites
- Ulceration
- Neoplasia
- Foreign bodies
- Dilation and volvulus
- Hiatal hernia
- Obstruction
- Motility disorders

Disorders of the Small Intestine
- Inflammatory bowel diseases
- Neoplasia
- Foreign bodies
- Intussusception
- Infectious enteritis (viral, bacteria, parasites)
- Intestinal dysbiosis

Disorders of the Large Intestine
- Colitis
- Obstipation
- Parasites

Abdominal Disorders
- Pancreatitis
- Peritonitis
- Neoplasia
- Hepatobiliary diseases
- Urinary tract rupture

Metabolic/Endocrine Disorders
- Uremia
- Diabetes mellitus
- Hyperthyroidism
- Hypoadrenocorticism
- Endotoxemia/septicemia
- Hepatic encephalopathy
- Gastrinomas
- Hyper-/hypoparathyroidism

Drugs, Poisons, and Chemical Agents
- Nonsteroidal antiinflammatory drugs
- Cardiac glycosides
- Erythromycin
- Chemotherapy agents
- Apomorphine
- Xylazine
- Penicillamine
- Tetracycline
- Lead
- Ethylene glycol
- Strychnine

Dietary
- Indiscretion
- Intolerance
- Allergies

Miscellaneous
- Heartworm (*Angiostrongylus vasorum*)
- Motion sickness

Table 56-2 Diagnostic Procedures of Value for the Differential Diagnosis of Vomiting

Procedure	Advantage	Disadvantage
Survey abdominal radiographs	Foreign bodies, masses, ileus, intussusception, estimating size and position of abdominal organs and masses	Can overlook partial obstructions Ascites
Barium contrast radiographs	Motility disorders	Possibility of missing lesions
Barium-impregnated polyethylene spheres	Estimating gastric emptying Partial obstructions, e.g., pylorus or intestine	Full-study contrast takes 24 hours
Fluoroscopy	Motility disorders	
Ultrasonography	Mural thickening/infiltration Masses Metastatic neoplasia Enhanced by ascites	Compromised by aerophagia Expensive equipment Experience is needed
Endoscopy	Minimally invasive Inspection of the lumen and mucosa Mucosal biopsies Foreign-body retrieval	Expensive equipment Experience is needed General anesthesia Likely to miss nonmucosal lesions and motility disorders
Laparoscopy	Direct observation Full-thickness biopsy	General anesthesia Intermediately invasive Risk of peritonitis
Exploratory laparotomy	Full-thickness biopsies Mural diseases in GI tract Evaluation of abdominal organs Correction of gastric dilation and volvulus Removal of foreign body	General anesthesia Invasive Risk of peritonitis

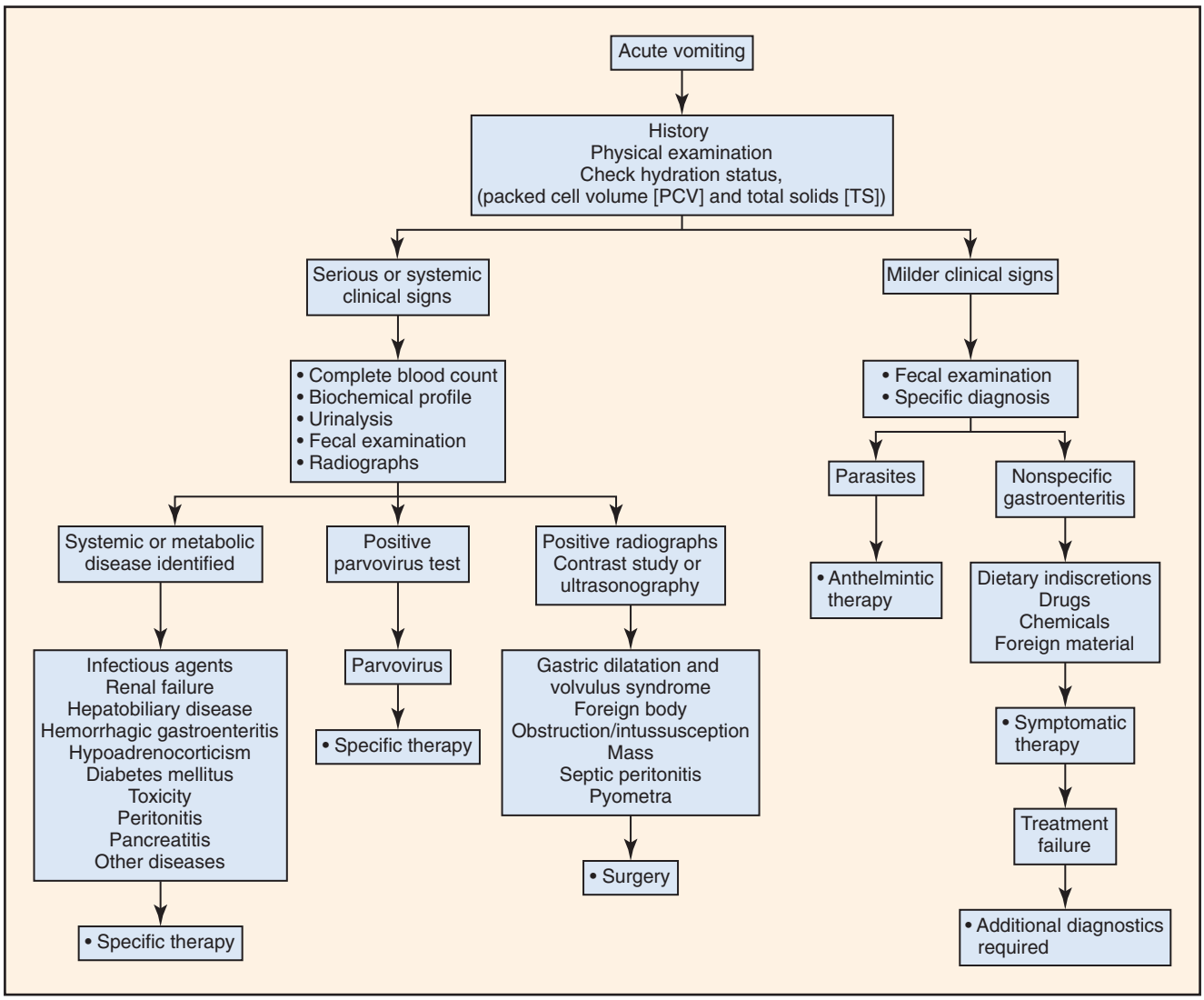

Figure 56-5 Diagnostic approach to the acute vomiting patient.

intestinal obstruction), and effusion (e.g., peritonitis). The occurrence of fever suggests infection or inflammation.

Based on the history and duration of clinical signs, the animal is classified as having either acute or chronic vomiting. The diagnostic approach depends on the duration of the clinical signs and whether the animal has other systemic signs (Figures 56-5 and 56-6). Chronic vomiting is often defined as vomiting that has persisted for 7 to 10 days or when there is no response to initial treatment.

Laboratory Data

Clinicopathologic testing is often warranted when differentiating primary gastric disorders from nongastric disorders. Complete blood cell count, serum chemistry, urinalysis, and fecal flotation should be considered when the patient is persistently vomiting or if there are signs of systemic diseases. Blood and urine samples should be obtained before treatment, which gives the clinician the chance to evaluate the metabolic consequences of the GI disease. Biochemical abnormalities in primary gastric diseases are usually consistent with mild to moderate loss of chloride, potassium, sodium, and bicarbonate. Prerenal azotemia is a result of dehydration. Elevated blood urea nitrogen without concurrently elevated serum creatinine may indicate gastric bleeding. Electrolytes and acid–base status are important parameters if symptomatic therapy is to be optimized in the vomiting animal.[3,4]

Laboratory data should be reviewed for evidence of systemic diseases; for example, kidney and liver insufficiency, toxemias (pyometra, peritonitis), anemia (chronic disease or GI bleeding), Addison disease, and diabetes mellitus. If the database suggests any of these disease entities, additional supportive evidence should be sought; for example, pre- and postadrenocorticotropic hormone (ACTH) cortisol, pre- and postprandial serum bile acids, pancreatic-specific lipase, and trypsin-like immunoreactivity. In cats with chronic vomiting, feline leukemia virus (FeLV) and feline immunodeficiency virus testing is warranted. In older cats, serum T_4 (thyroxine) should be measured as standard for the test for hyperthyroidism in which vomiting is a common clinical sign.

In patients with extensive GI bleeding (melena or hematemesis), an assessment of coagulation is essential. Severe GI bleeding as a consequence of coagulopathy caused by infection with *Angiostrongylus vasorum* has been reported in dogs. When gastric acid hypersecretion is suspected, as with gastrinoma, gastric secretory testing

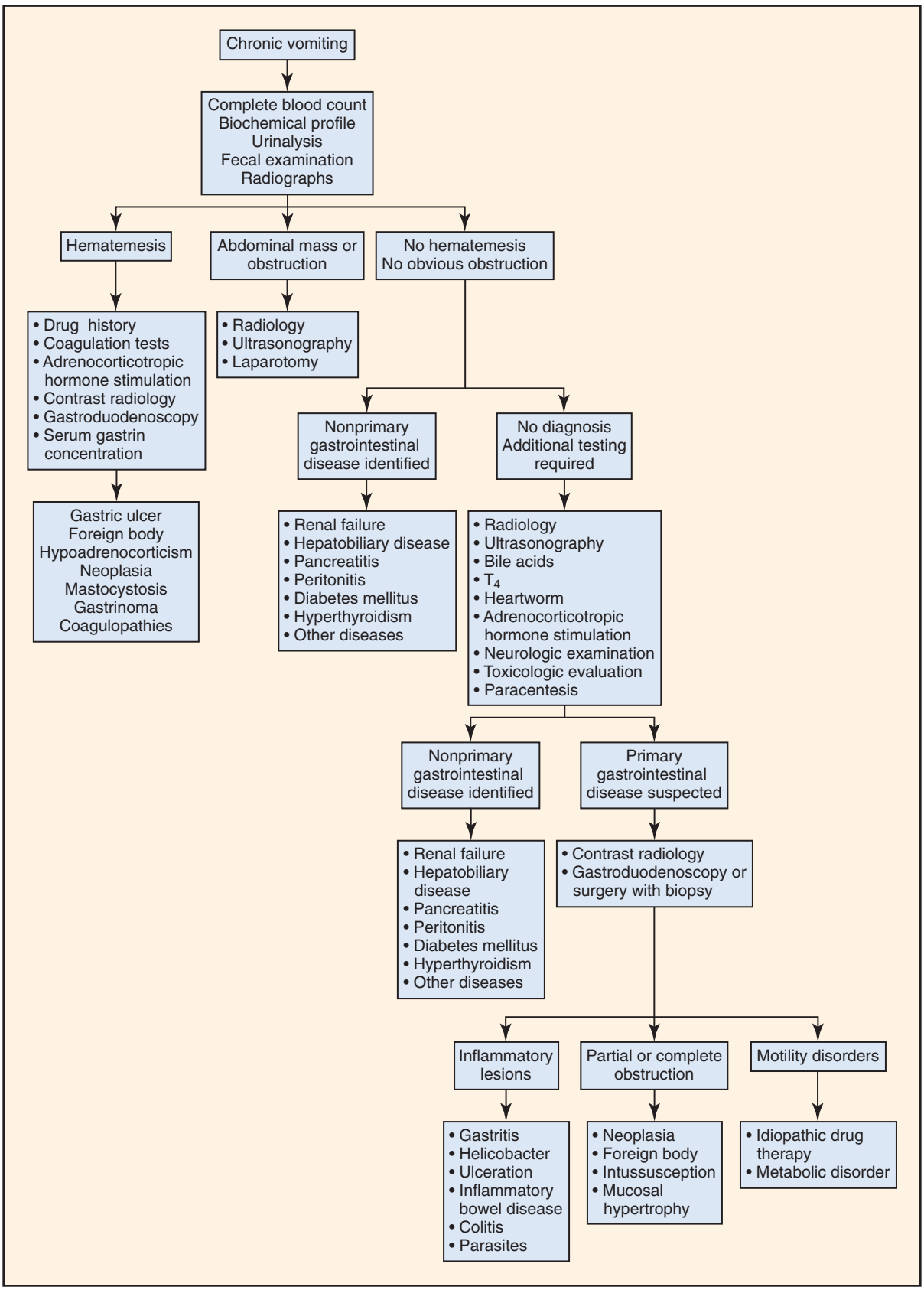

Figure 56-6 Diagnostic approach to the chronic vomiting patient.

(e.g., gastrin and fasting gastric pH measurement) should be performed.[5] The reader is referred to Chapter 25 for further detail.

Fecal examination is important in the detection of helminths, *Giardia* spp., *Salmonella* spp., *Campylobacter* spp., and parvovirus (as detected by enzyme-linked immunosorbent assay [ELISA]) as a cause of vomiting and diarrhea.

The pH of the vomitus can be used to differentiate vomiting from regurgitation. Additional laboratory evaluation for volume and content such as food, bile, foreign ingested material, digested or fresh blood, and parasites (ascarids, *Physaloptera* spp., cestodes, and *Capillaria* spp.) may be needed. Small clusters of fresh blood may be secondary to capillary microtrauma during the forceful vomiting process, but large amounts of digested blood usually indicate significant upper GI bleeding. Microscopic evaluations of the vomitus may sometimes reveal inflammatory or neoplastic cells, eggs of *Physaloptera* spp., and larvae or adult stages of *Ollulanus tricuspis*.

Gastric Imaging Techniques

Survey abdominal radiographs are often the initial diagnostic test when evaluating vomiting, abdominal pain, or abdominal distention. Radiographs provide information about gastric position, size, and content, which may help to diagnose GI obstruction, foreign bodies, gastric masses, ileus, intussusception, and gastric dilation or GDV. Survey radiographs are recommended in all animals in which GI foreign body such as carpet, socks, toys, bones, stones, or trash is suspected.

Contrast radiographs with barium sulfate liquid are also useful when inspecting size, shape, position, and motility of the stomach, as well as when nonradiographic foreign bodies, for example, socks, are missed on survey radiographs. Over time, the combination of ultrasonography and endoscopy have minimized the use of barium-contrast studies when evaluating mucosal conditions such as inflammation, neoplasia, and foreign bodies in the stomach.

When delayed gastric emptying is suspected, evaluation of gastric emptying is carried out using barium contrast (liquid or mixed with food), barium-impregnated polyethylene spheres, fluoroscopy, nuclear scintigraphy, or ^{13}C-octanoate breath test (see Chapter 26 and Table 56-1).[6-8]

The effects of sedation or other medications on gastric emptying times should always be taken into account when interpreting abdominal radiographs.

Ultrasonography is widely used when evaluating GI clinical signs. The gastric fundus is evaluated in left lateral recumbency, and the pylorus is evaluated in right lateral recumbency. Longitudinal and transversal views of stomach are required to measure the size of the organ and thickness of the gastric wall. Ultrasound may be used to assess wall thickness, wall layer identification, wall symmetry, extent of lesions, GI content, and motility. Diseases such as gastric cancer, chronic gastropathy, uremic gastritis, and delayed gastric emptying disorders have been diagnosed by ultrasonography in cats and dogs.[9-11] The test is noninvasive and requires little in the way of patient preparation. Ascites may enhance the image of abdominal organs in those patients with ascites. Aerophagia, on the other hand, may compromise identification of gastric or other organ pathology.

Endoscopy

Endoscopic evaluation and biopsy of the stomach is a commonly used procedure to evaluate the gastric mucosa in cats and dogs.[12] Endoscopy permits direct observation of the lumen and provides a noninvasive method of obtaining biopsy specimens for histopathologic evaluation. Brush cytology, fluid aspirations with culture, and foreign-body retrieval are all possible during routine endoscopy.

Endoscopy provides direct observation of the lumen and mucosa, but may miss extramural diseases. Endoscopy has the additional disadvantages of equipment expense, the need for general anaesthesia, and the inability to obtain full-thickness biopsies. Furthermore, the procedure does not permit the diagnosis of motility disorder or partial obstructions of the intestine. Endoscopy procedures are described in further details in Chapter 27.

Histopathologic Evaluation for Inflammation

Gastritis is a common finding in chronic vomiting dogs and cats. A diagnosis of gastritis requires histopathologic examination of gastric biopsy specimens. The histopathologic evaluation of the biopsy specimens includes cell types and number of infiltrating cells (lymphocytes, plasma cells, mononuclear cells, eosinophils, and neutrophils) and the presence of atrophy or hypertrophy, metaplasia, fibrosis, edema, or lymphoid follicles. Disagreements do exist among classification systems used by different pathologists when evaluating gastric biopsy specimens, making it important for the clinician, together with the pathologist, to define the criteria upon which the diagnosis is made. Figure 56-7 illustrates a visual scale grading system from 0 to 3 based on a photographic scale of cellular infiltrate, atrophy, and fibroses. Grade 0 is normal gastric mucosa and grade 3 is severe gastritis.[13] A standardized system of characterizing gastric cellularity and morphology has been developed by the World Small Animal Veterinary Association Gastrointestinal Standardization Group.[14]

There is an increasing interest in characterizing mucosal proinflammatory and immunomodulatory cytokines in cats and dogs with gastritis. Perhaps this will help the clinician's understanding of the immunologic response in the stomach and help the clinician's understanding of the mechanisms of gastritis.[13] Gastric biopsies can also reveal infections with parasites (*O. tricuspis*) or bacteria (*Helicobacter* spp.).[13,15,16] The reader is referred to other sections (Gastric Inflammation, Gastric Infection) in this chapter for more specific detail.

Evaluation for Gastric *Helicobacter* spp. Infection

Gastritis is often of unknown etiology in dogs and cats. *H. pylori* is accepted as an important pathogen in human gastroenterology and is believed to be the primary cause of chronic gastritis, gastric and duodenal ulceration, and even gastric carcinoma. For several years, interest in *Helicobacter* spp. infections as a cause of chronic gastritis in cats and dogs has been increasing. Several studies show that gastric infection with *Helicobacter* spp. is common in dogs, with a prevalence ranging from 67% to 100% in clinically healthy pet dogs, and 41% to 86% prevalence and in clinically healthy cats. Cats and dogs are infected with *Helicobacter felis*, *Helicobacter bizzozeronii*, *Helicobacter heilmannii*, *Helicobacter salomonis*, *Helicobacter bilis*, and *Flexispira rappini*.[17-22] The dilemma is that the pathogenicity of *Helicobacter* spp. is well described in several other species, such as ferrets, mice, and cheetahs, but is still evolving in cats and dogs. Investigations of the pathogenicity of *Helicobacter* spp. in dogs and cats with naturally acquired infections have so far been inclusive and indicate an overlap in the type and severity of gastric inflammation in infected and uninfected dogs and cats.

Several methods are available to diagnose *Helicobacter* infection in cats and dogs. Mucosal biopsies and histopathologic

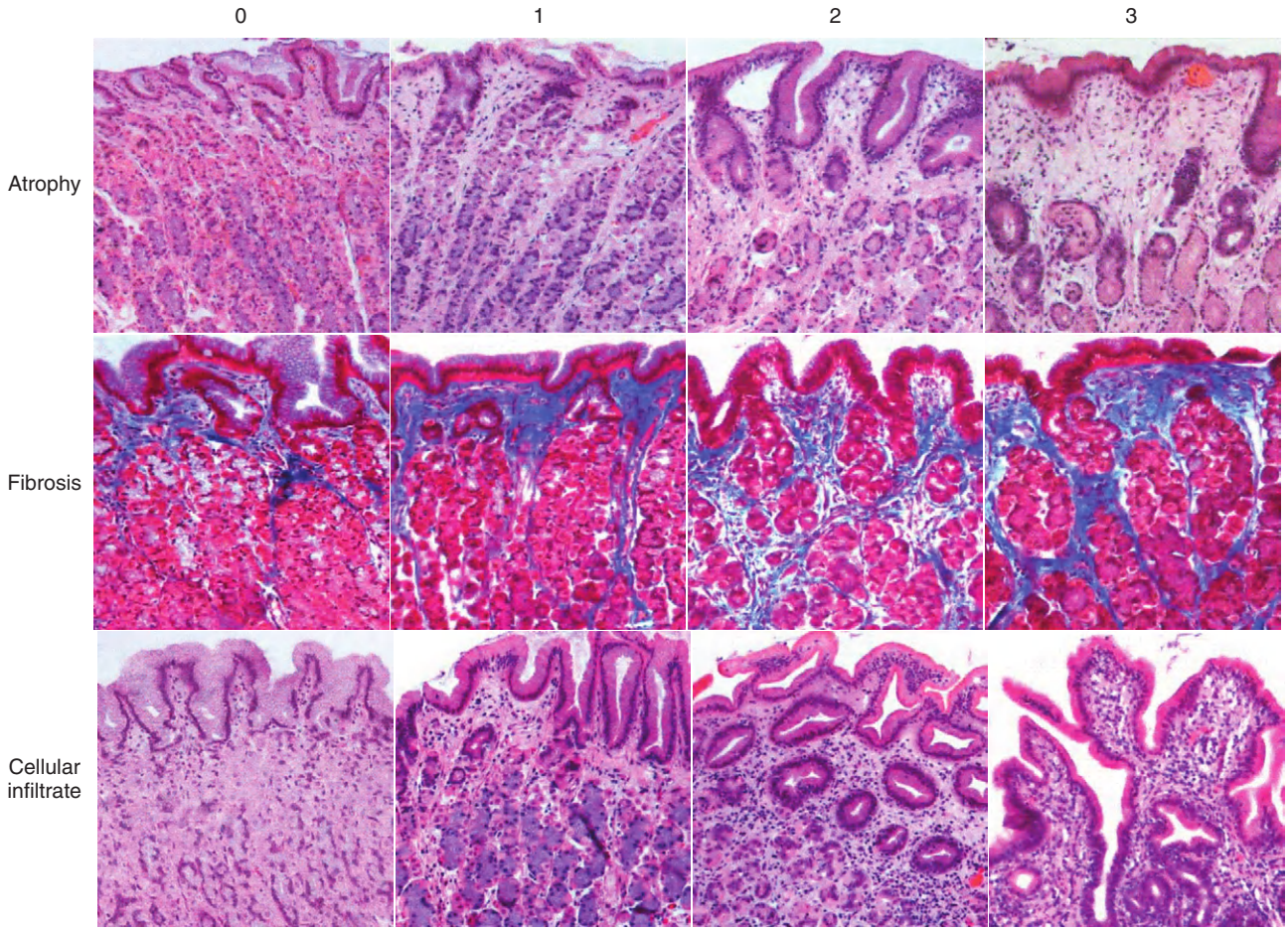

Figure 56-7 Photographic scale used to standardize the evaluation of atrophy, fibrosis, cellular infiltrate in fundic biopsies. A grade normal [0], mild gastritis [1], moderate gastritis [2], severe gastritis [3]. Magnification ×100; staining method: Masson trichrome (fibrosis) and hematoxylin and eosin (atrophy and cellular infiltrate). (From Wiinberg B, Spohr A, Dietz HH, et al: Quantitative analysis of inflammatory and immune response in dogs with gastritis and their relationship to *Helicobacter* spp. infection. *J Vet Intern Med* 19:4–14, 2005.)

evaluation have been used for many years. *Helicobacter* spp. can be recognized in a standard hematoxylin and eosin stain in the mucus and/or intracellularly in the epithelium. If *Helicobacter* spp. are present in very small numbers a Warthin-Starry silver stain may prove more useful.[13,15] *Helicobacter* spp. are a strong producer of urease and mucosal biopsies can be tested for urease activity with an "on site" rapid urease tests (e.g., CLO [*Campylobacter*-like organism] test). Urease breaks down urea and produces a high local concentration of ammonia, which makes it possible for *Helicobacter* spp. to survive the low pH of the gastric lumen. Rapid urease tests consist of a urea-rich medium with a pH sensitivity dye. Recent use of antibiotic, bismuth, or acid secretory inhibitors in the patient may interfere with the test and provide false-negative results. The ^{13}C breath test can be used to evaluate the effect of eradication.[23,24]

Polymerase chain reaction (PCR) techniques have proven very useful in the detection of *Helicobacter* spp. infections after DNA extraction of gastric biopsy specimens.[13] This method includes use of genus and species-specific primers to detect species verification. Brush cytology of the mucus are useful for detecting *Helicobacter* spp. in both cats and dogs.[25] The role of *Helicobacter* spp. in canine and feline gastritis is still unknown and much remains to be learned about the infection.

Exploratory Laparotomy

In some cases, exploratory laparotomy may be necessary to diagnose mural diseases of the GI tract that are beyond the reach of the endoscope, when perforation is suspected, or when multiorgan biopsy or full-thickness biopsy is required to obtain a definitive diagnose. At the time of exploratory laparotomy, full-thickness biopsy specimens of the stomach and intestine should always be considered, even with apparently normal macroscopic appearance. All abdominal organs must be examined and additional biopsies of the liver, lymph nodes, and masses should be obtained when indicated. If serum protein levels are low, this may influence tissue repair and increase the risk of biopsy-related complications. Fine-needle aspirates can be obtained from masses and lymph nodes when indicated. Cytology results may provide a preliminary result that will help the clinician initiate therapy before histopathology results are available. The complication rate following laparotomy is approximately 30% with 60% of the complications related to the primary disease and the rest related to surgical or anesthetic problems.[26]

INFLAMMATION

Kenneth W. Simpson

Gastric disease is typically the result of inflammation, ulceration, neoplasia, or obstruction. Clinical manifestations include vomiting, hematemesis, melena, retching, belching, hypersalivation, abdominal distention, abdominal pain, and weight loss. The clinical approach is guided by considering gastric disease as a group of clinical syndromes that segregate on the basis of etiology, pathology, and clinical presentation (Table 56-3).[1]

A large and varied group of gastric and nongastric disorders can cause similar clinical signs, so a systematic approach is essential to determine the cause. The diagnostic approach focuses initially on historical and physical findings, with clinicopathologic testing and diagnostic imaging used in patients with systemic involvement or chronic signs. This section focuses on etiopathogenesis, diagnosis, and treatment of acute and chronic gastritis.

Acute Gastritis

Etiology

Acute gastritis is the term applied to the syndrome of vomiting of sudden onset suspected to be associated with gastric mucosal insult or inflammation (Box 56-2). In most patients the cause is inferred from the history (e.g., dietary indiscretion), the diagnosis is rarely confirmed by biopsy, and treatment is more symptomatic and supportive than disease specific. Animals with acute gastritis associated with drug toxicity, foreign-body ingestion, or metabolic disorders frequently present with hematemesis, melena, concurrent diarrhea, or other signs of systemic illness and require a more thorough diagnostic approach to determine the cause and to provide optimal care. There is little evidence in the literature to suggest that viral infections such as parvovirus, distemper, or infectious canine hepatitis, have a role in acute gastritis.

Table 56-3 Diseases of the Stomach

Clinical Syndrome	Predominant Features
Acute gastritis	Sudden onset of vomiting
Ulceration or erosion	Vomiting, hematemesis, melena, ± anemia
Gastric dilation volvulus	Nonproductive retching, abdominal distention, tachycardia
Chronic gastritis	Chronic vomiting of food or bile
Delayed gastric emptying	Acute to chronic vomiting more than 8 to 10 hours after feeding
Neoplasia	Chronic vomiting, weight loss, ± anemia

Box 56-2 Causes of Acute Gastritis

- Dietary indiscretion or intolerance (nonallergic and allergic)
- Foreign bodies (e.g., bones, toys, hairballs)
- Drugs and toxins (e.g., antibiotics, digoxin, nonsteroidal antiinflammatory drugs, corticosteroids, heavy metals, plants, cleaners, bleach, dietary contaminants)
- Systemic disease (e.g., hypoadrenocorticism, uremia, liver disease)
- Parasites (e.g., *Ollulanus, Physaloptera* spp.)
- Bacteria (e.g., bacterial toxins, *Helicobacter*)
- Viruses

Clinical Examination

Vomiting of sudden onset is the principal clinical sign of acute gastritis. In some instances it is accompanied by hematemesis or melena and a variable degree of systemic involvement. The history may reveal access to garbage, toxins, medications, foreign bodies or ingestion of spoiled food. Signs of toxicity may be evident, such as jaundice and pallor with zinc ingestion, salivation or defecation with organophosphate toxicity or mushroom ingestion, and hypersalivation and oral ulceration with chemical ingestion.

Diagnosis

A diagnosis of acute gastritis is usually based on clinical findings and the response to symptomatic treatment. A specific diagnosis may be sought if the patient has access to foreign objects or toxins, is systemically ill, or has hematemesis, melena, and vomiting that fails to respond to symptomatic therapy, or other signs of more serious disease.

Laboratory testing in most animals with primary acute gastritis reflects mild dehydration and is often not performed in the absence of a suspicion of more serious disease. Abdominal radiographs can be taken to detect foreign objects or GI obstruction. Further diagnostics, such as ultrasonography and endoscopy, are rarely indicated, and most animals with simple gastritis respond to symptomatic therapy and "tincture of time."

Treatment

Therapy for uncomplicated acute gastritis is an empirical combination of symptomatic and supportive agents such as fluids, dietary restriction and modification, mucosal protectants or adsorbents, and possibly antacids.[2,3]

Fluid Therapy

Small amounts of oral fluids, little and often, can be given in the face of vomiting, with the volume increasing and frequency decreasing as vomiting subsides. Subcutaneous administration of an isotonic balanced electrolyte solution may be sufficient to correct mild fluid deficits (<5%), but is insufficient for patients with moderate to severe dehydration. Patients requiring intravenous fluids should undergo a more extensive diagnostic evaluation. Chapter 48 has more detailed information on fluid therapy.

Dietary Restriction and Modification

Where vomiting is acute, oral intake is typically discontinued for 24 hours. However, a liquid diet can be offered in the face of vomiting to maintain GI barrier function.[4] This can be transitioned to a homemade, nonspicy, fat-restricted, bland diet (e.g., boiled chicken and rice, low-fat cottage cheese and rice [1:3]) or a commercial fat-restricted, rice-based diet that is fed little and often. After a week or so, the normal diet can be reintroduced gradually.

Protectants and Adsorbents

Bismuth subsalicylate, kaolin-pectin, activated charcoal and magnesium, and aluminum- and barium-containing products are often administered in acute vomiting or diarrhea to bind bacteria and their toxins and to coat the GI mucosa. These agents are probably safer and more efficacious than antibiotics or motility modifiers in acute gastroenteritis. Pepto-Bismol (1 mL/5 kg PO TID), bismuth subcitrate, kaolin pectin (1 to 2 mL/kg PO TID), and sucralfate (0.25 to 1 g PO TID) are often employed although evidence-based

data in support of their usage is still incomplete. Acid-reducing drugs such as H_2-receptor antagonists can be administered, but are usually reserved for patients with signs of gastric erosion or ulceration (e.g., melena or hematemesis) or persistent gastritis as described below.

Antiemetic agents may be used in patients with acute gastritis but spontaneous resolution may take place without them. Chapters 23 and 35 provides more detailed information about the use of antiemetic agents.

Prognosis

The prognosis for complete recovery for uncomplicated acute gastritis is usually good to excellent.

Chronic Gastritis

Etiology

The diagnosis of chronic gastritis is currently based on the histologic examination of gastric biopsies and is subclassified according to histopathologic changes and etiology. Histopathologic evidence of gastritis is a common finding in dogs, with 35% of dogs investigated for chronic vomiting and 26% to 48% of asymptomatic dogs affected.[5,6] The prevalence in cats has not been determined.

Gastritis in dogs and cats is usually categorized according to the nature of the predominant cellular infiltrate (e.g., eosinophilic, lymphocytic, plasmacytic, granulomatous, lymphoid follicular), the presence of architectural abnormalities (e.g., atrophy, hypertrophy, fibrosis, edema, ulceration, metaplasia), and their subjective severity (e.g., mild, moderate, severe). A standardized visual grading scheme has been proposed by Happonen et al.[6] and has been adapted for pathologists.[7]

It should be noted that even with standardized grading schemes there is often poor agreement between pathologists.[7,8] Gastritis in dogs and cats is most commonly described as mild to moderate superficial lymphoplasmacytic gastritis, with or without concomitant lymphoid follicle hyperplasia. Eosinophilic, granulomatous, atrophic, and hyperplastic gastritis are less commonly reported.

Pathophysiology

Despite the high prevalence of gastritis in the companion animal population an underlying cause is rarely identified. In the absence of systemic disease, ulcerogenic or irritant drugs, gastric foreign objects, parasites (*Physaloptera* and *Ollulanus* spp.), and in rare instances fungal infections (*Pythium insidiosum*, *Histoplasma* spp.), chronic gastritis is usually attributed to dietary intolerance or allergy, occult parasitism, *Helicobacter* infection, or unknown pathogens. Treatment is often used to further define the cause of gastritis (e.g., diet responsive, antibiotic responsive, steroid responsive, or parasitic).

Although the basis of the immunologic response in canine and feline gastritis is unknown, recent studies have shed light on the immunologic environment in the GI tract and reveal a complex interplay between the microflora, epithelium, immune effector cells such as lymphocytes and macrophages, and soluble mediators such as chemokines and cytokines.[9-14] In health, this system avoids active inflammation by antigen exclusion and the induction of immune tolerance. The development of intestinal inflammation in mice lacking interleukin (IL)-10, transforming growth factor (TGF)-β, or IL-2 indicates the central importance of cytokines in damping-down mucosal inflammation. In many of these murine models, GI inflammation only develops in the presence of endogenous intestinal microflora, leading to the hypothesis that spontaneous mucosal inflammation may be the result of a loss of tolerance to this microflora. The role of these mechanisms in outbred species such as the dog and cat remains to be determined, but clearly loss of tolerance to bacterial or dietary antigens should be considered.

The epithelial cell is also emerging as a central coordinator in the inflammatory response. Epithelial cells are involved in sensing luminal constituents (e.g., bacteria) through pattern recognition receptors (also known as Toll-like receptors) and coordinating the inflammatory response. Gram-negative or pathogenic bacteria can induce proinflammatory cytokine secretion (e.g., IL-8, IL-1β) by epithelial cells, whereas "commensals" or bacteria such as *Streptococcus faecium* or *Lactobacillus* spp. induce the production of the immunomodulatory cytokines TGF-β or IL-10.[10] The proinflammatory cytokines produced by epithelial cells are modulated by the production of IL-10 from macrophages and potentially by the epithelial cells themselves.[15] In this context, dogs with lymphoplasmacytic gastritis of undetermined etiology show a correlation between the expression of the immunomodulatory cytokine IL-10 and proinflammatory cytokines (interferon [IFN]-γ, IL-1β, IL-8).[7] Mucosal pathology is related to cytokine messenger RNA (mRNA) expression (e.g., neutrophil infiltration in response to IL-8 and IFN-γ; macrophage and lymphocyte infiltration to IFN-γ; and fibrosis to IL-1β).

Histologic severity of lymphoplasmacytic gastritis in dogs correlates with atrophy, infiltration with lymphocytes and macrophages, and expression of IL-10 and IFN-γ.[7] Simultaneous expression of IL-10 and IFN-γ mRNA has also been observed in the intestines of Beagle dogs (lamina propria cells and the intestinal epithelium) in the face of a luminal bacterial flora that was more numerous than that of control dogs.[16] Thus it is tempting to visualize a "homeostatic loop" consisting of proinflammatory stimuli and responses, countered by immunomodulation and repair, with an imbalance in either of these arms manifest as gastritis.

Clinical Findings

The major clinical sign of chronic gastritis is vomiting of food or bile. Other clinical signs, like decreased appetite, weight loss, melena, and hematemesis, are variably encountered. The concurrent presence of dermatologic and GI signs raises the possibility of dietary intolerance.[17] Access to toxins, medications, foreign bodies, and dietary practices (including nutraceuticals) should be thoroughly reviewed. The signalment should not be overlooked as certain syndromes are breed restricted. Hypertrophy of the fundic mucosa is frequently associated with a severe enteropathy in basenjis[18] and stomatocytosis, hemolytic anemia, icterus, and polyneuropathy have not been noted in the Drentse Patrijshond.[19] Hypertrophy of the pyloric mucosa is observed in small brachycephalic dogs such as the Lhasa Apso and is associated with gastric outflow obstruction.[20,21] Atrophy of the gastric mucosa that may progress to adenocarcinoma has been reported in Lundehunds with protein-losing gastroenteropathy.[22,23]

Young, large-breed, male dogs in the Gulf States of the United States may have granulomatous gastritis caused by *Pythium* spp. with infection more prevalent in fall, winter, and spring.[24] Physical examination is often unremarkable. Abdominal distention may be related to delayed gastric emptying caused by obstruction or defective peristalsis. Abdominal masses, lymphadenopathy, or ocular changes may be encountered in dogs with gastric fungal or algae infections.

Diagnosis

A serum biochemical profile, complete blood count, urinalysis, and measurement of T_4 concentration (in cats >5 years old) should be performed as a basic screen for metabolic, endocrine, infectious, and other non-GI causes of vomiting, as well as the acid–base and

electrolyte changes associated with vomiting, outflow obstruction, or acid hypersecretion. Clinicopathologic tests are often normal in patients with chronic gastritis.

Eosinophilia may prompt the consideration of gastritis associated with dietary hypersensitivity, endoparasites, and mast cell tumors. Hyperglobulinemia and hypoalbuminemia may be present in basenjis with gastroenteropathy, or dogs with gastric pythiosis. Panhypoproteinemia is a feature of gastroenteropathy in the Lundehund breed, moderate to severe generalized IBD, GI lymphoma, and GI histoplasmosis. More specific testing, such as an ACTH stimulation test, or serology for *P. insidiosum*, is performed based on the results of these initial tests. Determination of serum food-specific immunoglobulin (Ig) E has not been proved useful in the diagnosis of dietary sensitivity in dogs or cats. The utility of non-invasive tests, such as serum pepsinogen and gastric permeability to sucrose, used to diagnose gastritis in people, has not been determined in dogs and cats.

Abdominal radiographs are frequently normal in dogs and cats with gastritis, but may show gastric distention or delayed gastric emptying (food retained for >12 hours after a meal). Contrast radiography may reveal ulcers or thickening of the gastric rugae or wall, but has largely been superseded by the combination of ultrasonography to detect mural abnormalities and endoscopy to observe and sample the gastric mucosa.

Endoscopic examination enables the visualization of foreign bodies, erosions, ulceration, hemorrhage, rugal thickening, lymphoid follicle hyperplasia (evident as mucosal pock marks), increased mucus or fluid (clear or bile stained), and increased or decreased mucosal friability. Discrete focal or multifocal mucosal nodules may be observed with *Ollulanus* spp. infection.

Gastric phycomycosis can be associated with irregular masses in the pyloric outflow tract and may prompt serologic testing by enzyme-linked immunosorbent assay (ELISA), western blotting, and culture of fresh gastric biopsies. Parasites such as *Physaloptera* spp. may be observed as 1- to 4-cm worms. Large amounts of bile-stained fluid are suggestive of duodenogastric reflux–associated gastritis, whereas abundant clear fluid may indicate hypersecretion of gastric acid. Gastric fluid can be aspirated for cytology (*Helicobacter* spp., parasite ova or larvae) and pH measurement. Impression smears of gastric biopsies are an effective way of looking for *Helicobacter* spp. and are more sensitive than the biopsy urease test (*Helicobacter* spp. produce urease). Serum gastrin should be measured in the face of unexplained gastric erosions, ulcers, fluid accumulation, or mucosal hypertrophy.[25-27]

The endoscopic procedure of dribbling dietary antigens onto the gastric mucosa to ascertain the presence of food allergy has not proved useful in dogs or cats. It is highly subjective, detects only immediate-type hypersensitivity reactions, and does not correlate very well with the results of dietary elimination trials. Biopsy samples should be taken from the gastric mucosa even when it looks grossly normal (usually three samples from each of the pylorus, fundus, and cardia). Thickened rugae may require multiple biopsies, and a full-thickness biopsy sample is often required to differentiate gastritis from neoplasia or fungal infection and to diagnose submucosal or muscular hypertrophy. The results of gastric ultrasonography can help to forewarn the clinician of these possibilities and to complement the endoscopic findings.[28]

Gastric sections should be stained with hematoxylin and eosin for the evaluation of cellularity and architecture, and a modified Steiner stain for gastric spiral bacteria. Fluorescence in-situ hybridization with oligonucleotide probes directed against bacterial 16S or 23S recombinant DNA can be used to document the presence of *Helicobacter* spp.[29] Special stains, such as Gomori methenamine silver, are indicated if pyogranulomatous inflammation is present to detect fungi. The Masson trichrome can be used to highlight gastric fibrosis, whereas Sirius red and toluidine blue help to reveal eosinophils and mast cells, respectively. Immunohistochemistry can be employed to help distinguish lymphoma from severe lymphocytic gastritis. Mucin staining has been performed in Lundehunds with gastric atrophy and reveals an abnormal presence of mucus neck cells and pseudopyloric metaplasia.[30]

The interpretation of gastric biopsy samples has important implications for patient care because biopsy findings are often used to guide treatment. For example, mild lymphoplasmacytic gastritis may be treated with a change in diet, whereas moderate lymphoplasmacytic gastritis without evidence of *Helicobacter* spp. infection or gastric parasites is often treated with corticosteroids. As the histopathologic evaluation of gastric biopsies is not uniform among pathologists, even when a standardized scoring scheme is used,[7,8] the prudent clinician should carefully review histologic sections to get a feel for the pathologist's interpretation. Even with optimum evaluation, similar histologic changes can be observed in patients with different underlying etiologies, so integrated evaluation of the clinical syndrome, presence or absence of concurrent intestinal disease, and well-structured treatment trials often form the basis of an etiologic diagnosis.

Treatment

Treatment of gastritis initially centers on the detection and treatment of underlying metabolic disorders and the removal of drugs, toxins, foreign bodies, parasites, and fungal infections.

Infection

Ollulanus tricuspis[31], *Physaloptera* spp, pythiosis[24], and *Helicobacter*–associated gastritis are discussed in the "Gastric Infection" section.

Chronic Gastritis of Unknown Cause

Lymphoplasmacytic gastritis of unknown cause is common in dogs and cats. It may be associated with similar infiltrates in the intestines, particularly in cats (that should also be evaluated for concurrent pancreatic and biliary disease). The cellular infiltrate varies widely in severity and it may be accompanied by mucosal atrophy or fibrosis, and less commonly hyperplasia.

Patients with mild, *Helicobacter*-negative, lymphoplasmacytic gastritis are initially treated with anthelminthics and dietary modification. The diet is frequently restricted in antigens to which the patient has been previously exposed, such as a lamb-based diet if the patient has previously been fed chicken and beef, or contains hydrolyzed proteins (usually chicken or soy) that may be less allergenic than intact proteins. Many of these diets are also high in carbohydrate and restricted in fat, which facilitates gastric emptying, and may contain other substances such as menhaden fish oil or antioxidants (vitamin C, vitamin E) that may ameliorate inflammation.

The test diet is fed exclusively for a period of about 2 weeks while vomiting is monitored.[17] If vomiting is improved a challenge with the original diet is required to confirm a diagnosis of food intolerance. The introduction of a specific dietary component to the test diet, such as beef, is required to confirm dietary sensitivity. If vomiting is unresponsive the patient may be placed on a different diet for another 2 weeks, usually the limit of client tolerance, or treated with prednisolone (1 to 2 mg/kg/day PO, tapered to every other day at the lowest dose that maintains remission over 8 to 12 weeks).

Patients with moderate to severe, *Helicobacter*-negative, lymphoplasmacytic gastritis are usually started on a combination of a test diet and prednisolone. If the patient goes into remission, it is maintained on the test diet while prednisolone is tapered and potentially discontinued. This regimen is typically supplemented with antacids and mucosal protectants if ulcers or erosion are detected at endoscopy or if hematemesis or melena is noted.

If gastritis is unresponsive to diet, prednisolone, and antacids, additional immunosuppression may be indicated. Gastric biopsies should be carefully reevaluated for evidence of lymphoma. In dogs, immunosuppression is usually increased with azathioprine (2 mg/kg PO SID for 5 days then every other day, on alternating days with prednisolone). Chlorambucil may be a safer alternative to azathioprine in cats and has been successfully employed in the management of IBD and small cell lymphoma. Prokinetic agents such as mosapride (Japan), prucalopride (Western Europe), cisapride, and erythromycin can be used as an adjunct where delayed gastric emptying is present and are discussed in more detail in Chapter 52.

Diffuse eosinophilic gastritis of undefined etiology is usually approached in a similar fashion to lymphoplasmacytic gastritis. The presence of eosinophilia, dermatologic changes, and eosinophilic infiltrates may be even more suggestive of dietary sensitivity or parasitic infection, or it may be a still ill-defined eosinophilic gastroenteropathy of the Rottweiler breed. In cats, it should be determined if these changes are part of a hypereosinophilic syndrome. Treatment for occult parasites, dietary trials, and immunosuppression can be carried out as described previously. Focal eosinophilic granulomas can be associated with parasites or fungal infection that should be excluded prior to immunosuppression with corticosteroids.

Atrophic Gastritis

Atrophic gastritis in dogs and cats is often associated with a marked cellular infiltrate. In people atrophy is associated with *Helicobacter* spp. infection and inflammation, and immune-mediated destruction.[32] Gastric disease is often not discovered until the patient presents with pernicious anemia secondary to cobalamin deficiency caused by a lack of gastric intrinsic factor. In people, atrophic gastritis, intestinal metaplasia of the gastric mucosa, hypergastrinemia and hypochlorhydria are thought to precede the development of gastric cancer.[33] The host inflammatory response is also thought to contribute to the development of atrophy and proinflammatory IL-1β and IL-10 gene polymorphisms in people are associated with increased inflammation, gastric atrophy, hypochlorhydria, and gastric cancer.[34-37]

Atrophic gastritis has been described infrequently in dogs and cats, but does share some similarities with people. Atrophic gastritis characterized by reduction in parietal cells and hyperplasia of neuroendocrine cells has been associated with gastric adenocarcinoma in Lundehunds.[38] Some of the adenocarcinomas displayed enterochromaffin-like cell differentiation, suggesting that hypergastrinemia secondary to fundic atrophy may be important in carcinogenesis. In murine models, the presence of concurrent gastric inflammation and hypergastrinemia is pivotal for the development of gastric cancer.[39] In dogs with lymphoplasmacytic gastritis of undetermined cause, gastric atrophy correlates with the expression of mRNA for IL-1β and IL-10 and the presence of neutrophils.[7] However, with the exception of the Lundehund, clear evidence that gastritis progresses to atrophy and gastric cancer in dogs or cats,[40] and the role of *Helicobacter* spp., regional or systemic neuroendocrine perturbations, and antigastric antibodies in the development of atrophy in dogs and cats remains to be determined.

In contrast to people, dogs and cats with atrophic gastritis have not been reported to develop cobalamin deficiency. This is probably because the pancreas, rather than the stomach, is the main source of intrinsic factor in these species.[41-43] Achlorhydria has been described in dogs and may enable the proliferation of bacteria in the stomach and upper small intestine, although this has not been proven. The treatment of atrophic gastritis has received limited attention, but *Helicobacter* spp. eradication and immunosuppression have been effective in people.

Hypertrophic Gastritis

Hypertrophy of the fundic mucosa is uncommon and is often part of the breed-specific gastropathies or gastroenteropathies mentioned previously. Measurement of gastric pH and serum gastrin can help to differentiate idiopathic hypertrophic pylorogastropathy from hypertrophy associated with hypergastrinemia.[25,26] Pancreatic polypeptide-producing tumors may also be associated with mucosal hypertrophy. Concurrent hypergastrinemia should prompt consideration of underlying hepatic or renal disease, achlorhydria, or gastrin-producing tumors, which should be pursued appropriately. Basenji gastroenteropathy is variably associated with fasting hypergastrinemia and exaggerated secretin-stimulated gastrin, and anecdotal reports suggest that affected Basenjis may respond to antimicrobial therapy. Brachycephalic, middle-aged, small-breed dogs such as Shih Tzus seem predisposed to the syndrome of hypertrophic pylorogastropathy, in which vomiting is secondary to pyloric outflow obstruction caused by hypertrophy of the pyloric mucosa and/or muscularis.[20,21] Antral hypertrophy of brachycephalic dogs causes outflow obstruction and is treated surgically.

When hypertrophic gastropathy, ulcers or erosions, or excessive gastric juice are encountered at endoscopy, intravenous H_2-antagonists or proton pump inhibitors can be given during the endoscopic procedure as prophylaxis for postoperative perforation or esophagitis.[2]

INFECTION

Kenneth W. Simpson and Robert J. Washabau

The stomach may be colonized by several types of infectious organisms (Table 56-4). The most important of these are the helminths (*Physaloptera* spp., *Ollulanus* spp., *Gnathostoma* spp., *Spirocerca* spp.), protozoa (*Cryptosporidium* spp.), fungi (*Histoplasma* spp.), oomycetes (*Pythium* spp.), and bacteria (*Helicobacter* spp.). The routine medical investigation of any dog or cat affected with chronic vomiting should include direct and indirect fecal examinations for helminth and protozoa, bacterial culture of feces, serologies, and molecular methodology. Some organisms appear to be of low pathogenicity, but it should be emphasized that even commensal organisms may become pathogens given the appropriate circumstance.

Helminth Infection

Physaloptera

Physaloptera spp. are approximately 2 to 6 cm long and may be detected sporadically in the stomachs of dogs and cats (Figure 56-8). *P. rara* are described most commonly and appear to be primarily a parasite of coyotes. Diagnosis is difficult as worm burden is often low and the eggs are transparent and difficult to see in sugar flotation.

Table 56-4 Etiology of Gastric Infection in the Dog and Cat

Infectious Agent	Geographic Distribution	Hosts	Location in the Host	Method of Infection
Helminths				
Physaloptera	Worldwide	Dogs	Stomach, intestine	Ingestion
Ollulanus	Worldwide	Cats	Stomach	Ingestion
Gnathostoma	Africa, Asia, Europe	Dogs, cats	Stomach, systemic migration	Ingestion
Spirocerca	Worldwide	Dogs	Stomach, esophagus	Ingestion
Protozoa				
Cryptosporidium	Worldwide	Dogs, cats	Stomach, small intestine	Ingestion
Fungi				
Histoplasma	Worldwide, temperate, subtropical	Dogs, cats	Stomach, intestine, colon	Ingestion
Oomycetes				
Pythium	Worldwide, tropical, subtropical	Dogs	Stomach, colon	Skin, GI tract
Bacteria				
Helicobacter	Worldwide	Dogs, cats	Stomach, colon	Ingestion

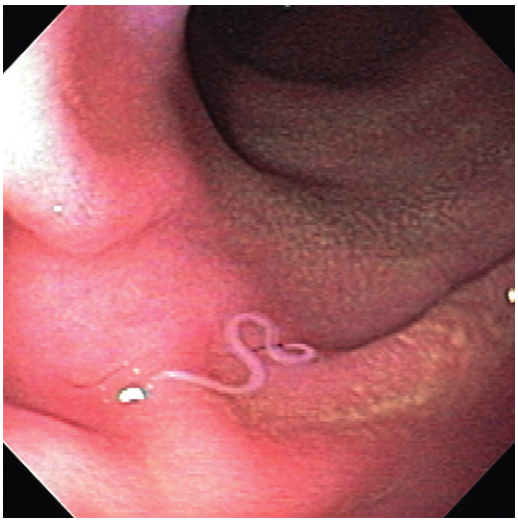

Figure 56-8 Endoscopic image of a mature *Physaloptera* worm in the gastric fundus of an 11-year-old mixed-breed dog. (Courtesy of Dr. Michael D. Willard of Texas A&M University.)

Treatment with pyrantel pamoate (5 mg/kg PO: dogs single dose; cats two doses 14 days apart) may be effective. Control of infection may be difficult because of the ingestion of intermediate hosts, such as cockroaches and beetles, and paratenic hosts, such as lizards and hedgehogs. Given the difficult diagnosis of *Ollulanus* and *Physaloptera* spp., empirical therapy with an anthelminthic such as fenbendazole (50 mg/kg PO daily for 5 days) may be warranted in dogs and cats with unexplained gastritis.[1]

Ollulanus

O. tricuspis is a microscopic worm (0.7 to 1 mm long, 0.04 mm wide) that infects the feline stomach. Its predominant cat-to-cat transmission is through ingestion of vomitus. It can also undergo internal autoinfection with worm burdens reaching up to 11,000 per stomach. Mucosal abnormalities range from none, to rugal hyperplasia, and nodular (2 to 3 mm) gastritis.

Histologic findings include lymphoplasmacytic infiltrates, lymphoid follicular hyperplasia, fibrosis, and up to 100 globular leukocytes per high-power field. *Ollulanus* spp. are not detected by fecal examination and require evaluation of gastric juice, vomitus, or histologic sections for the presence of larvae or worms. Gastric lavage and xylazine-induced emesis have been described to aid diagnosis. Treatment with fenbendazole (50 mg/kg PO daily for 5 days) may be effective.[2]

Gnathostoma

Gnathostomes (e.g., *Gnathostoma spinigerum*, *Gnathostoma binucleatum*) are parasitic nematodes of dogs and cats.[3] Any organ system may be involved, but the most common manifestations of infection are localized swelling of the skin and gastric mucosa. Following ingestion of infective larvae, the larvae excyst in the stomach, penetrate the gastric wall, and migrate through the liver to more distant connective tissue and muscle. After 4 weeks, they migrate once again to the gastric wall where they produce an inflammatory response, and mature into adults in 6 to 8 months. At 8 to 12 months after initial ingestion, the worms mate, and eggs are passed in the feces of the host.

Spirocerca

Spirocercosis affects primarily the dog and is caused by the nematode *S. lupi*.[4] Typical clinical signs are regurgitation, vomiting, and dyspnea. Ingested larvae follow a specific migratory route, penetrating the gastric mucosa of the host, migrating along arteries, maturing in the thoracic aorta before eventually migrating to the caudal esophagus (Figure 56-9). The worm lives in nodules provoking a severe mixed inflammatory/neoplastic-like response. Radiographic lesions regarded as diagnostic for spirocercosis are esophageal nodules, aortic aneurysms and mineralization, and caudal thoracic spondylitis. Doramectin is the current drug of choice, effectively killing adult worms and decreasing egg shedding. In endemic areas, monthly administration of a combination of imidacloprid 10%/moxidectin 2.5% in puppies starting at 2 to 4 months of age achieves effective and safe protection of canine spirocercosis.[5]

Protozoal Infection

Cryptosporidium

Cryptosporidium spp. are protozoan parasites of a large number of vertebrate species, including humans, cats, and dogs.[6]

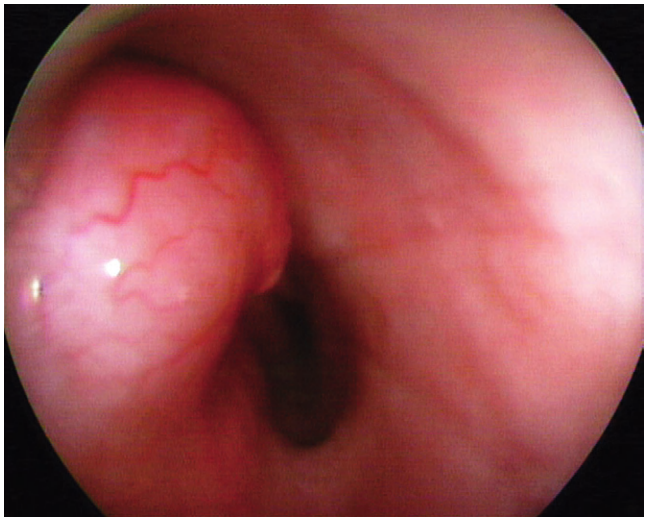

Figure 56-9 Endoscopic appearance of a *Spirocerca lupi*-induced fibrosarcoma of the gastroesophageal junction in an 8-year-old mixed-breed dog. (Courtesy of Dr. Michael D. Willard of Texas A&M University.)

Cryptosporidia have a worldwide distribution and are important pathogens of veterinary and public health concern because of their ability to produce debilitating GI disease. Cryptosporidia are obligate, intracellular parasites generally of the gastric and intestinal epithelium. Diarrhea is the most important clinical sign, but other clinical findings include nausea, vomiting, abdominal pain, lethargy, and malaise. Clinical signs are not always present, indeed some infections are discovered only through routine surveillance. Recent studies of *Cryptosporidium* infection rates in cats and dogs have reported prevalence rates in dogs ranging from 0.5% to 44.1%, and in cats from 0% to 29.4%, and, of course, cats and dogs may serve as an important source of human infection.[6] Cryptosporidial infections may not be associated with active shedding of oocysts; acid-fast staining, immunofluorescent antibody staining of a fecal smear, and fecal antigen ELISA may aid in the identification of cryptosporidial oocysts. No treatment is currently registered for *Cryptosporidium* infection in small animals. Tylosin has been used successfully in cats but requires a long course of therapy.[6]

Fungal Infection

Histoplasma

Etiology

Histoplasmosis is a systemic fungal disease of dogs and cats caused by *Histoplasma capsulatum*. In the environment, *Histoplasma capsulatum* organisms are mycelial, saprophytic soil fungi. In infected tissue or when cultured at 30°C (86°F) to 37°C (98.6°F), the organism is a yeast. The fungus is endemic throughout most of the temperate and subtropical regions of the world. Most cases of histoplasmosis in the United States occur in the central states, with the geographic distribution following the Mississippi, Ohio, and Missouri Rivers.[7,8]

Pathophysiology

Infection is probably via inhalation or ingestion of infective conidia from the environment. The respiratory system is thought to be the primary route of infection in cats and dogs, although the GI tract may also be an important route in the dog. After inhalation or ingestion, conidia transform from the mycelial phase and are phagocytized by macrophages, where they grow as facultative intracellular organisms. Hematogenous and lymphatic dissemination results in multisystemic disease. Organisms can be disseminated to any organ system, but the lungs, diffuse GI tract, lymph nodes, liver, spleen, bone marrow, eyes, and adrenal glands are the most common organs of dissemination in dogs; lungs, liver, lymph nodes, eyes, and bone marrow are most commonly affected in cats. Cell-mediated immunity induces a granulomatous inflammatory response in most infection.[9]

Clinical Examination

Dogs with GI histoplasmosis are typically presented with mild fever, anorexia, lethargy, weight loss, vomiting, diarrhea, hematochezia, and tenesmus. Cachexia is a common physical examination finding. Other historical and physical examination findings (dyspnea, cough, ascites, lameness, oropharyngeal ulcerations, chorioretinitis, neuropathy) depend upon organ and tissue involvement.

Diagnosis

Organism identification is required for definitive diagnosis. The most common means of organism identification is cytology. Cytology from affected tissue reveals pyogranulomatous inflammation, often with numerous small, round to oval intracellular yeast cells (2 to 4 μm in diameter) characterized by a basophilic center and a light halo. Exfoliative cytology during endoscopy is particularly useful in diagnosing the disease.[10] Histopathology is helpful if cytology is nondiagnostic or inconclusive. Multiple endoscopic biopsies are usually sufficient to diagnose the disease. The yeast form does not stain well with routine hematoxylin and eosin stains, so special stains such as periodic acid-Schiff and Gomori methenamine silver stain are often used to demonstrate organisms. Fungal culture from affected tissue can be used for diagnosis but is rarely needed in clinical cases. Currently available serologies have poor specificity and sensitivity.[9]

Treatment

Itraconazole (5 mg/kg PO BID for 2 to 4 months) is considered the treatment of choice for feline histoplasmosis. In one study, itraconazole therapy cured histoplasmosis infections in all eight study cats.[11] Ketoconazole and amphotericin B have been described as the treatments of choice for canine histoplasmosis (see Chapter 36). With gastric, intestinal, and colonic involvement, additional GI therapy may be useful in affected dogs, for example, dietary modification, treatment for small intestinal bacterial overgrowth, and direct antidiarrheal therapy. Corticosteroids may have been used successfully in the treatment of airway obstruction secondary to hilar lymphadenopathy in chronically infected dogs.[12]

Prognosis

There may be important species differences in prognosis although the paucity of reports, especially of prospective clinical trials, makes it difficult to generalize. It would seem that the prognosis is guarded in dogs, but fair to good in cats.

Oomycetes Infection

Pythium

Etiology

P. insidiosum is an aquatic oomycete that causes severe GI pathology in a range of hosts in the tropical and subtropical climates.[13] Based on ribosomal RNA gene sequence data, members of the Class *Oomycetes* are phylogenetically distinct from the Kingdom *Fungi*, and are

more closely related to algae than to fungi.[14] The oomycetes differ from fungi in two important properties: cell wall and cell membrane composition. Chitin is an essential component of the fungal cell wall, but it is generally lacking in the oomycete cell wall. Oomycetes also differ from fungi in that ergosterol is not a principal sterol in the oomycete cell membrane. This difference may explain why ergosterol-targeting drugs like itraconazole are less effective in the medical treatment of pythiosis.[14]

Pathophysiology

The infective state of *P. insidiosum* is thought to be the motile zoospore, which is released into stagnant water in warm environments, and likely causes infection either by encysting in the skin, or by being ingested into the GI tract. Ingested zoospores encyst and adhere to the gastric, jejunal, and colonic epithelium with a polarity oriented toward the submucosa for rapid tissue penetration following germ tube eruption. *Pythium* induces a chronic pyogranulomatous response in the GI tract and mesenteric lymph nodes. The gastric outflow tract and ileocolonic junction are the most frequently affected portions of the GI tract, and it is not uncommon to find two or more segmental lesions in the same patient.[15] Inflammation in affected regions is typically centered on the submucosa, with variable mucosal ulceration and occasional extension of disease through serosal surfaces, resulting in adhesion formation and peritonitis.

Clinical Examination

Weight loss, vomiting, diarrhea, and hematochezia are the most important clinical signs. Physical examination often reveals emaciated body condition and a palpable abdominal mass. Signs of systemic illness such as lethargy and depression are not typically present unless intestinal obstruction, infarction, or perforation occurs.

Diagnosis

Gastric outflow obstruction, ileocolonic wall thickening, obliteration of the normal layered appearance, and regional lymphadenopathy are common ultrasonographic features of canine intestinal pythiosis.[16] Of course, these findings cannot be readily differentiated from those associated with GI malignancy. Definitive diagnosis requires histologic demonstration or immunohistochemical staining of the organism and/or positive ELISA or PCR assays. The histologic findings associated with pythiosis generally are characterized by eosinophilic granulomatous to pyogranulomatous inflammation with fibrosis. Affected tissue typically contains multiple foci of necrosis surrounded and infiltrated by neutrophils, eosinophils, and macrophages. Discrete granulomas composed of epithelioid macrophages, plasma cells, multinucleate giant cells, and neutrophils and eosinophils may also be observed. *Pythium* zoospores may be cultured directly from affected tissue in antibiotic-containing (e.g., streptomycin and ampicillin) media. More recently, sensitive and specific ELISA and PCR assays have been developed for the accurate diagnosis of pythiosis in dogs.[17-19]

Treatment

Aggressive surgical resection remains the treatment of choice for pythiosis in dogs. Because it provides the best opportunity for long-term cure, complete resection of infected tissue should be pursued whenever possible. Segmental lesions of the GI tract should be resected with 3- to 4-cm margins whenever possible. Medical therapy for the oomycetes has not been very promising. This may relate to the absence of ergosterol (cell membrane target of most currently available antifungal drugs) in the oomycete cell membrane. Clinical and serologic cures have been obtained in a small number of dogs following therapy with amphotericin B lipid complex (2 to 4 mg/kg QOD administered to a cumulative dose of 24 to 27 mg/kg) or itraconazole (10 mg/kg q24h for 6 to 9 months).

Prognosis

Unfortunately, most dogs with GI pythiosis are not presented to the veterinarian until late in the course of the disease, when complete excision is not possible. The anatomic site of the lesion (e.g., pylorus or ileocolic sphincter) may also prevent complete excision. Consequently, the prognosis is usually grave in most animals.[14]

Bacterial Infection

Helicobacter

Etiology

The importance of bacteria and unrecognized pathogens (obligate or opportunistic) in the development of gastric inflammation is best demonstrated by the gastric bacterium *H. pylori*, a Gram-negative bacterium, that chronically infects more than half of all people worldwide.[20] Chronic infection of human adults with *H. pylori* is characterized by the infiltration of polymorphonuclear and mononuclear cells and the upregulation of proinflammatory cytokines and the chemokine IL-8. Mucosal T cells in infected individuals are polarized toward the production of IFN-γ, rather than IL-4 or IL-5, indicating a bias toward a T-helper (Th)1 response.[21,22] This sustained gastric inflammatory and immune response to infection appears to be pivotal for the development of peptic ulcers and gastric cancer in people.[23-25]

The prevalence of gastric *Helicobacter* spp. infection ranges from 67% to 100% of healthy pet dogs, 74% to 90% of vomiting dogs, 100% of laboratory Beagles and 40% to 100% of healthy and sick cats.[26,27-39] In contrast to people, in whom *H. pylori* infection predominates, dogs and cats are colonized by a variety of large spiral organisms (5 to 12 μm). In cats from Switzerland, the United States, and Germany, *H. heilmannii* is the predominant species, with *H. bizzozeronii* and *H. felis* much less frequent. In dogs from Finland, Switzerland, the United States, and Denmark, *H. bizzozeronii* and *H. salomonis* are most common, followed by *H. heilmannii* and *H. felis*; *H. bilis* and *F. rappini* have also been described. Cats can also be colonized by *H. pylori* (2 to 5 μm) but infection has been limited to a closed colony of laboratory cats.

Pathophysiology

The large *Helicobacter* spp. found in dogs and cats do not attach to the epithelium, but colonize the superficial mucus and gastric glands, particularly of the fundus and cardia, and may also be observed intracellularly.[27,28,35,36] Degeneration of gastric glands, with vacuolation, pyknosis, and necrosis of parietal cells is more common in infected than uninfected animals. Inflammation is generally mononuclear in nature and ranges from mild to moderate in severity. Gastric lymphoid hyperplasia is common and can be extensive in dogs and cats infected with *Helicobacter* spp. In addition to this local gastric immune response, a systemic response characterized by increased circulating anti-*Helicobacter* IgG has been detected in sera from naturally infected dogs and cats.[29,30] However, the gastritis observed in cats and dogs infected with large spiral bacteria is generally less severe than that observed in *H. pylori*–infected people (where neutrophilic aggregates, and moderate to severe gastritis, are commonly encountered), and GI ulcers, gastric neoplasia, or changes in serum gastrin or acid secretion have not been associated with *Helicobacter* spp. infection in dogs and cats.[27,28,37]

The effect of eradicating *Helicobacter* spp. on gastritis and clinical signs, the main form of evidence supporting the pathogenic role of *H. pylori* in human gastritis, has not been thoroughly investigated to date in dogs and cats. Antibiotic trials in dogs and cats with gastritis and *Helicobacter* spp. infection showed that vomiting improved in 90% of 63 dogs and cats, and 86% of 24 dogs.[38,39] In one trial, 14 of the 19 animals having repeat endoscopy had resolution of gastritis and no evidence of *Helicobacter* spp. in gastric biopsies.[38] Another study found that gastritis scores in dogs that were *Helicobacter*-negative at 6 months were decreased, whereas those in *Helicobacter*-positive dogs increased.[39] With such limited information from eradication trials, most current knowledge about the pathogenicity of *Helicobacter* spp. in dogs and cats comes from evaluation of animals with and without infections and clinical signs, and a small number of experimental infections.

Clinical Examination and Diagnosis

The interspecies differences in *Helicobacter*-associated gastritis in people, dogs, and cats may be attributed to differences in the virulence of the infecting *Helicobacter* spp., or the host response. Studies that address this issue indicate that *H. pylori* evokes a more severe proinflammatory cytokine and cellular response in dogs and cats than natural or experimental infection with large *Helicobacter* spp.[40,41] The limited mucosal inflammatory response and absence of clinical signs in the vast majority of dogs and cats infected with non–*H. pylori Helicobacter* spp., despite significant antigenic stimulation (evidenced by seroconversion and lymphoid follicle hyperplasia), suggest that large gastric *Helicobacter* spp. are commensal rather than pathogenic for the population in general. With this in mind, it is interesting to speculate that enhanced susceptibility to *Helicobacter* spp. conferred by differences in host genetics or an environmental trigger, rather than the innate pathogenicity of these bacteria, could explain the development of gastritis and clinical signs in some, but not all *Helicobacter*-infected dogs and cats. This is consistent with recent thinking on IBD[42] and much still remains to be learned about the role of *Helicobacter* spp. in canine and feline gastritis.

Ownership of dogs and cats has been correlated with an increased risk of infection of *H. heilmannii* in people.[43] Case reports have also suggested the transmission of *Helicobacter* spp. from pets to man.[44] Recent studies clearly confirm that dogs and cats harbor *H. heilmannii*, but the subtypes of *H. heilmannii* present in dogs and cats (types 2 and 4) are of minor importance (approximately 15% of cases) to people, who are predominantly colonized by *H. heilmannii* type 1 (the predominant *Helicobacter* sp. in pigs).[34]

The finding of *Helicobacter* DNA in the oral cavity of dogs raised potential for transmission through contact with oral secretions; however, it has been shown recently that *Wolinella* rather than *Helicobacter* spp. are the dominant *Helicobacteraceae* in the canine oral cavity.[45,46]

Treatment

The general lack of knowledge of the pathogenicity of gastric *Helicobacter* spp. has meant that veterinarians are faced with the dilemma of either treating or ignoring spiral bacteria observed in biopsy samples from patients with chronic vomiting and gastritis. In light of their pathogenicity in humans, ferrets, cheetahs, and mice, and results of recent antibiotic trials in dogs and cats, it would seem prudent to attempt to eradicate gastric *Helicobacter* spp. prior to initiating treatment with immunosuppressive agents to control gastritis. However, this must be decided on an individual basis. For example, in the patient with a lymphoplasmacytic infiltrate of the stomach and small intestine and concomitant gastric *Helicobacter* spp. infection, should one treat for IBD, *Helicobacter*, or both?

The authors recommend treating symptomatic patients that have biopsy-confirmed *Helicobacter* spp. infection together with gastritis (typically described as lymphoplasmacytic with lymphoid follicular hyperplasia). Current treatment protocols are based on those found to be effective in people infected with *H. pylori*. An uncontrolled treatment trial of dogs and cats with gastritis and *Helicobacter* spp. infection showed that clinical signs in 90% of 63 dogs and cats responded to treatment with a combination of metronidazole, amoxicillin, and famotidine, and that 14 (74%) of 19 animals subject to repeated endoscopic examination had no evidence of *Helicobacter* spp. in gastric biopsies.[38] A controlled trial of amoxicillin (15 mg/kg PO BID for 14 days), metronidazole (10 mg/kg PO BID for 14 days) and bismuth ± famotidine in 24 dogs found a similar decrease in vomiting (86.4%) and reduced gastritis scores in dogs that were *Helicobacter*-negative 6 months later.[39] The use of famotidine did not improve resolution of clinical signs or eradication of *Helicobacter*. Unfortunately, only 43% of dogs were free from *Helicobacter* at 6 months,[39] which echoes the results of controlled studies in asymptomatic *Helicobacter*-infected dogs and cats. Treatment combinations evaluated in these asymptomatic animals included (a) amoxicillin (20 mg/kg PO BID for 14 days), metronidazole (20 mg/kg PO BID for 14 days), and famotidine (0.5 mg/kg PO BID for 14 days) in dogs[37]; (b) clarithromycin (30 mg PO BID for 4 days), metronidazole (30 mg PO BID for 4 days), ranitidine (10 mg PO BID for 4 days), and bismuth (20 mg PO BID for 4 days) (CMRB) in *H. heilmannii*–infected cats[47]; and (c) azithromycin (30 mg PO SID for 4 days), tinidazole (100 mg PO SID for 4 days), ranitidine (20 mg PO SID for 4 days), and bismuth (40 mg PO SID for 4 days) (ATRB) in *H. heilmannii*–infected cats.[47] Reevaluation of infection status at 3 days (dogs) or 10 days (cats) after treatment revealed six of eight dogs and 11 of 11 CMRB- and four of six ATRB-treated cats to be free of *Helicobacter* spp. on the basis of histology and urease testing (dogs) or ^{13}C-urea breath test (dogs and cats).[47,48] However, at 28 days (dogs) or 42 days (cats) after completing antimicrobial therapy, eight of eight dogs, four of 11 cats that received CMRB, and five of six cats that received ATRB, were found to be reinfected. A transient effect of combination therapy (amoxicillin 20 mg/kg PO TID for 21 days, metronidazole 20 mg/kg PO TID for 21 days, and omeprazole 0.7 mg PO SID for 21 days) on bacterial colonization also has been observed in six cats with *H. pylori* infection.

Further analysis of gastric biopsies from infected dogs and *H. pylori*–infected cats using PCR and *Helicobacter*-specific primers revealed persistence of *Helicobacter* DNA in gastric biopsies that appeared negative on histology and urease testing. These studies suggest that antibiotic regimens that are effective against *H. pylori* in people may only cause transient suppression, rather than eradication, of gastric *Helicobacter* spp. in dogs and cats. The reason for the much higher apparent recrudescence or reinfection rate in dogs and cats than people (1% to 2% per year observed after treatment of *H. pylori*) could be a result of antimicrobial resistance of non–*H. pylori Helicobacter* spp. or the relatively high proportions of intracellular *Helicobacter* in dogs and cats.[35-37] Antibiotic sensitivity testing of cultivable *Helicobacter* spp. infecting dogs and cats indicates they are sensitive to most commonly selected antibiotics, but can harbor resistance against metronidazole.[49]

In a recent study, metronidazole (11 to 15 mg/kg PO BID), amoxicillin (22 mg/kg PO BID), and bismuth subsalicylate (0.22 mL/kg PO TID-QID) were administered to five *Helicobacter*-infected animals (three dogs and two cats) for 21 days, and there was resolution of vomiting and long-term eradication of *Helicobacter* (9 to

38 months) in all animals. The combination of amoxicillin (20 mg/kg PO BID), clarithromycin (7.5 mg/kg PO BID), and metronidazole (10 mg/kg PO BID) for 14 days has been used to successfully eradicate *H. pylori* infection in cats.

Prognosis

These studies suggest that a longer duration of treatment (21 days) or the use of antibiotics that can eradicate intracellular *Helicobacter* spp. (e.g., clarithromycin) may improve eradication, but further studies are required before clear guidelines regarding the treatment of gastric *Helicobacter* spp. in dogs and cats can be made.

Diffuse Gastrointestinal Infection

Some GI pathogens infect the entire span of the GI tract from stomach to anorectum. Infection with these pathogens (e.g., *Giardia, Campylobacter, Salmonella, Clostridium*) is more often associated with small and/or large intestinal pathology, but gastric pathology (inflammation, edema, necrosis) and clinical signs (anorexia, vomiting, hematemesis) may be evident concurrently. A recent study reported that for dogs in which intestinal biopsy specimens and gastric biopsy specimens were collected, concurrent pathologic changes were recorded in 72% of dogs. These data support the notion that GI pathology, including GI infection, may span the entire GI tract.[50]

OBSTRUCTION

Jean A. Hall

Gastric outlet obstruction refers to an inability of food and/or water to properly exit from the stomach because of mechanical blockage at or near the pylorus.[1] There are four main causes for this problem: (a) foreign objects and/or intraluminal masses, (b) mucosal or muscular proliferative and/or infiltrative disease, (c) compression of the outflow tract by masses and/or organs outside the stomach, or (d) malpositioning of the stomach. Diagnosis of mechanical obstruction is usually straightforward and can be made radiographically (e.g., failure of barium to leave the stomach, finding a mass or object in the pyloric antrum), endoscopically, ultrasonographically, or surgically. Surgical removal of the foreign object or the affected area is often the preferred therapy.

Gastric Dilation and Volvulus

Etiology

GDV is an acute life-threatening condition characterized by malposition of the stomach, rapid accumulation of air in the stomach, increased intragastric pressure, and shock. Although some progress has been made in determining risk factors, understanding the pathophysiology, and in developing new treatments, the cause is still speculative.[2] Overall mortality rate for GDV is 33%.[3] Early diagnosis and treatment have improved survival rate significantly, although mortality remains high at 15% even with current treatments.[4-6]

Risk factors for GDV include purebred status, large- or giant-breed conformation (especially breeds with a deep and narrow thorax such as the Great Dane, Weimaraner, St. Bernard, Gordon Setter, and Irish Setter), middle to older age (mean age approximately 7 years), and a first-degree relative that had GDV (see Chapter 62).[3,7-9] Controlled epidemiologic studies show that eating fewer meals per day and a rapid rate of eating increased susceptibility to GDV; dogs characterized by their owners as happy or easygoing were at lower risk than nervous or fearful dogs.[7,10] Dogs fed a larger volume of food per meal were at significantly increased risk of GDV, regardless of the number of meals fed daily.[11] The risk of GDV was highest for dogs fed a larger volume of food once daily.[11] Rapid eating and a raised feeding bowl were also associated with an increased risk of GDV.[12] The only breed-specific characteristic significantly associated with a decreased incidence of GDV was an owner-perceived personality trait of happiness.[13] Despite popular opinion, epidemiologic studies have not supported a causal relationship between feeding soy-based or cereal-based dry dog food and GDV.[14] There is no clinical evidence that fermentation is the cause of gastric gas production. In fact, dry foods containing fats or oils among the first four label ingredients predispose high-risk dogs to GDV, but soy- and cereal-based ingredients do not.[14] Scientific studies do not overwhelmingly support the role of previously proposed causes, including hypergastrinemia, exercise after ingestion of large meals of highly processed foods or water, and inflammatory bowel disease.[2,3,7,15-18] A seasonal increase in GDV incidence was noted in one population of military working dogs.[19]

It is well known by veterinarians that dogs can experience GDV when no food is in the stomach. Pathologists have performed necropsies on dogs with GDV that had only a small amount of fluid in the stomach, or had empty stomachs. Anesthesia, surgery, trauma, and parturition have all been observed to be associated with GDV.[20]

Certain anatomic considerations are important for the development of GDV. In healthy awake dogs, gastric distention with nitrogen consistently decreases lower esophageal sphincter pressure and is followed by eructation.[21] The same is true in GDV dogs.[21] The gastroesophageal sphincter pressure was not significantly increased compared with normal dogs in dogs tested more than 9 months after treatment for and recovery from GDV.[16] Thus, it is unlikely that elevated gastroesophageal sphincter pressure inhibits orad movement and relief of gastric distention in GDV dogs. The gastroesophageal sphincter is physiologically unable to retain gas within the stomach unless volvulus is present. During abdominal surgery, the stomach in normal dogs can be forcibly rotated into a volvulus position, but it immediately returns to a normal position when released because the pylorus is tightly fixed to the right side of the abdomen by the hepatoduodenal and hepatogastric ligaments. The stomach of a dog that has experienced GDV, however, can easily be placed in the volvulus position and remains in an abnormal position once released. With volvulus and twisting of the gastroesophageal sphincter, swallowed air cannot be easily eructated and gastric dilation persists. Therefore, volvulus must precede dilation for gastric distention from aerophagia to occur, which is contrary to the alternative premise that dilation precedes a volvulus. It is well known that chronic gastric volvulus exists, and malpositioning of the stomach may be constant or intermittent. It is also known that adaptive relaxation allows the proximal stomach to stretch and accommodate some degree of gastric distention without an increase in intraluminal pressure (see receptive relaxation and accommodation in Chapter 1). Gastric emptying of liquids can even be normal in dogs with chronic gastric volvulus.[22] Initially food, air, and saliva can enter the stomach in the presence of volvulus. At some point, however, perhaps related to the degree of rotation, volvulus prevents further air from entering or leaving the stomach. Up until that point, gas accumulation occurs. Rotation of the stomach is likely the factor that initiates aerophagia. Swallowing of air is accompanied by swallowing of saliva. A considerable amount of gas

accumulates because the volvulus prevents belching of air (and vomiting of ingesta) and inhibits pyloric emptying into the duodenum.

Delayed gastric emptying of solid particles fed with a meal has been documented in dogs with GDV following surgical treatment and recovery,[23,24] whereas the liquid phase of gastric emptying is not similarly affected.[22,25] Using radiopaque particles mixed with food, gastric emptying was assessed in healthy dogs not subjected to surgery, in healthy dogs 9 to 35 days after circumcostal gastropexy, and in dogs 1 to 54 months after surgical treatment and recovery from GDV. Circumcostal gastropexy surgery did not alter the 90% gastric emptying time for radiopaque particles in healthy dogs. However, 90% gastric emptying time was significantly increased after circumcostal gastropexy in dogs with GDV, compared with healthy dogs after the same surgical procedure and recovery period. These results suggest that dogs with GDV have delayed gastric emptying of solid particles, although it is still not clear whether delayed gastric emptying of markers in affected dogs after surgical treatment and recovery is the result or the cause of GDV. Other studies indicate that delayed gastric emptying in the GDV syndrome is associated with increased gastric slow wave propagation velocity in the fed state.[26] Atypical fasting state phase III activity suggests that gastric emptying may be impaired in the fasting state as well.[26] Recordings were not altered in healthy dogs after short-term experimental gastric dilation suggesting that altered electrical and contractile activities in GDV dogs are not likely to be secondary to the process of acute gastric dilation.[27] These results imply that electrophysiologic abnormalities in gastric smooth muscle cells may be associated with delayed gastric emptying. Because delayed gastric emptying predisposes to chronic gastric distention, which could stretch the gastrohepatic ligament and permit increased stomach mobility, it has been hypothesized that a primary disorder of gastric motility might precede and predispose the dog to GDV.[28] The length of hepatogastric ligaments in GDV-affected dogs is significantly longer than those of control dogs.[28] Others have also speculated that gastric dysrhythmias may predispose to GDV.[29,30]

Two dogs were reported to develop GDV 2 and 17 months after splenectomy for treatment of splenic torsion. Splenic displacement and torsion may stretch the gastric ligaments, allowing increased mobility of the stomach. After splenectomy, an anatomic void may be created in the cranioventral part of the abdomen, contributing to the mobility of the stomach.[31]

Acute GDV has been reported rarely in cats. Two of five cats reported on in one case series and three cats in another had concomitant diaphragmatic hernia.[32,33] Clinical signs and therapeutic management are similar in cats and dogs.

Pathophysiology

Gastric dilation refers to distention of the stomach, caused most often by swallowed air, fluid, and/or food. Gastric dilation implies an innocuous condition that can easily be corrected by passing a stomach tube to relieve the distention. GDV is different, however, from simple engorgement because of overeating (a syndrome that occurs most commonly in young animals) or gastric distention as a consequence of aerophagia. In GDV, the air-filled stomach becomes tympanic because of the large volume of air present.[34] Dogs experiencing gastric dilation almost invariably have gastric volvulus.[35] A fundamental abnormality associated with GDV is laxity of the hepatoduodenal and hepatogastric ligaments, leading to a high degree of mobility of the stomach within the abdomen.[35] This allows the stomach to twist on its longitudinal axis at the esophageal cardia and the pylorus. In normal dogs, the pylorus is tightly fixed to the cranial right quadrant of the abdomen by the hepatoduodenal ligament, lesser omentum, and common bile duct. Even though the pylorus in normal dogs can be forced to the left and placed in a volvulus position, it immediately returns to its normal position once released. The stomach of a dog that has experienced GDV, however, can easily be placed in the volvulus position and remains in the abnormal position once released. Thus, a predisposition for gastric volvulus must be present to produce the GDV syndrome.

Generally, the stomach rotates in a clockwise direction when viewed from the surgeon's perspective (with the dog on its back and the clinician standing at the dog's side, facing cranially). The rotation may be 90 to 360 degrees, but is usually 220 to 270 degrees.[36] When the stomach twists, the pylorus and duodenum move ventrally, passing under the stomach and to the left of midline, finally coming to rest dorsally above the cardia on the dog's left side. Because the spleen is attached to the greater curvature of the stomach via the gastrosplenic ligament, twisting of the stomach usually displaces the spleen to the right ventral side of the abdomen and causes congestion and splenomegaly.

GDV results in occlusion of the cardia and obstruction of the pylorus. This prevents belching of air or vomiting of ingesta, and inhibits pyloric emptying into the duodenum. It is postulated that after volvulus develops, swallowed air can pass the twisted gastroesophageal junction but cannot escape the stomach. Analysis of gastric gas supports aerophagia as the cause of gastric distention, with dilation explained by an inability to eructate or empty air into the intestines.[34] The bicarbonate in swallowed saliva reacts with hydrochloric acid in the stomach to produce carbon dioxide. This may be the reason why carbon dioxide concentrations in gastric gas of GDV dogs are higher than atmospheric carbon dioxide concentrations. Swallowed air is the only explanation for the presence of nitrogen and oxygen in relatively high concentrations in gastric gas of GDV dogs. Caywood's study[34] showed that neither hydrogen nor methane were present in sufficient quantities in the gastric gas samples from dogs with GDV to support fermentation as the source of gastric gas. Gastric dilation results in increased gastric wall tension, decreased blood flow, local ischemic injury, and gastric wall necrosis. Normal gastric secretion and transudation of fluids into the gastric lumen secondary to venous congestion contribute to fluid accumulation. The most commonly infarcted area is along the greater curvature in the area served by the short gastric vessels.[37] GDV also causes splenic engorgement and compression of major abdominal vessels returning blood to the heart.[38] Occlusion of the portal vein and posterior vena cava reduces venous return to the heart, which in turn dramatically decreases cardiac output and mean arterial pressure, leading to hypovolemic shock. Inadequate tissue perfusion affects multiple organs, including the heart (myocardial ischemia), kidney (acute renal failure), pancreas (myocardial depressant factor is an arrhythmia-inducing compound produced by the ischemic pancreas),[39,40] liver (depressed reticuloendothelial cell function prevents removal of endotoxin),[41] and small intestine (local acidosis, subepithelial hemorrhage and edema, followed by hemorrhagic enteritis). In addition, occlusion of the portal vein and caudal vena cava cause marked passive chronic congestion of the abdominal viscera. The organs suffer from ischemia as well as accumulation of endotoxin (from the GI tract), which, in turn, activates many inflammatory mediators (e.g., histamine, prostaglandins, leukotrienes, and cytokines). Endotoxemia and endothelial damage lead to coagulation cascade activation, and disseminated intravascular coagulation may result. The enlarged stomach also encroaches on the thoracic diaphragm, which decreases tidal volume of the

lungs and further impairs ventilation-perfusion matching. Ultimately, shock reaches a point of irreversibility (likely caused by endotoxemia), wherein death ensues regardless of therapy.[35]

Clinical Examination

Dogs with GDV may present with a history of an acute, progressively distending abdomen, nonproductive retching, hypersalivation, restlessness, depression, weakness, and abdominal pain.[1] Physical examination usually reveals abdominal distention with tympany, although it may be difficult to detect gastric distention in heavily muscled large-breed or very obese dogs. There is also evidence of poor tissue perfusion and/or shock, such as weak peripheral pulses, tachycardia, prolonged capillary refill time, pale mucous membranes, or dyspnea. Eventually, depression and a moribund state may occur.[42] Cardiac arrhythmias, such as ventricular premature beats or ventricular tachycardia, may be detected on initial examination or may develop up to 72 hours after presentation.[43]

Clinicopathologic findings often show an increased hematocrit, and a variety of acid–base and electrolyte abnormalities.[43] Metabolic acidosis and hypokalemia are the most common finding in about 25% of dogs. Metabolic acidosis is likely the result of tissue hypoperfusion, anaerobic metabolism, and lactic acid accumulation. However, metabolic alkalosis also may occur as a result of sequestration of gastric acid and vomiting. Acid–base abnormalities predispose to cardiac arrhythmias and muscle weakness. Coagulation abnormalities are most consistent with disseminated intravascular coagulation (DIC).

Diagnosis

Usually GDV is diagnosed in the examination room based on signalment, history, and physical examination findings, and therapy is begun immediately. It is impossible to differentiate between gastric dilation and GDV on the basis of ability or inability to pass an orogastric tube. If unsure, radiographic evaluation may be necessary, although caution should be exercised because positioning these dogs for radiographs may further impair cardiopulmonary function. Affected animals should be decompressed and rehydrated before radiographs are taken. Right lateral and dorsoventral radiographic views are preferred.[44] In a right lateral view of a dog with GDV the smaller, gas-filled pylorus lies dorsal and cranial to the larger, ventrally positioned fundus. The dorsally positioned pylorus is separated from the rest of the stomach below by a soft-tissue fold (antral wall folding back). On the dorsoventral view, the pylorus appears as a gas-filled structure to the left of midline. Free abdominal air suggests gastric rupture. Blood should be collected for a complete blood cell count, serum biochemistry profile, and blood gas analysis prior to treatment.

Treatment

Shock

One or more large-bore intravenous catheters are placed in jugular or cephalic veins. High-volume isotonic fluids (60 to 90 mL/kg/h), low-volume hypertonic saline (7% NaCl solution in 6% dextran, 4 to 5 mL/kg over 5 to 15 minutes), hetastarch (5 to 10 mL/kg over 10 to 15 minutes), or a mixture of 7.5% saline and hetastarch (dilute 23.4% saline with 6% hetastarch until a 7.5% solution is achieved; administer at 4 mL/kg over 5 minutes) are administered.[45,46] If hypertonic saline or hetastarch is given, the rate of subsequent crystalloid fluid administration must be adjusted accordingly. The animal should be monitored closely and fluid administration rate decreased if clinical improvement occurs. If clinical signs of shock persist, then fluid administration should continue at a high rate until a response is noted. The packed cell volume (PCV) and total protein should be monitored regularly during fluid therapy for shock. Whole blood or plasma should be administered if the PCV falls below 20% or total protein falls below 3.5 g/dL, respectively.[35] Although controversial, corticosteroids (dexamethasone sodium phosphate, 4 mg/kg, or prednisone sodium succinate, 20 mg/kg IV) may be administered for endotoxemia and to stabilize lysosomal membranes. Administration of systemic antibiotics is reasonable as mesenteric congestion caused by the enlarged stomach predisposes to infection and endotoxemia.[42] Bactericidal antibiotics should be administered intravenously (e.g., cefazolin or ampicillin plus enrofloxacin). Flunixin meglumine is sometimes recommended (0.5 to 1.1 mg/kg IV once) to decrease prostaglandin synthesis and attenuate the effects of endotoxemia, although it may place the patient at risk for severe GI ulceration.[47] Sodium bicarbonate is administered if indicated based on the blood gas analysis.[48] Sequestration of hydrogen ions in the gastric lumen can offset the lactic acidosis, causing the blood pH to be normal. Therefore, bicarbonate therapy should not be routinely administered.

Gastric Decompression

Gastric decompression should be performed at the same time as the other components of shock therapy.[49] Gastric decompression improves cardiac output and arterial blood pressure by relieving caudal vena cava and portal vein occlusion. An orogastric tube is premeasured from the point of the nose to the last rib, and a tape mark is made on the tube so that when it is passed it is not advanced too far. Placing the animal in different positions (sitting, on a tilt-table, or with front legs elevated on a table) may help to advance the tube by shifting the weight of the abdominal viscera. A well-lubricated tube is advanced with firm pressure and in a twisting motion. If an orogastric tube will not pass, then intragastric pressure should be reduced by gastrocentesis. Gastrocentesis is performed in an aseptically prepared area caudal to the costal arch on the right flank with several 16-gauge hypodermic needles. The region should be percussed to determine the location of the spleen. Relief of intragastric pressure by gastrocentesis will usually allow passage of an orogastric tube. Once positioned, the tube is used to remove as much gastric liquid and gas as possible. Gastric lavage using warm water may help to remove ingesta. One should note whether there is evidence of blood in the gastric contents.[1]

To facilitate intubation, the animal may be lightly sedated with diazepam (0.1 mg/kg IV) plus either butorphanol (0.5 mg/kg IV) or oxymorphone (0.1 mg/kg IV).[43] If the stomach tube still cannot be passed after gastrocentesis, temporary decompression may be achieved by performing a temporary gastrostomy. However, this procedure carries a high risk for peritoneal contamination and must be closed before the permanent gastropexy is performed.

Surgery

Several studies show no association between the time from admission to a clinic to the time of surgery and outcome.[4,5] The presence of gastric necrosis at surgery is, however, associated with a much higher risk of dying.[4-6] If there is no blood present in the gastric contents, it may be advantageous to stabilize the patient's condition for a few hours, or even overnight, before performing corrective surgery and gastropexy.[1] If the stomach is twisted, it will continue to have impaired mucosal perfusion even with de-rotation[50]; therefore, surgery should only be delayed as long as is necessary to make the patient the best anesthetic risk possible. The benefits of delaying surgery are that surgery can be performed at a convenient time, the dog can be safely transported to a referral center, and a full

preoperative diagnostic evaluation can be performed.[49] A pharyngostomy tube may be used to maintain gastric decompression. For example, if immediate surgery is not possible and the stomach dilates rapidly again after decompression, the stomach tube can be exteriorized through a pharyngostomy approach. The disadvantages of delaying surgery include failure to detect necrosis or leakage of gastric contents, emergence of more serious cardiac arrhythmias, and continued damage to the gastric mucosa. An electrocardiogram should be monitored to detect cardiac arrhythmias.

If blood is found in the gastric contents, surgery should be performed as soon as the patient is capable of withstanding anesthesia because of the danger of gastric wall devitalization and perforation because of devitalization. The stomach is repositioned and if necessary devitalized gastric wall tissue is resected, or preferably to prevent perforation and abdominal contamination, a partial gastric invagination technique may be performed.[51] If there is splenic necrosis or significant splenic infarction, partial or complete splenectomy should be performed. A permanent gastropexy is performed to prevent recurrence of GDV. Many surgical procedures have been developed to permanently attach the stomach to the body wall and prevent recurrence of GDV.[52,53] These include tube gastropexy,[54,55] circumcostal gastropexy,[56-60] muscular flap gastropexy,[61] belt-loop gastropexy,[62] and incisional gastropexy.[63,64] Randomized controlled trials comparing different types of gastropexy have not been conducted. The choice of a particular technique often depends on individual preference. Probably the most critical factors in success rate are the surgeon's familiarity with a technique and ability to perform it proficiently and in a timely manner.[2] Failure rates are in the range of 3% to 8%. Right-sided percutaneous gastrostomy is not recommended as a means of prophylactic gastropexy despite the use of that procedure for nutritional management in other situations.[65] Corrective pyloric surgery is no longer recommended.[52,66] Intermittent gastric dilation may occur after gastropexy.[64,67]

Ischemia–Reperfusion Injury

Restoration of tissue perfusion and oxygenation can initiate deleterious biochemical reactions that contribute to further tissue damage. This phenomenon is called ischemia–reperfusion injury.[68,69] During ischemia, conditions develop that predispose to the production of oxygen free radicals upon reperfusion. First, adenosine triphosphate undergoes degradation resulting in accumulation of hypoxanthine. Second, intracellular calcium increases and activates calpain, a protease which converts xanthine dehydrogenase to xanthine oxidase. Xanthine oxidase catalyzes the conversion of hypoxanthine into superoxide radicals in the presence of oxygen. Superoxide radicals are converted into hydrogen peroxide by superoxide dismutase. Superoxide radicals and hydrogen peroxide react, forming hydroxyl radicals. During reperfusion an overabundance of free radicals are generated, which overwhelms the normal antioxidant defense mechanisms (superoxide dismutase, catalase, glutathione peroxidase, α-tocopherol, ascorbate, beta-carotene). The hydroxyl radical is a potent oxidizing agent, which initiates cell membrane lipid peroxidation. This results in increased cell membrane permeability, increased microvascular permeability, tissue edema, inflammatory cell influx, hemorrhage, and mucosal necrosis. Neutrophils play a major role in the pathophysiology of reperfusion injury. Neutrophil activation and degranulation leads to synthesis and release of numerous enzymes (proteases) and oxygen-free radicals. Inhibition of neutrophil adhesion or neutrophil depletion has been shown to reduce or prevent GI tract injury. Intestinal mucosal injury can be attenuated by both protease inhibitors and scavengers of oxygen free radicals.

Lipid peroxidation activity in the duodenum, jejunum, colon, liver, and pancreas was significantly less during reperfusion in dogs with experimentally induced GDV treated with a lipid peroxidation inhibitor.[70,71] Free radical scavengers such as deferoxamine and allopurinol may also protect abdominal organs against reperfusion injury. These results suggest that use of drugs that prevent lipid peroxidation (e.g., lazaroids such as U74389G) may be useful for reducing the mortality associated with GDV. These agents work best if given before reperfusion occurs, that is, prior to untwisting a volvulus.

Cardiac Arrhythmias

Arrhythmias are a common sequela of GDV and usually begin 12 to 36 hours postoperatively.[72,73] Electrocardiographic monitoring should be performed in all GDV patients throughout hospitalization. Ventricular tachyarrhythmias (premature ventricular contractions, paroxysmal ventricular tachycardia, and multifocal ventricular tachycardia) are most frequently described.[72-74] They are generally self-limiting and resolve after 2 to 4 days.[35] The mechanisms that initiate and maintain these arrhythmias are varied and include acid–base abnormalities, electrolyte abnormalities, autonomic imbalances, myocardial depressant factors, and myocardial ischemia.[72] Cardiac damage is common as evidenced by increased serum concentrations of troponin.[75] They should be treated if they are severe enough to decrease cardiac output, that is, the origin is multifocal, ventricular rate exceeds 160 beats/min, pulses are weak, shock is present, or subsequent premature beats are inscribed on the wave of the previous complex (R on T phenomenon).[35,36] Intravenous lidocaine is the preferred antiarrhythmic drug. Lidocaine is administered in boluses of 2 mg/kg up to a total dose of 8 mg/kg IV; if this is successful then an IV drip at 50 to 75 μg/kg/min is used as a constant rate infusion. If lidocaine is ineffective, procainamide may be administered slowly IV as a bolus at 10 to 15 mg/kg or as a continuous IV infusion at 25 to 60 μg/kg/min. Contributing factors (to the arrhythmias) should be corrected. Hypokalemia, acidosis, and hypoxia promote arrhythmogenesis and the patient becomes resistant to antiarrhythmic therapy and, therefore, must be resolved with treatment.[1] The presence of cardiac arrhythmias may not be associated with an unfavorable outcome.[4,5] In contrast, others have reported mortality rates as high as 38% in dogs with preoperative cardiac arrhythmias.[6]

Postoperative Care

Fluid, electrolyte, and acid–base status should be monitored postoperatively. Fluid therapy is based on clinical findings. Shock that persists into the postoperative period must be treated vigorously with crystalloid fluids. Whole blood and plasma must be administered to maintain the PCV and total protein above critical levels. Intravenous fluid therapy is continued until hydration can be maintained by oral fluid intake. Hypokalemia is common and requires potassium supplementation. Sepsis and DIC are also potential complications.[76] Gastritis secondary to mucosal ischemia is also common and may result in gastric hemorrhage or vomiting. Antiemetic agents and histamine H_2-receptor blockers (e.g., cimetidine, ranitidine, or famotidine) may be beneficial to control vomiting and to decrease gastric acidity. Ranitidine may also promote gastric emptying.[77] Metoclopramide may be useful as an antiemetic agent, but would be unlikely to promote increased gastric emptying.[78] Cisapride is recommended as a prokinetic agent to improve gastric emptying in dogs with GDV but is available only through compounding pharmacies.[79,80] If mosapride and pruclaopride are available in regional practices, they are now considered superior to cisapride.

Prognosis

The prognosis for GDV in general is guarded, and dependent upon how quickly the condition is diagnosed and treated. Mortality rate for dogs receiving current treatment recommendations for GDV is approximately 15%.[43] Early therapy improves the prognosis, whereas a delay lasting more than 5 hours between onset of signs and presentation to the veterinarian's office worsens the prognosis. Hypothermia at admission, preoperative cardiac arrhythmias, increased preoperative blood lactate concentrations, gastric wall necrosis, severe DIC, partial gastrectomy, splenectomy, and postoperative development of acute renal failure seem to worsen the prognosis.[42] The presence of gastric necrosis can be predicted by measuring plasma lactate concentration, with a value greater than 6 mmol/L having a specificity of 88% and a sensitivity of 61% for necrosis.[81]

Several studies have been conducted to examine survival and recurrence data following acute GDV. Dogs depressed or comatose upon admission were three and 36 times, respectively, more likely to die than alert cases, whereas cases with gastric necrosis were 11 times more likely to die.[4] Recurrence rate ranges from 54.5% to 75.8% for those cases that do not have gastropexy and from 4.3% to 6.6% for those that do.[4,64,82,83] Thus, a gastropexy should be performed even when conservative management successfully alleviates the gastric malpositioning. In another prospective study, the recurrence rate of GDV was 9% after circumcostal gastropexy and 20% after gastrocolopexy (not significantly different between treatments).[84]

In dogs at high risk for GDV, it is prudent to consider gastropexy as an elective surgery to prevent GDV. Circumcostal gastropexy has not been shown to delay gastric emptying nor to alter gastric myoelectric activity.[23,85] Gastropexy would be effective in preventing a first episode of GDV in a genetically predisposed dog. Owners of high-risk breeds, for example, Bloodhounds and Great Danes, should be advised to consider prophylactic gastropexy at the time of elective surgical neutering.

Chronic Gastric Volvulus

Etiology

Chronic gastric volvulus[22,86,87] is less common and more difficult to recognize than acute GDV.[1] The causes for partial, intermittent, or chronic gastric volvulus may be the same as for acute GDV.[42]

Pathophysiology

Malpositioning of the stomach may be constant or intermittent. These dogs do not present with the life-threatening characteristics of acute GDV. Between bouts, dogs may appear normal. Some dogs are asymptomatic despite having chronic volvulus with gastric displacement.

Clinical Examination

Vomiting with or without abdominal distention and/or pain may be reported. The signs may be intermittent and mild so that the diagnosis of chronic gastric volvulus is not considered initially. Affected dogs may vomit food several hours after eating, but otherwise feel well. Anorexia and/or weight loss may occur.

Diagnosis

Multiple radiographs are needed over a period of days or weeks to confirm the diagnosis.[1] Contrast studies may also be helpful to confirm malpositioning of the stomach. Chronic volvulus is rarely diagnosed by endoscopy.[42]

Treatment

Surgical repositioning and gastropexy to adhere the stomach to the body wall to prevent subsequent gastric volvulus are required.

Prognosis

The prognosis is good once the problem is diagnosed and surgically corrected.

Gastric Foreign Bodies

Etiology

Simple Foreign Objects

Vomiting caused by foreign body ingestion is very common in dogs (especially puppies) and less so in cats because of their more discriminating eating habits. Many gastric foreign bodies are eliminated by vomiting, dissolved by gastric acid, or passed uneventfully through the GI tract. Approximately 50% of the objects retained in the stomach cause vomiting.[88] Unless an object obstructs the outflow or irritates the mucosa, it can remain in the stomach for months without clinical signs. Thus, not all vomiting animals in which a gastric foreign body is discovered are vomiting because of the foreign body.

Linear Foreign Objects

Linear foreign objects may have one end lodged in the pylorus with intestinal pleating at the leading edge of the foreign body.[89] Rapid diagnosis is preferred because of the potential for duodenal perforation and subsequent peritonitis.

Hairballs

Hairballs are common and form in cats of all ages. They are often recurring problems.

Pathophysiology

Vomiting may result from gastric outlet obstruction because of mechanical blockage at or near the pylorus.[1] Occasionally, a foreign body that obstructs the pylorus and causes severe clinical signs may be dislodged by vomiting, yet remain in the stomach. Cyclic signs may develop as the foreign body reobstructs the pylorus. Chronic pyloric obstruction can cause delayed gastric emptying with postprandial gastric distention and discomfort, vomiting of food more than 8 hours after a meal, and weight loss.[88] Some animals may be asymptomatic and/or anorexic without vomiting. Hair should empty from the stomach during the fasting state by a motility pattern similar to the MMC in dogs.[90] Gastric retention of hair, with subsequent formation of hairballs, may reflect abnormal gastric motility.

Clinical Examination

Acute onset of vomiting in an otherwise normal animal, especially a puppy, is typical. Cats with hairballs may vomit food many hours after eating.

Diagnosis

Diagnosis is based on history (seeing the animal eat something or have an acute onset of vomiting after a toy or object disappears), physical examination (palpation of the object), radiography (survey abdominal radiographs may demonstrate radiopaque objects whereas a barium contrast study may be needed to demonstrate a filling defect if the object cannot be visualized), and/or endoscopy. Clinical pathology sometimes reveals hypochloremic, hypokalemic

metabolic alkalosis as significant complications of gastric outlet obstruction.[1]

However, these changes may be absent in animals with gastric obstruction and present in animals without obstruction.[42]

Treatment

Foreign objects may be removed surgically, or endoscopically to avoid the morbidity and risks associated with surgery. Useful endoscopic retrieval forceps include rat-tooth, snare, and basket forceps. It is helpful to insufflate the stomach with air to dilate the gastroesophageal sphincter. Alternatively, some foreign objects may be allowed to pass through the alimentary tract back into the environment (e.g., even glass, needles, and fish hooks), or the animal may be given an emetic agent to stimulate vomiting if the object does not have sharp edges or points and is small enough to pass easily.[42] There are risks, however, that the object may cause obstruction or perforation of the small intestine if allowed to pass, or esophageal laceration if vomiting is induced. Common sense and good communication skills with the client are essential. It is often preferable to remove objects by surgery or endoscopy to avoid potential complications. If the foreign object is fixed at the base of the tongue and has been present for less than 2 to 3 days, and if the patient does not have evidence of peritonitis, it is reasonable to cut the object at its point of attachment to see if it will pass through the GI tract uneventfully.[91] However, the patient must be monitored for signs of abdominal pain or depression (indications for surgery). One may also attempt to remove the foreign object endoscopically if present for less than 2 to 3 days, especially if it is a thick mass of cloth or cotton. It is possible to rupture a previously intact intestine, however, if one applies traction to a linear foreign object that has already compromised the intestine. One should not hesitate to proceed to surgery if the risk of perforation seems significant.[1] Before the animal is anesthetized for surgery or endoscopy, it is best to evaluate the electrolyte and acid–base status because hypokalemia, for example, predisposes to cardiac arrhythmias and should be corrected before anesthesia is induced.[42] A final set of radiographs are always obtained before anesthesia to ensure that the object is still in the stomach.

Prognosis

The prognosis is generally good if the obstruction can be removed. The prognosis is more guarded if there is septic peritonitis secondary to gastric perforation. Hairballs are often recurring problems, and preventive measures (petroleum-based lubricants and frequent grooming) are important to avoid repeated problems.[88]

Congenital and Adult Forms of Antral Pyloric Hypertrophy

Etiology

Stenosis of the pyloric canal is one of the more common causes of gastric outlet obstruction.[92] The narrowing can be caused by hypertrophy of the circular muscle of the pylorus, by hyperplasia of the antropyloric mucosa, or by a combination of both muscular and mucosal thickening. Hypertrophy of the pyloric muscle exclusively is the least common form of the disease and usually is seen as a congenital disorder in Boxers, Bulldogs, and Boston Terriers (see Chapter 62).[93,94] This disorder is referred to as congenital pyloric stenosis, benign muscular hypertrophy, benign antral muscular hypertrophy, benign muscular pyloric hypertrophy, congenital hypertrophic stenosis, and congenital pyloric muscle hypertrophy.[95] Most adult dogs with stenosis of the pyloric canal are affected by either hypertrophy of the mucosa exclusively or by a combination of muscular and mucosal hypertrophy. The hypertrophic mucosa may be focal (a polyp or single mucosal fold), multifocal (multiple polyps or folds), or generalized (involving the entire pyloric antrum). Synonyms for the adult syndrome include acquired antral pyloric hypertrophy, chronic antral mucosal hypertrophy, chronic hypertrophic pyloric gastropathy, acquired pyloric stenosis, pyloric or gastric mucosal hypertrophy, chronic hypertrophic gastritis, multiple polyps of the gastric mucosa, and acquired hypertrophy.[95] For simplicity, it has been suggested that the disorder be referred to as congenital and adult forms of antral pyloric hypertrophy in recognition of the two ages of dogs affected, the involvement of the antrum in addition to the pylorus, the hypertrophic nature of the lesions, and the probability of nonspecific etiology.[93]

Adult forms of antral pyloric hypertrophy affect older, predominantly male dogs of the smaller breeds (e.g., Lhasa Apso, Pekingese, Maltese, Shih Tzu; see Chapter 62).[1,93,96-100] Histopathologic changes include hypertrophy of the mucosal or muscular layers of the pylorus, or both, with or without inflammation. Hyperplastic gastropathy has also been reported in the cat.[101]

Congenital antral pyloric hypertrophy is less common than acquired antral pyloric hypertrophy. The cause is unknown. Most affected dogs are male, young to middle-aged, brachycephalic or small breeds. The congenital form may also be seen in cats.[102]

Pathophysiology

The cause of muscular hypertrophy is unknown, although neuroendocrine (hypergastrinemia) and stress-related causes have been postulated, because many of the cases are observed in highly excitable and nervous small breeds.[103] Mild congenital pyloric stenosis or dysfunction could lead to gastric distention that in turn would stimulate gastrin secretion. Gastrin's trophic effects on pyloric musculature would eventually exacerbate the disease by encouraging pyloric muscular hypertrophy.[93] Neural dysfunction may be the underlying cause of abnormal antral motility. Acute stress, inflammatory disease, or trauma may stimulate the sympathetic innervation, reducing gastric motility and thereby causing retention. Distention associated with delayed gastric emptying may then lead to increased gastrin secretion and subsequent hypertrophy.[95]

The cause of acquired antral mucosal hypertrophy is also unknown. It may result from mucosal irritation because of chronic retention of indigestible material.

Clinical Examination

Vomiting with or without weight loss is the most common clinical sign. Dogs often have been vomiting intermittently for several months to years, and the frequency of vomiting increases as the obstruction worsens. The vomiting often occurs many hours after eating, usually contains food, and may be projectile.[93] Some cats may vomit so much that secondary esophagitis, megaesophagus, and regurgitation occur.[42,104] Clinical pathology sometimes reveals hypochloremic, hypokalemic metabolic alkalosis, but this is inconsistent and nonspecific for this disorder.[42]

Vomiting is usually first observed in animals with congenital pyloric stenosis shortly after weaning or at an early age. The animal is usually hungry but thin and often reingests the vomitus. Chronic intermittent vomiting usually becomes more severe with time.

Diagnosis

Positive-contrast radiographic studies are useful in documenting gastric outflow obstruction. Ultrasonography can help identify a thick hypoechoic layer of pyloric muscle and a thickened gastric wall.[105] The diagnosis is suggested by the endoscopic appearance of enlarged

mucosal fold(s) surrounding the pyloric orifice and by exclusion of other causes, for example, neoplasia, by mucosal biopsy.[106] Endoscopic biopsies are usually of sufficient quality to detect mucosal changes characteristic of the disease, but the changes are subtle.[106,107] At surgery, with congenital muscular hypertrophy, the serosa is grossly normal, but the pylorus feels thickened upon palpation. With acquired antral mucosal hypertrophy, there should be no evidence of submucosal infiltration (suggestive of neoplasia) or muscular thickening (suggestive of congenital muscular hypertrophy).

The radiographic features of pyloric stenosis include gastric distention, delayed gastric emptying time, pyloric filling defects, a narrow and blunted pyloric canal, or failure of contrast to fill the pyloric canal and empty into the duodenum. Stenosis may result in a "beak sign" when barium appears as a beak-like projection entering the pyloric canal. The canal may also appear elongated and narrow, with a string of contrast passing through. In some cases only barium mixed with food demonstrates an obstruction, whereas liquids pass through the pylorus uneventfully. Once gastric outlet obstruction has been documented, pyloric hypertrophy is diagnosed by finding muscular thickening (with perhaps redundant mucosal folds). Redundant mucosal folds may resemble a submucosal neoplasm, thus biopsy is necessary for a definitive diagnosis to rule out neoplasia.

Treatment

Surgery is the treatment of choice for these benign lesions. The goal is to remove the obstruction and reestablish normal gastric emptying.[95] A full-thickness biopsy must be taken to ensure that the thickening is benign. Redundant tissue is resected in combination with a pyloroplasty or a pyloric antral resection (e.g., Y-U pyloroplasty or Billroth I procedure).[95,96,108,109] Some clinicians prefer pyloromyotomy because it has fewer potential complications.[98] Pyloromyotomy is easier to perform than pyloroplasty, but does not seem as reliable in enlarging the pylorus, and is therefore not recommended.[95,98,110]

Prognosis

Surgery should be curative. The prognosis is excellent if there are no postoperative problems.[1,111,112] A poor outcome may result if there is dehiscence or leakage, or when an inappropriate surgical technique is performed.[95]

Gastric Neoplasia

The role of gastric neoplasia in gastric outflow obstruction is detailed in the "Neoplasia" section.

Gastric Phycomycosis

The role of gastric phycomycosis in gastric outflow obstruction[113-116] is detailed in the "Gastric Infection" section.

Miscellaneous Causes of Gastric Obstruction

Cryptococcosis resulting in a granulomatous gastritis mimicking carcinoma has been reported in a Doberman Pinscher as a cause of gastric outlet obstruction.[117] Granulomatous gastritis and severe eosinophilic gastritis can also cause pyloric obstruction. Duodenal–gastric intussusception is uncommon, but has been reported in the dog.[118] Hepatic or pancreatic abscesses may result in pyloric obstruction via external compression. Endoscopy or exploratory laparotomy and biopsy are required for definitive diagnosis. Treatment and prognosis depend upon the underlying cause. GI prokinetic agents are contraindicated in treating patients with mechanical obstruction of the pylorus.[119]

Iatrogenic gastric outflow obstruction in two dogs appeared to be caused by prior gastric surgery. This may be prevented by minimizing tissue inversion into the gastric lumen when surgery is performed near the pyloric outflow tract. It is important to preserve the continuity of the outflow tract when large lesions near the pylorus are resected surgically.[111]

DYSMOTILITY

Robert J. Washabau and Jean A. Hall

Gastric Physiology

Anatomically, the stomach is composed of five distinct anatomic components: cardia, fundus, corpus, antrum, and pylorus. Physiologically, the stomach can be thought of as a two-component model: a proximal stomach (cardia, fundus, first one-third of the corpus) characterized by slow tonic contractions, and a distal stomach (distal two-thirds of the corpus and antrum) characterized by phasic propagating contractions (Figure 56-10).[1] Slow waves without action potentials give rise to the sustained tonic contractions of the proximal stomach. During swallowing, gastroesophageal sphincter and intragastric pressure decrease to accommodate emptying of solids and liquids. This phenomenon, referred to as *receptive relaxation*, takes place with each swallow, and as a consequence, large volumes can be accommodated with minimal increases in intragastric pressure. The proximal stomach becomes much less compliant with fundic disease or fundectomy.

A pacemaker site in the proximal fundus of the greater curvature generates action potentials and phasic contractions that propagate from the site of origin circumferentially and distally to the pylorus.[2] During feeding, phasic contractions of the distal stomach trigger a repetitive cycle of propulsion, trituration, and retropulsion that progressively reduce the size of the ingesta. Thus, the peristaltic qualities of the distal stomach regulate the emptying of solid particles into the duodenum. Antral disease or antrectomy abolishes this physiologic effect resulting in a "dumping syndrome" because of accelerated gastric emptying, nutrient overload in the small intestine, and an osmotic type of diarrhea.

Gastric emptying is regulated by several physiologic parameters, including (a) pyloric resistance and pressure differential between the

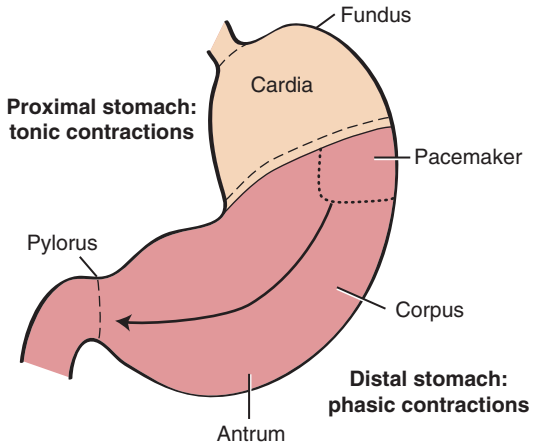

Figure 56-10 Functional model (proximal and distal) of the stomach.

stomach and duodenum; (s) water content—liquids are emptied more rapidly than solids; (c) nutrient composition—carbohydrates are emptied more rapidly than proteins, which, in turn, are emptied more rapidly than lipids; (d) nutrient acidity—delayed at acid or alkaline pH; (e) nutrient osmolality—delayed at high osmolality; and (f) hot or cold temperatures. Duodenal, jejunal, and ileal braking mechanisms also feedback inhibit gastric emptying through activation of mucosal sensory receptors for fatty acids, tryptophan, osmolality, and acid. Intestinal braking mechanisms serve to prolong transit time and nutrient contact time.[1]

During the fasting state the stomach is ordinarily empty, aside from swallowed saliva, a small amount of mucus, and cellular debris that collects in the gastric lumen. In addition, there may be particles of indigestible solids left over from the previous meal. A special mechanism exists to empty this fasting content called the MMC. The ability of the MMC to completely empty the stomach of its residue is so striking that it is sometimes referred to as the "interdigestive housekeeper" of the GI tract.[1] The GI hormone, motilin, is involved in the regulation of this MMC pattern. Cats and rabbits do not have a MMC, and instead have a less-vigorous emptying pattern known as the *migrating spike complex*.[3,4]

Clinical Signs of Disease

Delayed gastric emptying most often results in the clinical signs of gastric distention and retention of food and vomiting. A gastric motility disorder should be considered when there is a history of chronic vomiting. Vomiting may or may not be associated with feeding. Typically, vomiting of undigested or partially digested food is observed 8 to 10 hours after feeding, at a time when the stomach should be empty of ingested solids. The character of the vomitus is dependent on time lapse since the last meal, degree of gastric trituration, amount of gastric secretions, and extent of hydrolytic digestion. Other signs of a gastric motility disorder may include anorexia, belching, polydipsia, pica, and weight loss. Animals may occasionally assume a position of relief referred to as the "praying posture" to relieve gastric pain. The physical examination may be normal or may reveal findings associated with the underlying disease process. Abdominal distention may be present, increased bowel sounds may be noted with abdominal auscultation, and nonspecific pain may be evoked on abdominal palpation. Palpable abdominal masses are most consistent with intestinal or other visceral neoplasia, foreign bodies, and intussusceptions. Neuromuscular abnormalities may also be observed in dogs with severe electrolyte or metabolic derangements secondary to chronic vomiting.

Pathophysiology of Gastric Outflow Obstruction

Anatomic lesions of the pylorus and adjacent duodenal segment impede gastric emptying because of mechanical obstruction (Figure 56-11).[5,6] In general, diagnosis of mechanical obstruction is usually straightforward and involves survey and contrast radiography, ultrasonography, or gastroscopy. Mechanical or anatomic obstructions of the stomach are discussed in great detail in the "Gastric Obstruction" section.

Pathophysiology of Functional Gastric Motility Disorders

See Figure 56-11 for the management of gastric outflow obstructions and gastric emptying disorders.

Accelerated Gastric Emptying

The best example of an accelerated gastric emptying disorder is the vomiting associated with the hyperthyroxinemia of feline hyperthyroidism. Hyperthyroxinemia induces a tachygastria and accelerated

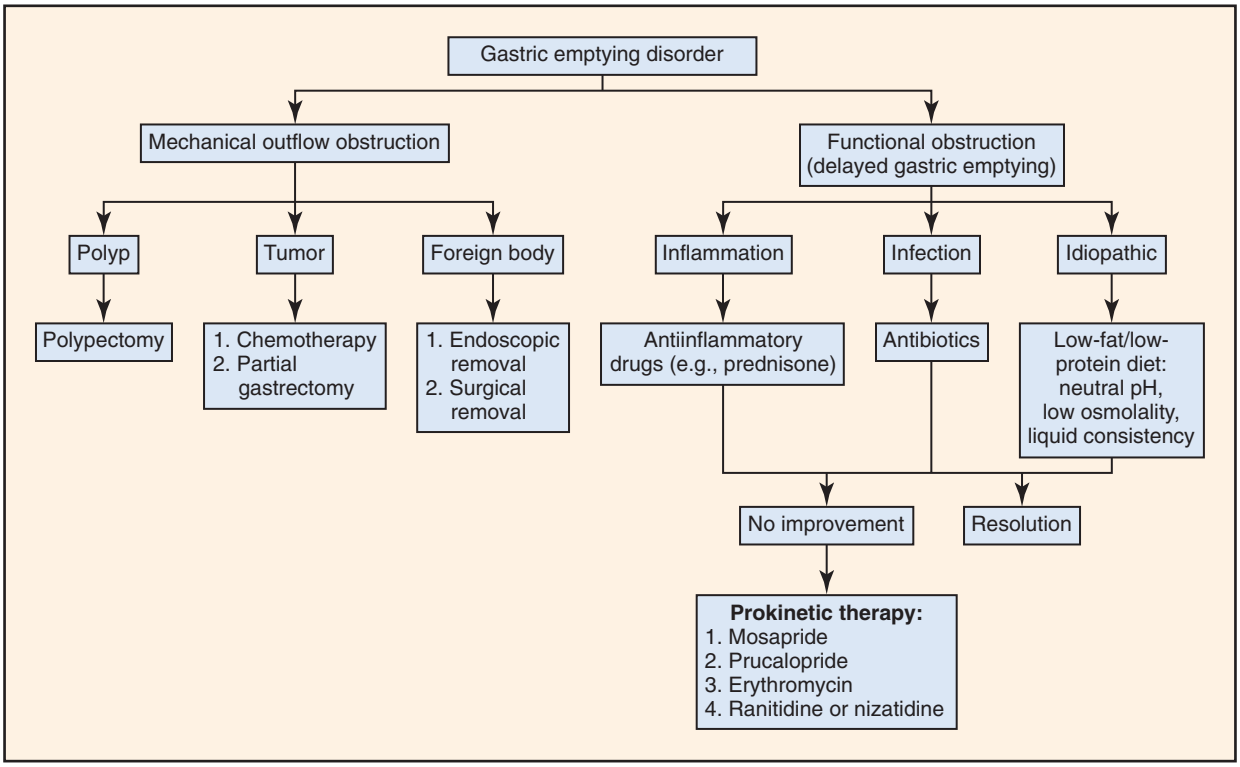

Figure 56-11 Management of gastric outflow obstruction and the delayed gastric emptying disorders.

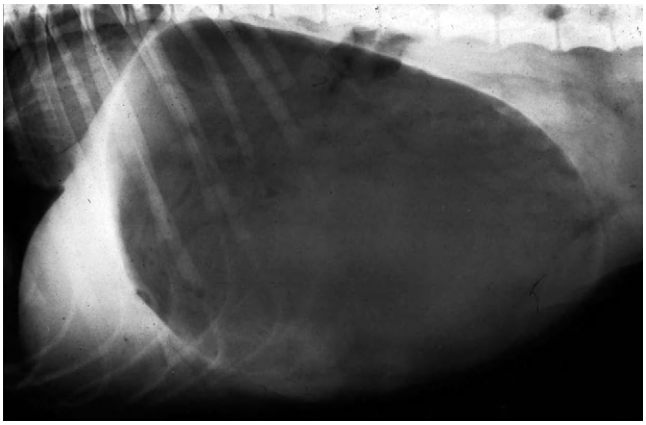

Figure 56-12 Severe gastric distention that persists following dilation and volvulus.

gastric emptying. Normal gastric emptying rhythm is restored following successful treatment of hyperthyroidism. Accelerated gastric emptying occasionally occurs in dogs following antral and/or pyloric resections for the treatment of gastric cancer. A postprandial "dumping syndrome" develops in these animals characterized by acute vomiting, abdominal pain, and diarrhea.

Retrograde Transit

Gastroesophageal reflux and duodenogastric reflux are the two best examples of retrograde transit disorders. Gastroesophageal reflux is an increasingly recognized clinical disorder in the dog, although clinical signs are more related to esophageal dysfunction.[7] Duodenogastric reflux may be the underlying pathogenesis of the so-called bilious vomiting syndrome in the dog. Affected animals tend to vomit small amounts of bile in the morning following an overnight fast.

Delayed Gastric Emptying

Delayed gastric emptying is now recognized as an important cause of upper GI tract signs.[8,9] Delayed gastric emptying has been reported in animals recovering from GDV (Figure 56-12), infectious and inflammatory gastric diseases, experimental gastric ulcer, and radiation gastritis. It has also been associated with several secondary conditions, including electrolyte disturbances (e.g., hypokalemia), metabolic disorders (e.g., hypoadrenocorticism, uremia, diabetes mellitus), concurrent drug usage (e.g., anticholinergics), and acute abdominal inflammation.[7-9]

Gastric Prokinetic Therapy

See Chapter 52 and Table 56-5 for a listing of mechanisms, sites of activity, indications, and doses of currently available GI prokinetic agents.

Dietary management should always be used as an adjunct to GI prokinetic therapy. Dietary management is based on the knowledge that liquids are emptied from the stomach more rapidly than solids, and that carbohydrates are emptied more rapidly than proteins, which, in turn, are emptied more rapidly than lipids. A low-fat, low-protein diet of liquid or semiliquid consistency should be fed at frequent intervals to facilitate gastric emptying. Diets should be selected for low acidity and low osmolality and should be fed at warm temperatures (22°C to 38°C [72°F to 100°F]). Gastric prokinetic agents should be considered in patients that fail to respond to dietary management alone.[10]

Dopaminergic Antagonistic Drugs

The dopaminergic antagonists are a group of drugs with GI prokinetic and antiemetic effects at peripheral (prokinetic) or central (antiemetic) dopamine D_2 receptors. The best representatives in this classification, metoclopramide and domperidone, reverse gastric relaxation induced by dopamine infusion in dogs, and they abolish vomiting associated with apomorphine therapy. Although the role of dopamine receptors in chemoreceptor trigger zone-induced vomiting is fairly well established, there is no definitive evidence that inhibitory dopaminergic neurons regulate GI motility. The prokinetic effects of metoclopramide and domperidone thus may not be readily or exclusively explained by dopamine receptor antagonism. Some dopaminergic antagonists (e.g., metoclopramide) have other pharmacologic properties, for example, 5-HT_3 receptor antagonism and 5-HT_4 receptor agonism. Domperidone also has α_2- and β_2-adrenergic receptor antagonistic effects. The characterization of these drugs as dopaminergic antagonists is convenient but may not properly describe their overall in vivo effects.

Serotonergic Drugs

Drugs acting on GI 5-hydroxytryptamine (5-HT or serotonin) receptors have potent motility effects. As prokinetic agents, the serotonergic drugs bind 5-HT_4 receptors on enteric cholinergic neurons inducing depolarization and contraction of GI smooth muscle. These drugs are not entirely selective for the 5-HT_4 receptor, however. Some of the putative 5-HT_4 receptor agonists also have 5-HT_1 and 5-HT_3 antagonistic effects on enteric cholinergic neurons, and direct noncholinergic (perhaps 5-HT_{2a}) effects on colonic smooth muscle. Cisapride and tegaserod were perhaps the best examples in this classification although they have been withdrawn from several markets, including the United States, Canada, and several Western European countries. Mosapride restores gastric motility in dogs with vincristine–induced gastric hypomotility, and therefore may be clinically useful in other gastric emptying disorders. Mosapride is marketed as Pronamid by DS Pharma Animal Health in Japan. Prucalopride also appears to stimulate gastric emptying in the dog. In lidamidine–induced delayed gastric emptying in dogs, prucalopride dose-dependently accelerates gastric emptying of dextrose solutions. Prucalopride is marketed as Resolor by Movetis in Europe.

The 5-HT_4 receptor appears to hold the most interest and promise for future drug development. 5-HT_4 receptor activation can cause relaxation or contraction depending on the region, cell type, and animal species. In the dog, the effects of selective 5-HT_4 receptor agonists suggest that these receptors are present on jejunal mucosa, ileal mucosa, gastric cholinergic neurons, and circular colonic smooth muscle cells. Increased motor activity following 5-HT_4 receptor activation results from increased release of acetylcholine from cholinergic neurons, and relaxation results from 5-HT_4 receptors on smooth muscle cells. Development of 5-HT_4 ligands is somewhat constrained by the effects these drugs have on cardiac 5-HT_4 receptors and the delayed rectifier potassium channel (I_{Kr}). Some, but not all, 5-HT_4 agonists prolong the Q-T interval and delay cardiac repolarization. Molecular biology experiments have revealed differences in the carboxyl terminus of smooth muscle and cardiac muscle 5-HT_4 receptors, but these amino acids differences are distant from the receptor binding site. Thus, receptor sub-types may exist but they may not be important from a functional or therapeutic standpoint.

Motilin-Like Drugs

The antibiotic properties of erythromycin and other macrolides were discovered in the early 1950s. Since then, erythromycin has been

Table 56-5 Mechanisms, Sites of Activity, Indications, and Doses of Currently Available Gastrointestinal Prokinetic Agents

Drug Classification/ Mechanism	Sites of Activity	Indications	Dose	Other Properties
Dopaminergic D_2 Antagonist Drugs				
Metoclopramide	GES, stomach, intestine, CRTZ	Vomiting disorders, gastroesophageal reflux, delayed gastric emptying, ileus/pseudoobstruction	0.2 to 0.5 mg/kg PO, IV TID; 0.01 to 0.02 mg/kg/h infusion	α_2-Adrenergic antagonist β_2-Adrenergic antagonist 5-HT_4 serotonergic agonist 5-HT_3 serotonergic antagonist
Domperidone	GES, CRTZ	Vomiting disorders, gastroesophageal reflux	0.05 to 0.10 mg/kg PO BID	α_2-Adrenergic antagonist β_2-Adrenergic antagonist
Serotonergic 5-HT_4 Agonist Drugs				
Cisapride	GES, stomach, intestine, colon, CRTZ	Gastroesophageal reflux, delayed gastric emptying, ileus/pseudoobstruction, constipation, chemotherapy-induced vomiting	0.1 to 0.5 mg/kg PO TID (doses as high as 0.5 to 1.0 mg/kg have been used in some dogs)	5-HT_3 serotonergic antagonist 5-HT_1 serotonergic antagonist 5-HT_2 serotonergic agonist
Mosapride	Stomach	Delayed gastric emptying	0.25 to 1.0 mg/kg PO BID	None
Prucalopride	Stomach, colon	Delayed gastric emptying, constipation	0.01 to 0.20 mg/kg PO BID	None
Tegaserod	Intestine, colon	Constipation, ileus/ pseudoobstruction	0.05 to 0.10 mg/kg PO or IV, BID	5-HT_1 serotonergic antagonist
Motilin-like Drugs				
Erythromycin	GES, stomach, intestine, colon	Gastroesophageal reflux, delayed gastric emptying, constipation (dogs)	0.5 to 1.0 mg/kg PO IV TID	5-HT_3 serotonergic antagonist
Acetylcholinesterase Inhibitors and Cholinomimetic Agents				
Ranitidine	Stomach, colon	Delayed gastric emptying, constipation	1.0 to 2.0 mg/kg PO BID-TID	H_2 histaminergic antagonist
Nizatidine	Stomach, colon	Delayed gastric emptying, constipation	2.5 to 5.0 mg/kg PO SID	H_2 histaminergic antagonist
Bethanechol	Esophagus	Canine idiopathic megaesophagus	Dog: 5 to 15 mg/dog PO TID	
Nitric Oxide Donors				
AMU-301	Stomach	Diabetic gastroparesis	Not yet established	
Prostanoids				
Misoprostol	Colon	Constipation	Dog: 2 to 5 µg/kg PO TID-QID	

CRTZ, chemoreceptor trigger zone; GES, gastroesophageal sphincter.

widely used in treating patients with Gram-positive and Gram-negative bacterial and mycoplasmal infections. Physicians and veterinarians noted that erythromycin therapy was accompanied by frequent GI side effects, including nausea and vomiting. This occurrence suggested to researchers that erythromycin might have effects on GI motility. It was subsequently demonstrated that microbially effective doses of erythromycin stimulate retrograde peristalsis and vomiting in dogs, and that lower microbially ineffective doses of erythromycin stimulate migrating motility complexes and antegrade peristalsis similar to that induced by the endogenous GI hormone, motilin.

Acetylcholinesterase Inhibitors and Cholinomimetic Agents

Ranitidine and nizatidine, classic histamine H_2 receptor antagonists, stimulate GI motility by inhibiting acetylcholinesterase activity. As parasympathetic potentiating agents, ranitidine and nizatidine stimulate gastric emptying and small intestinal and colonic motility. The prokinetic effects of ranitidine and nizatidine appear to be more prominent in the proximal GI tract (e.g., gastric emptying). Other members of this classification, for example, cimetidine and famotidine, apparently have no effect on GI motility. Bethanechol is a cholinomimetic agent that binds muscarinic cholinergic receptors and stimulates motility throughout the GI tract.

Nitric Oxide Donors

Diabetes mellitus is the most common endocrinopathy of the domestic dog.[11] Long-standing undiagnosed or untreated diabetes mellitus is associated with significant gastroparesis in the dog,[12,13] just as it in humans. The pathogenesis of gastroparesis in diabetes mellitus is complex and probably multifactorial, involving one or more of the cellular elements (neurons, smooth muscle cells, interstitial cells of Cajal) regulating gastric motility.[14] An important pathophysiologic mechanism appears to be the loss of neuronal nitric oxide synthase, the enzyme responsible for the production of

nitric oxide, an inhibitory neurotransmitter that is required for relaxation of smooth muscle and therefore a critical component of normal GI motility. In the absence of nitric oxide, the stomach cannot relax, resulting in bloating, satiety, nausea, and vomiting.[15]

Cisapride, metoclopramide, and erythromycin have all been used with variable effect in diabetic gastroparesis. Therapy aimed instead at restoring nitrergic neurotransmission could have intrinsic beneficial effects in canine diabetic gastroparesis. AMU-301, a nitric oxide donor, is recognized as an effective treatment for diabetic gastroparesis in streptozocin-induced diabetic rat models of delayed gastric emptying, and may eventually prove useful in spontaneous canine diabetes mellitus.[16]

NEOPLASIA

Takeo Minami

Etiology

Gastric tumors account for less than 1% of all malignancies in dogs. These tumors include gastric adenoma, adenocarcinoma,[1] leiomyoma,[2] leiomyosarcoma,[3] lymphoma,[4] carcinoid,[5] and GI stromal tumor (GIST).[6] One review of gastric tumors reported 61 cases in 10,179 dogs representing a prevalence in this population of 0.18%.[1] Although the etiology is not definitively known, long-term administration of nitrosamines may induce carcinomas in dogs.[7] A predisposition to gastric carcinoma was found in Rough Collies and Staffordshire Bull Terriers[8] and a familial occurrence of gastric carcinoma has been reported in Belgian Shepherd dogs.[9] Affected dogs range in age from 3 to 16 years (mean: 7.5 years).[10-12] One study reported a male-to-female ratio of 1:5 for adenomas and 17:7 for adenocarcinomas.[11] Males are more commonly affected with gastric lymphoma than females.[4] Leiomyomas tend to occur in very old dogs (mean age: 15 years).[13]

Pathophysiology

Most malignant gastric tumors in dogs are adenocarcinomas. The stomach is generally firm with thickened walls. Lesions can be focal or extend to involve the entire wall (Figure 56-13) and they are commonly found on the lesser curvature.[14] They tend to be polypoid and can ulcerate into the mucosa.[12] Metastases are frequently present. One report described metastasis in 14 (74%) of 19 dogs with gastric adenocarcinomas. Metastatic sites included gastric lymph nodes, the omentum, liver, duodenum, pancreas, spleen, esophagus, adrenal glands, and lungs.[14]

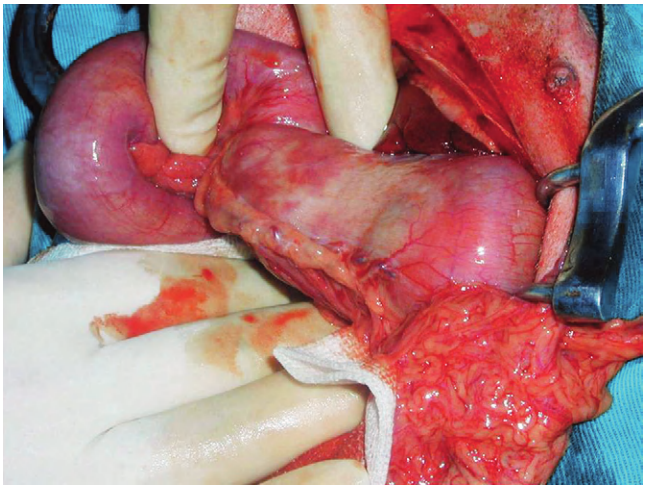

Figure 56-13 Canine gastric adenocarcinoma. The serosal surface is pale white and the gastric wall is firm and not expandable.

Other malignant gastric tumors include leiomyosarcoma, lymphoma, mast cell tumor, and fibrosarcoma. Leiomyosarcomas occur predominantly in males (82%) with a mean age of 11 years (range: 8 to 17 years). These tumors tend to metastasize and common sites include the stomach (76%), esophagus (4%), and intestine (10%). Median survival time in dogs with GI leiomyosarcoma is reported as 7.8 months.[6]

In human medicine, immunohistochemistry of GI tumors has led to reclassification of some tumor types. Some leiomyosarcomas have now been renamed as GISTs.[15] GISTs occur equally in males and females with a mean age of 11 years (range: 5 to 14 years). GISTs can occur throughout the intestine, but were located in the stomach in 19% of cases (four of 21) in one report. In that study, 52% of the tumors expressed CD117 (KIT) and 33% were positive for smooth muscle markers, but none expressed desmin or S-100 protein (Figure 56-14). In a further study, 28 (67%) of 42 leiomyosarcomas were reclassified as GISTs when new criteria were applied.[6] These GISTs were found more commonly in the cecum and large intestine. Only two of the 28 GISTs were located in stomach. With this tumor median survival time was 11.6 months in dogs without surgical intervention. Median survival for dogs with GIST was prolonged with surgery to 37.4 months.[6] One report described 29% of dogs with GIST as having metastasis to the liver or abdominal cavity at the time of diagnosis.[15]

Gastric lymphoma can be primary or represent GI involvement in the multicentric form of the disease. Gastric mast cell tumor is also documented.[16]

Lymphomas are the most common gastric tumors in cats. Most cats with gastric lymphoma are negative for FeLV.[17,18] It has been suggested that chronic *Helicobacter* infection raises the risk for gastric lymphoma in humans and ferrets. Only tentative evidence has been shown for this association in cats.

The benign proliferative lesions of the stomach include leiomyoma, hypertrophy of muscle, and adenoma.

Clinical Examination

The most common clinical sign of a gastric tumor is chronic progressive vomiting. Physical examination in patients with gastric tumor is nonspecific. Weight loss and lethargy may be due to reduced food intake, maldigestion, bleeding from mucosal ulcers or tumor cachexia. Hemorrhagic ulcers or hemorrhage from a gastric mass may lead to anemia and dark stool or melena can be present. Scleral icterus may occur if biliary drainage is obstructed. Dehydration and metabolic alkalosis may be present secondary to chronic vomiting.

Most animals with gastric tumors are relatively asymptomatic until the disease is advanced enough to disturb gastric or intestinal function (Figure 56-15). It may take several months for a small lesion to produce clinical signs and by the time of clinical presentation the tumor is often at an advanced stage.

Diagnosis

Laboratory Findings

Laboratory changes in dogs and cats with gastric tumors are usually nonspecific.

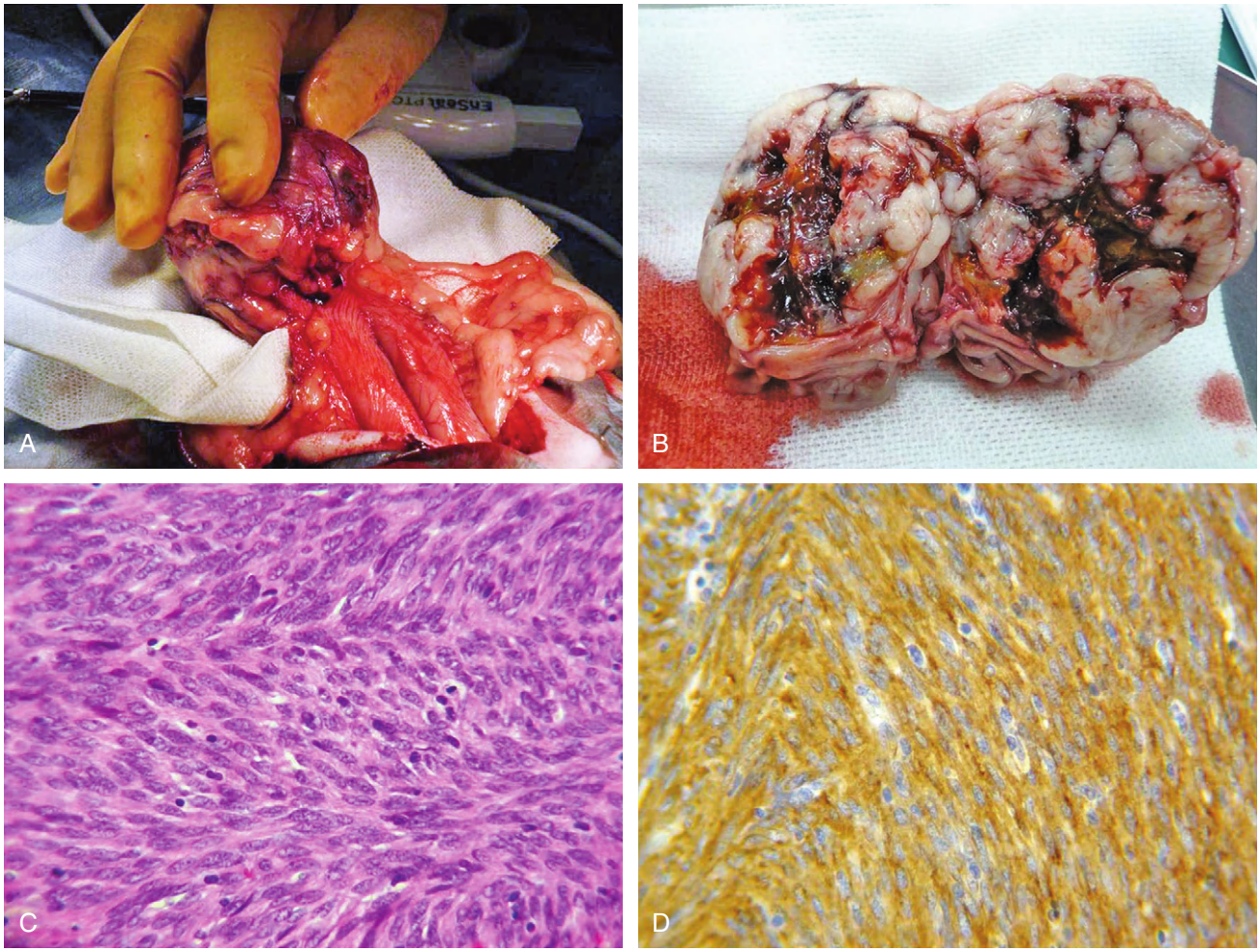

Figure 56-14 **A**, Canine gastric GI stromal tumor. The mass is pedunculated and well-circumscribed. **B**, The cut surface shows fibrous tissue and multifocal hemorrhage. **C**, The microscopic appearance is of interwoven bundles of spindle cells (hematoxylin and eosin stain). **D**, On immunohistochemistry, the cells are positive for c-kit.

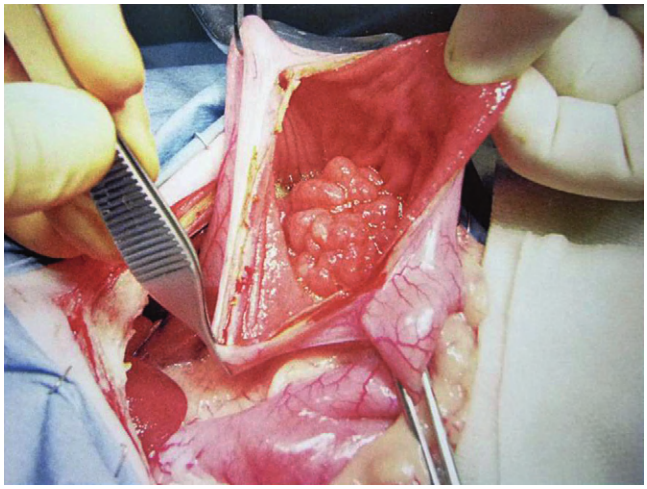

Figure 56-15 Canine gastric adenocarcinoma. This large mass occupies most of the stomach.

Diagnostic Imaging

Plain films and survey radiographs are generally nondiagnostic; however, thoracic radiographs can help rule out pulmonary metastasis. A variety of findings may be present with gastric tumors on barium studies. These include filling defects, delayed gastric emptying, ulcers, loss of normal rugal folds, mucosal thickening, or loss of gastric wall compliance. Contrast radiography is less frequently undertaken now because of the advantages that ultrasound and endoscopy have over such procedures.

Ultrasonographically, gastric neoplasia is associated with mural thickening with loss of normal wall echo texture and diminished to absent local motility. An ultrasound-guided fine-needle aspirate or needle core biopsy may provide a preoperative diagnosis in affected animals. Ultrasonography may also detect metastasis to the liver or regional lymph nodes and help to define the anatomy of gastric lesions.[19-21]

Endoscopy

Endoscopy is the preferred diagnostic test as it allows biopsy of the observed lesion. Some tumors may be difficult to sample if they are completely submucosal or if they are scirrhous. Even without a biopsy sample endoscopic evaluation of the gross appearance of the stomach can be very suggestive of neoplasia and this may help the

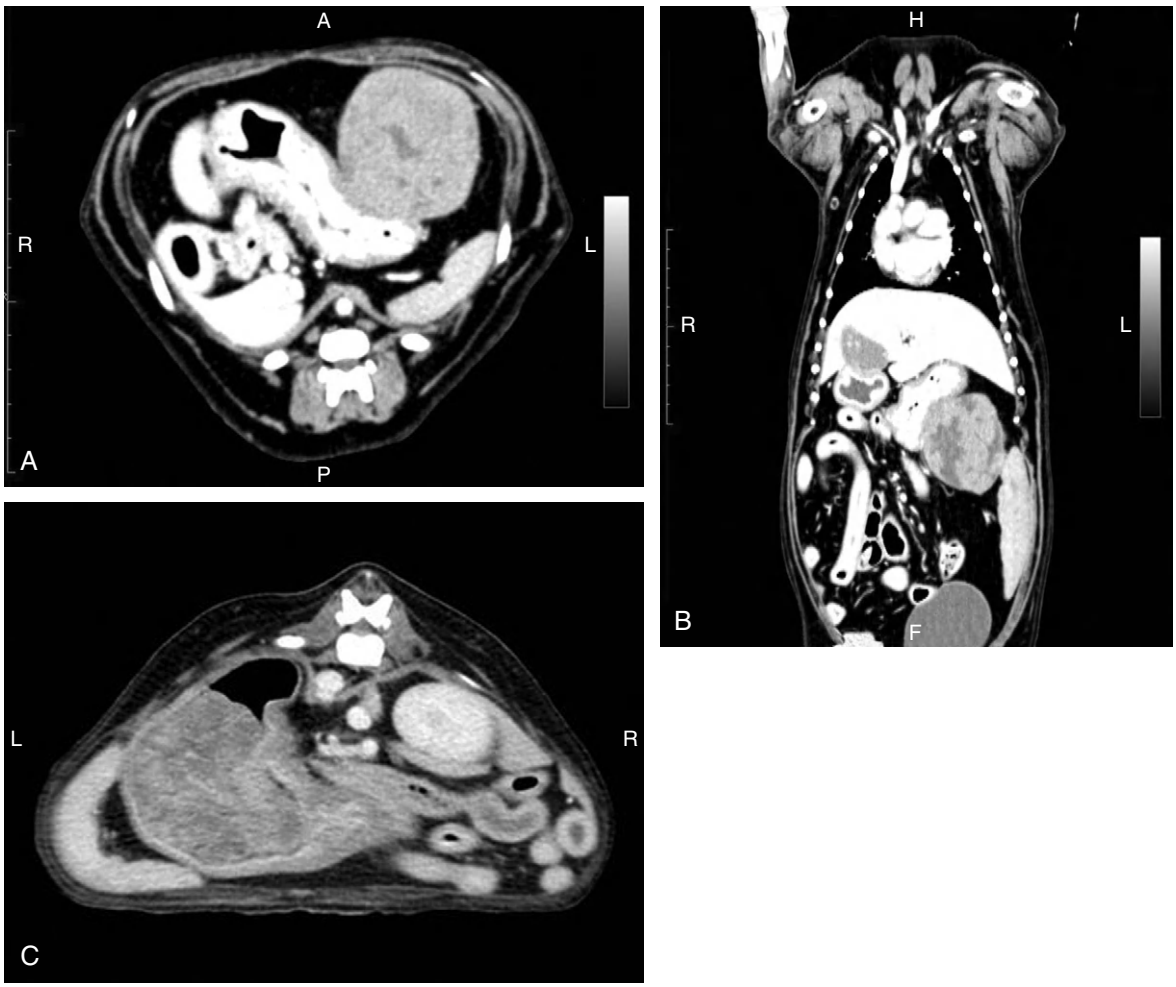

Figure 56-16 **A**, Axial CT image of canine gastric GI stromal tumor. The mass extends from the stomach and is pedunculated. **B**, Coronal CT image of canine gastric GIST. The mass is pushing against the abdominal wall, but there are no hepatic metastases. No areas of the mass are filled by contrast agent. **C**, Axial CT image of canine gastric adenocarcinoma. The mass fills the stomach cavity.

client decide if surgery is appropriate. Finding a deep ulcer with a firm, dense, necrotic base surrounded by raised or distorted mucosa is very suggestive of scirrhous carcinoma. Scirrhous tumors are very dense, and it may be impossible to sample the lesion. Because muscular tissue is located beneath the submucosa, leiomyomas and leiomyosarcomas are usually deep in location. They may or may not be associated with ulceration. These tumors are also hard to biopsy with flexible endoscopic forceps, but a diagnostic sample can usually be obtained if the sample is taken from deeper tissue.

Advanced Imaging

Computed tomography (CT) or magnetic resonance imaging allows visualization of the primary lesion, its extent, and the presence of synchronous lesions, and both local and distant metastases. The thickness of the gastric wall and the size of regional lymph nodes are seen with these techniques (Figure 56-16). Contrast enhancement can help to identify metastases as small as 1 mm in diameter in the liver, spleen, and thoracic cavity.

Treatment

Medical Management

Medical management depends on the severity of the clinical signs. If possible, electrolyte, acid–base, hydration, and coagulation abnormalities should be corrected before surgery. No effective chemotherapy is known for adenocarcinoma and sarcomas of the stomach.

Radiation therapy is rarely utilized because of the poor radiation tolerance of surrounding normal tissue (liver and intestine). Nonresectable lymphoma burden may be dramatically reduced with lower doses of radiation than required for other tumors.

In people and dogs, GISTs may be responsive to inhibitors of c-kit, and as these drugs have become available in veterinary medicine, they could theoretically have efficacy against this tumor.[16,22,23]

Surgical Treatment

Preoperative Management

Food should be withheld for 12 hours before surgery. Antibiotics may be given at the time of induction of anesthesia and continued for several days after surgery.

Surgical Technique

The patient must be under general anesthesia. An upper midline skin incision is performed to open the abdominal cavity. If there is ascites or visible metastatic lesions, cytology must be performed to look for neoplastic cells. If there are neoplastic cells, radical surgery is not optimal. At the time of surgery, the operator must search for metastatic lesions in abdominal organs, the peritoneal wall,

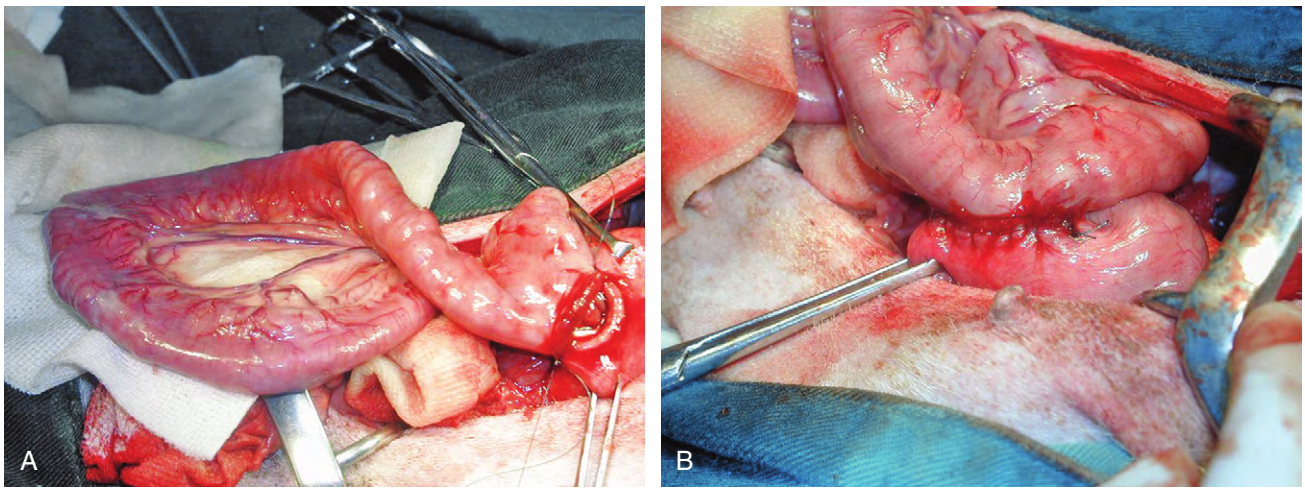

Figure 56-17 **A**, Surgical approach to gastrojejunostomy. Full-thickness incisions are made and both sides are ligated. A one-layer closure is made on both sides. **B**, The completed gastrojejunostomy.

omentum, mesentery, and lymph nodes. Excisional margins in the stomach are determined based upon the anatomy of the tumor. Stomach arteries and veins are ligated and regional lymph nodes are dissected. The stomach wall and tumor is excised (Figure 56-17). Resection strategies include a partial (proximal, body, and distal) gastrectomy and total gastrectomy. If there is a sufficient portion of the upper duodenum remaining, a Billroth 1 procedure is performed, where the remaining portion of stomach is anastomosed to the duodenum proximal to the bile duct and pancreatic duct. If the stomach cannot be anastomosed to the duodenum a Billroth 2 procedure is performed. In this procedure, the remaining portion of the duodenum is sealed off, an opening is cut into the jejunum and stomach is reattached at this point (Figure 56-17). If complete gastrectomy is needed, a Roux-en-Y method is performed. Abdominal lavage is performed and the abdominal cavity is closed.[2,24]

With the exception of lymphoma, surgery is the only potentially curative treatment for gastric tumors. Solitary gastric lymphoma is rarely cured by surgery alone, and chemotherapy is only palliative for diffuse lymphoma.

ULCER

Caroline S. Mansfield and Linda A. Abraham

Etiology

Gastric ulceration is defined as a defect in the gastric wall that extends through the muscularis mucosae into the deeper layers of the wall (submucosa or the muscularis propria). Erosion of blood vessels in this deeper tissue can lead to life-threatening hemorrhage.[1] In humans, defects are required to be greater than 0.3 cm in diameter with considerable depth to fulfill the true criteria of gastric ulceration.[2] When the disruption is confined to the mucosa and does not extend to the muscularis mucosae, it is defined as a gastric erosion.[2] Duodenal ulcers appear to be far less common in companion animals. With severe ulceration, perforation of the gastric wall may occur, leading to contamination of the peritoneal cavity.

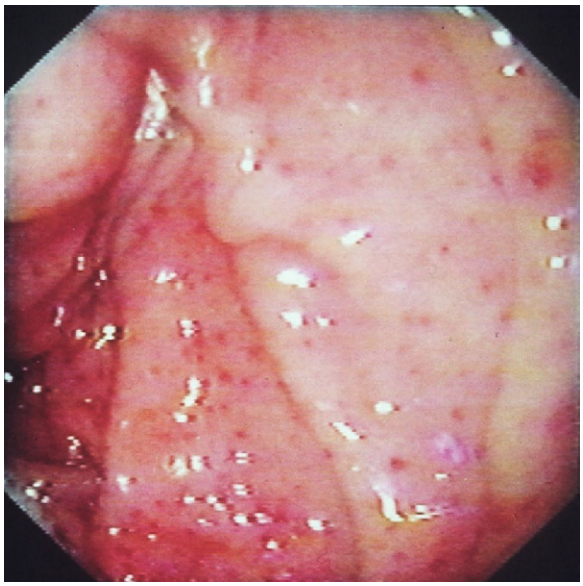

Figure 56-18 Shallow and small gastric erosions observed on endoscopy in a dog with atypical hypoadrenocorticism. They did not cause abdominal pain or noticeable blood loss.

Gastric ulceration is more commonly reported in dogs than in cats.[3-6] Many studies of gastric ulceration, particularly pharmacologic studies, define gastric ulceration as the presence of shallow erosions or ulcerations visible by endoscopy, such as is evident in Figure 56-18. These shallow erosions may not always be clinically significant, and may not truly fulfill the definition of gastric ulceration (Figure 56-19).

There are many different causes of gastric ulceration reported in dogs and cats. The most commonly reported causes in companion animals are drug-associated injury, mast cell tumors, and primary gastric tumors.[3,4,7]

Intravenous administration of high-dose corticosteroids, particularly in dogs with intervertebral disk disease, is associated with severe GI hemorrhage and ulceration.[8] NSAIDs, particularly aspirin, are also reported to cause substantial gastric ulceration.[4,7] This effect is enhanced when NSAIDs are given in conjunction with

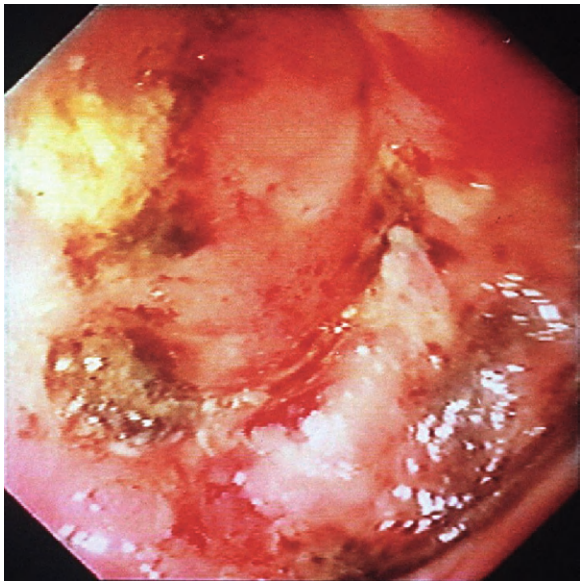

Figure 56-19 A deep and large gastric ulceration observed on endoscopy in a dog displaying signs of abdominal pain and melena. The final diagnosis was gastric adenocarcinoma.

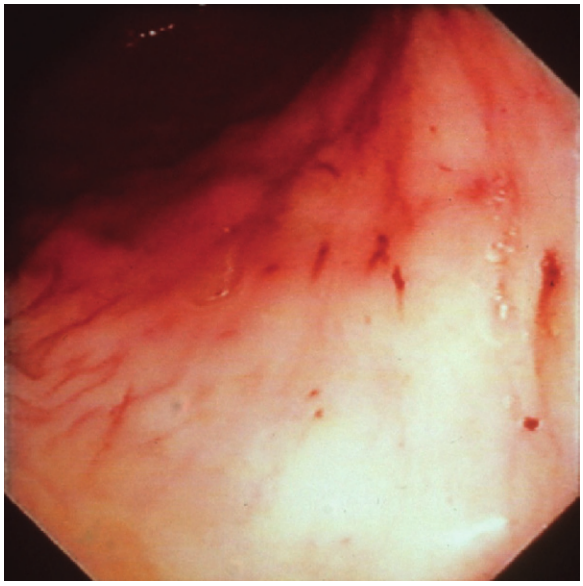

Figure 56-20 Linear gastric erosions secondary to severe vomiting in a dog. Garbage ingestion was the suspected underlying cause.

corticosteroids, and reduced when cyclooxygenase-2 selective NSAIDs are concurrently used.[2,9]

Excessive production of gastric acid (which overwhelms the protective mechanisms of the stomach) is infrequently reported in association with gastrinomas (Zollinger-Ellison syndrome), and mast cell tumors.[10-15] The resulting gastric ulceration can be quite severe. Zollinger-Ellison syndrome is characterized by gastric or duodenal ulceration, diarrhea, and gastric hyperacidity.[11-13] It is usually caused by a gastrin-producing tumor in the pancreas.

Conditions that directly disrupt the gastric mucosa can also cause significant ulceration. Gastric neoplasia is rare, accounting for less than 1% of all malignancies.[16] Primary gastric (adeno)carcinoma is the most commonly reported gastric malignancy in dogs, although leiomyomas/leiomyosarcomas, GISTs, and lymphoma have also been reported in the canine stomach. Lymphoma is more commonly reported in the feline stomach.[5,17-24] Belgian Shepherds, Rough Collies, and Staffordshire Bull Terriers are reported to be predisposed to developing malignant gastric (adeno)carcinomas, but not all studies support a breed predisposition.[20,21,24] There is a tendency for malignant gastric tumors to affect the lesser curvature (incisura angularis) or pyloric antrum. Leiomyomas or GISTs, on the other hand, tend to be found more commonly on incidental finding in older dogs.[16,18,24]

Other primary gastric diseases implicated in the pathogenesis of gastric ulceration include *Helicobacter*-associated inflammation and IBD.[6,9,17] The amount of gastric erosion caused by chronic vomiting is often self-limiting or mild in nature (Figure 56-20).

Systemic disease is also frequently cited as causing gastric ulceration, in particular pancreatitis, DIC, hypoadrenocorticism, liver disease, and uremia. Although the degree of gastric ulceration may be substantial in these conditions, often the other associated clinical signs are more clinically obvious. In one study, only dogs with severe uremia developed gastric ulceration, despite many of the dogs having GI signs.[25] The most common gastric histologic abnormality found in the study of uremic dogs was gastric mineralization.[25] The exact incidence of gastric ulceration in other systemic diseases has not been fully assessed.

Strenuous exercise, particularly in Alaskan sled dogs, is also associated with increased intestinal permeability and GI ulceration.[26,27] Other less-common conditions include parasitic disease, hypereosinophilic syndrome, and pyloric outflow obstruction.[3] GDV is also associated with gastric ulceration and necrosis.

Pathophysiology

The gastric mucosal barrier is one of the main mechanisms by which the stomach protects itself against acid injury (see Chapter 1). This barrier has low permeability for sodium and hydrogen ions.[28,29] The barrier is formed and supported by intact apical cell membranes with tight epithelial cell junctions; bicarbonate secretion; mucus production; a rich blood supply; active cell renewal; surface active phospholipids; and endogenous prostaglandins.

Mucus is produced by surface mucosal cells in the gastric glands. The surface mucosal cells also secrete bicarbonate across a concentration gradient into the surface mucus layer.[30,31] Bicarbonate secretion is dependent on blood flow to the mucosa, as well as serum bicarbonate concentrations and the acid productivity of oxyntic (or parietal) cells. Prostaglandins are responsible for stimulating the bicarbonate secretion from mucosal cells.[31] The bicarbonate-rich mucus layer neutralizes hydrogen ions and leads to the formation of carbonic acid, which is then converted by carbonic anhydrase to form carbon dioxide and water for excretion.[30]

If the bicarbonate-mucus layer is breached, intracellular bicarbonate is another mechanism that protects epithelial cells against acid backdiffusion.[32,33] Proton (H^+) pump exchanges on the basolateral membrane also protect against increasing intracellular acid. Epithelial cells undergo rapid replication and restitution, with surface mucous cells migrating from the gastric pit to the overlying epithelium in as little as 3 days. This rapid renewal is mediated by a number of factors, of which epidermal growth factor is the most prominent.[34] If there is excessive intraluminal acidity (pH < 3), gastric epithelial cell renewal is impaired, unless there is a sufficient compensatory increase in bicarbonate.[30,33] When the stomach is exposed to acidic stimulants, there is localized hyperemia caused by

increased mucosal blood flow. This, in turn, increases the bicarbonate-rich mucus secretion locally and protects against further damage.

It can thus be deduced that gastric ulceration can develop if there are perturbations in any of these protective mechanisms. The most commonly implicated pathophysiologic mechanisms for gastric ulceration in veterinary medicine are decreased mucosal blood flow, depletion of surface prostaglandins, increased gastric acid secretion, and loss of the epithelial cell tight junctions because of inflammatory or neoplastic infiltration.

NSAIDs, especially aspirin, are reported to exert their adverse effects by direct toxicity to the gastric mucosa as well as by inhibition of the cyclooxygenase-1 pathway, thereby decreasing gastric mucus and bicarbonate production.[35] The pathogenesis of corticosteroid-induced gastric ulceration is not yet fully elucidated, as it is not necessarily caused by depletion of prostaglandin synthesis. Other factors, including poor mucosal blood supply associated with the underlying condition necessitating glucocorticoid administration, may contribute as well. Similarly, the underlying pathophysiologic mechanism by which sled dogs develop gastric ulceration is not well understood, but they do respond to treatment with gastric cytoprotective agents (see Chapter 45).[36] Increased epithelial permeability, and potentially altered local mucosal blood flow as well, may play an important roles under these circusmtances.[27]

Systemic disease, such as uremia, more commonly causes mineralization, mucosal edema, and vasculopathy rather than gastric ulceration per se.[25] When gastric ulceration does develop in uremic animals, it may well be a result of reduced circulating blood volume and consequently altered gastric mucosal blood flow. Similarly, hypotension, liver disease, DIC, hypoadrenocorticism, and pancreatitis may all alter gastric mucosal blood flow by causing splanchnic hypoperfusion resulting from hypotension and hypovolemia.[33] Other potential contributing causes, such as proinflammatory cytokine production or changes in surface prostaglandins, have not been investigated in companion animals. In addition to the reduction in bicarbonate and mucus secretion secondary to poor gastric mucosal blood flow, GI motility is often reduced in these conditions, thereby increasing the exposure time to gastric acid and pepsin.[33] It is postulated that reperfusion injury may ensue following restoration of circulating blood volume, mediated by nitric oxide synthetase, further exacerbating gastric epithelial cell damage in critically ill humans.[33] It is unknown if this syndrome occurs in critically ill companion animals.

Mast cell degranulation releases histamine, which stimulates excessive gastric acid production via parietal H_2 histamine receptors. Malignant mast cells contain up to 50 times more histamine than nonmalignant mast cells.[37] Additionally, dogs with mast cell tumors have higher serum histamine concentrations and lower serum gastrin concentrations than normal dogs.[14] This low serum gastrin is postulated to be a result of negative feedback from gastric hyperacidity. The histamine concentration is not linearly related to the tumor burden.

Gastrinomas, tumors of the endocrine pancreas (δ cells) that produce gastrin, induce hypergastrinemia and gastric hyperacidity. Gastrin directly stimulates secretion of hydrochloric acid from the parietal cells, as well as indirectly stimulating acid production by releasing histamine from fundic enterochromaffin-like cells.[12] The amount of gastric acid stimulated overwhelms the protective mechanisms, and reduces the epithelial cell turnover because of the high acidity.

Theoretically inflammatory conditions of the stomach, such as chronic gastritis or *Helicobacter*-associated gastritis, can cause disruption of the tight junctions and gastric mucosal barrier. However, even though ulceration may be detected microscopically, it requires severe disease for overt gastric ulceration to develop. The true pathogenicity of *Helicobacter*-related disease in companion animals is still under debate, but may be less ulcerogenic than in humans.

Clinical Examination

A careful and thorough physical examination, including rectal examination, is very important in animals with gastric ulceration. Special attention should be made to gentle palpation of the cranial abdomen, as well as assessment of the skin for any ulcerated or newly identified masses that potentially could be mast cell tumors.

The findings on clinical examination are highly dependent on the underlying disease process. Animals with significant gastric ulceration often show signs of focal or diffuse abdominal pain. This may be manifested as a hunched appearance, groaning, or reluctance to get up from a recumbent position. This finding is not pathognomonic for gastric ulceration, however, and other conditions causing true or referred abdominal pain, such as pancreatitis or intervertebral disk disease, should be considered.

Melena is the presence of digested blood pigments in feces, causing a dark, tarry appearance and a foul odor as a consequence of oxidized iron derived from hemoglobin. This may not be reported by the pet owner, but should be apparent on examination of the feces. Experimentally, one study has shown that grossly detectable melena develops 12 to 36 hours after administration of 350 to 500 mg/kg of hemoglobin.[38] This equates roughly to sudden gastric hemorrhage of between 70 and 107 mL in a 30-kg dog. As such, the absence of gross melena does not rule out gastric ulceration.

In some animals, the volume and degree of blood lost into the stomach may cause significant hematemesis (vomiting of blood; Figure 56-21). Consequently, the animal may also show signs of anemia, with pale mucus membranes. If anemia is severe, profound weakness and lethargy may also be apparent. If gastric perforation develops, an inflammatory and septic peritonitis usually follows. Animals may have palpable free abdominal fluid, and show signs of shock and severe inflammatory disease.

Dependent on the underlying cause of gastric ulcer, weight loss resulting in poor body condition score may well be present. This is often associated with a decreased appetite because of the significant gastric pain, but may also be a consequence of cancer cachexia syndrome. Alternatively, the initial stages of gastric digestion may be impaired along with the perturbations in gastric emptying.[12]

Figure 56-21 Substantial hematemesis in an aged dog. (Courtesy of Peter Irwin, Murdoch University, Perth, Western Australia.)

Diagnosis

Historical information and physical examination may suggest predisposing causes, such as recent treatment with NSAIDs, or detection of dermal masses consistent with mast cell tumors. In animals with severe, acute illness, the associated history may be all that is necessary to reach a tentative diagnosis.

Clinical pathology testing may provide further evidence of diseases associated with gastric ulceration, and is also useful to determine the consequences of vomiting and severity of blood loss. Platelet counts and clotting times are helpful in the assessment of primary and secondary hemostasis when a coagulopathy is considered the likely cause of blood loss (see Chapter 9). Acute and chronic blood loss may be associated with anemia and chronic blood loss may exhibit features of iron deficiency (hypochromic, microcytic red cell indices, with associated thrombocytosis). Eosinophilia may be present if the underlying condition is associated with eosinophilic gastroenteritis, mastocytosis, hypoadrenocorticism, and hypereosinophilic syndrome.

Serum chemistry survey in conjunction with urinalysis may indicate pre-renal or renal azotemia, acute or chronic liver failure, and hypoproteinemia. Serum bile acid assays may be indicated to confirm liver dysfunction when the serum biochemistry is only weakly supportive of liver dysfunction. Serum bile acid determinations may also be used to determine the site of protein loss when there is hypoproteinemia.

Electrolyte and acid–base changes are helpful diagnostically and will influence the choice of intravenous fluid therapy. Electrolyte and acid–base abnormalities may reflect severe vomiting. Hyponatremia with a Na^+:K^+ ratio of less than 27:1, however, could suggest hypoadrenocorticism and other biochemical changes supportive of such a diagnosis include hypercalcemia, azotemia, hypoglycemia, hypoalbuminemia, hypocholesterolemia, and increased serum liver enzyme activities. ACTH stimulation test is indicated if the electrolyte changes and clinical presentation are consistent with a diagnosis of hypoadrenocorticism. Hyponatremia and a low Na^+:K^+ ratio can alternatively be caused by *Trichuris vulpis* or *Salmonella* infection (pseudohypoadrenocorticism)[39] and definitive diagnosis is typically made by finding ACTH normoreactivity and a positive fecal flotation. Hypokalemia, hypochloremia, and metabolic alkalosis in combination are suggestive of a proximal intestinal tract obstruction which should be considered and ruled out. Survey radiographs or ultrasound examination of the abdomen are often used for this purpose.

Fecal occult blood tests assist in confirming the site of blood loss although the test is limited in many situations by the requirement for dietary modification prior to the test.[40,41]

Dermal masses and enlarged lymph nodes should be cautiously aspirated to detect mast cell or lymphoma origin. Smears are routinely stained with Romanowsky-type stains although some mast cell granules may not stain strongly unless the slides are immersed in the alcohol fixative for several minutes when staining with rapid modified Romanowsky type such as Diff-Quik.[42]

Diagnostic imaging has limited value in the diagnosis of gastric ulceration per se, but is valuable for ruling out other causes of vomiting and may also detect early evidence of perforation.[43] Radiographic changes associated with GI perforation include lack of serosal detail, pneumoperitoneum, and leakage of positive contrast medium. Complementary use of abdominal ultrasound can assist in the localization of the abnormality and identification of the underlying cause of perforation.[43,44] Double-contrast radiologic techniques have been used to identify benign gastric ulceration, and demonstrate good agreement with endoscopic diagnosis.[45] In addition, radiographic features have been used to predict ulcers that may be refractory to treatment with H_2-histamine receptor antagonists.[46] Positive contrast studies are less useful in small animals, and have the associated risk of aspiration.

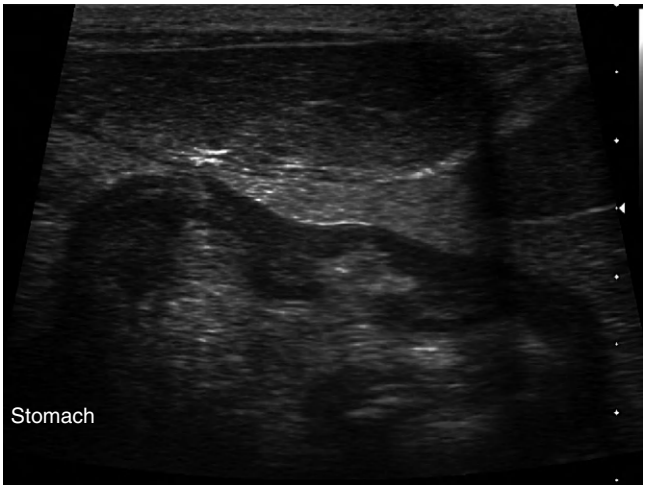

Figure 56-22 Ultrasound image of the stomach of a dog with severe gastric ulceration. There is loss of layering almost through the entire gastric wall (*arrowheads*), with the defect filled with ingesta. (Courtesy of Catherine Beck, University of Melbourne.)

Ultrasonography may be used to examine the stomach wall for changes in thickness, presence of a defect or crater, and loss of the normal layering patterns (Figure 56-22).[43,47] A small amount of orally administered water and positional changing may enable a more complete examination of the stomach. It should be noted that a normal study does not rule out the presence of ulceration, and that ultrasound does not readily distinguish between benign and malignant ulcers. Perforation of the GI tract is associated sonographically with bright mesenteric fat, peritoneal effusion, pneumoperitoneum, thickened GI wall with or without loss of layering, and dilated fluid filled stomach or intestines.[44] Evaluation of lymph nodes and other abdominal organs for the presence of metastasis is possible using ultrasound, and collection of fine-needle aspirates may assist in the definitive diagnosis of neoplasia such as systemic mastocytosis and lymphosarcoma.

CT virtual endoscopy has been proposed as a noninvasive screening test for gastric disease in humans.[48] The technique has yet to be developed adequately for dogs,[49] and until that time conventional endoscopy remains the preferred endoscopic technique. Endoscopy permits direct observation of the depth and diameter of the gastric ulcer, as well as enabling routine acquisition of tissue biopsies. During endoscopy the entire stomach should be examined. The use of a J or retroflex maneuver is recommended to allow complete inspection of the cardia. Malignancies tend to occur in the antrum and lesser curvature of the stomach, but theoretically could be present anywhere in the stomach. Erosions associated with NSAID use are located predominantly in the antrum, although there is no specific location for mast cell tumor–induced lesions.[3]

Biopsies of the ulcerated areas are obtained to rule out primary gastric infiltrative disease. Biopsies should be taken from the periphery of the ulcer to reduce the risk of perforation, and multiple biopsies should be taken from the abnormal region. Endoscopic biopsies, however, may not be adequate to diagnose gastric tumors and full-thickness biopsies taken at laparotomy may ultimately be required for a definitive diagnosis.

Measurement of gastric pH and serum histamine and gastrin concentrations may be useful in the diagnosis of hypersecretory states as a result of mast cell tumors or gastrinomas. Mast cell tumors are associated with acidic gastric pH, low plasma gastrin, and high plasma histamine concentrations, with the gastrin concentration being inversely related to the histamine concentration.[14] In contrast, a gastric pH lower than 3 and markedly high plasma gastrin concentration are typically associated with gastrinoma.[50] In cases where the plasma gastrin concentration is normal or only mildly increased, provocative testing, with feeding or secretin administration, can confirm the diagnosis of gastrinoma.[51-53] It should be recognized that treatment with proton pump inhibitors or H_2-histamine receptor antagonists will cause an increase in plasma gastrin concentration due to lack of negative feedback inhibition. In humans, it has been shown that gastrinomas cannot be diagnosed by means of a fasting plasma gastrin concentration in patients treated with proton pump inhibitors or H_2-receptor antagonists.[54] Plasma gastrin may also be increased in renal failure, hepatic disease, and enteropathies. These alternative conditions should be considered and ruled out, and the presence of a tumor confirmed by diagnostic imaging.

The diagnostic imaging modality of choice to localize gastrinomas in small animals is debatable given the small number of reports of this rare tumor. In humans, all forms of cross-sectional imaging may be unsuccessful at localizing these tumors.[55,56] CT, magnetic resonance imaging, and transabdominal ultrasound all have similar sensitivities for diagnosis (29%).[55] A combination of endoscopic ultrasound with somatostatin receptor scintigraphy, resulted in an improved detection rate of 93%.[56] CT imaging can be helpful in the diagnosis of insulinomas in dogs[57] and it may be a useful modality for detection of gastrinomas in dogs and cats, as well. Ultrasound examination of the abdomen and pentetreotide scintigraphy are typically indicated to confirm the presence of a gastrinoma.[58] In addition, positive somatostatin receptor scintigraphy may predict whether use of somatostatin analogues will be beneficial clinically. However, this has not been validated in small animals to date.

Treatment

Treatment aims are to treat the underlying disease process if possible; reverse fluid, electrolyte, and acid–base derangements; and restore the gastric mucosal barrier to limit further damage. Antiemetics may be required in the initial treatment regimen. The reader is directed to other sections in this chapter for details on treatment of gastric neoplasia and *Helicobacter* infection (see also Chapter 61 for details on liver failure.) When animals are painful, analgesia may be necessary as well. Opioid analgesics are best tolerated, although morphine should be avoided because of its emetic properties.

Surgery may be required for ulcers that are refractory to medical management, have perforated or are at risk of perforation, and to make a definitive diagnosis where there is no apparent cause for the ulceration.

Treatment of preexisting conditions is mandatory. NSAID and corticosteroid therapy should be discontinued as soon as possible. Hypoadrenocorticism is treated with lifelong supplementation of mineralocorticoid (e.g., desoxycorticosterone pivalate or fludrocortisone) and variable glucocorticoid replacement. The reader is directed to other sections in this chapter for discussion of the treatment used for gastric neoplasia, liver failure, and *Helicobacter* (see also Chapter 61).

Treatment of gastrinoma is aimed at surgical removal of the primary tumor, which is often small and often difficult to localize. Management is complicated by the frequent presence of metastases at the time of diagnosis.[53,58-64] Medical therapy may be adjunctive, or in many cases is the sole therapy for controlling clinical signs associated with acid hypersecretion. Long-term survival (2 years) has been reported with omeprazole monotherapy.[65] Combination therapy with antisecretory drugs, sucralfate, and octreotide has also been described.[58] The use of octreotide is thought to be dependent on positive somatostatin receptor scintigraphy, and has had variable success in the limited numbers of dogs treated.

Mast cell tumor treatment is dependent on the grade and stage of the tumor, neither of which correlate very well with the degree of hyperhistaminemia.[14] Treatment with histamine receptor (types 1 and 2) antagonists should reduce some of the effects of histamine. They may be helpful prior to surgery when degranulation of mast cells with histamine release is anticipated from tumor handling. Similarly, treatment with omeprazole will decrease the gastric acidity associated with hyperhistaminemia. Direct treatment of the tumor may consist of surgery, chemotherapy or radiation therapy, dependent on the location of the tumor as well as histologic grading.

Maintenance of normal hydration is an important component of treatment, and administration of fluid therapy will depend on the degree of dehydration or hypovolemia. The administration rate for crystalloids is calculated to restore losses and provide ongoing maintenance requirements over a 24-hour period. In animals that present with evidence of shock or poor peripheral perfusion, crystalloids should be given at an initial rate of 60 to 90 mL/kg/h for 1 to 2 hours before decreasing to a rate that maintains the circulation. Packed red blood cells or whole-blood transfusion is indicated in severe anemia, as is plasma or colloid support when there is severe hypoproteinemia. Treatment aimed at restoring the gastric mucosal barrier comprises administration of anti-secretory drugs together with mucosal protectants. This is required regardless of the underlying cause. Histamine receptor (type 2) antagonists and proton pump inhibitors are the two classes of drugs used to reduce acid secretion and are discussed in Chapter 45 together with mucosal protectants. Sucralfate is typically used in combination with antisecretory drugs, but its efficacy is unproven, especially when given in conjunction with a gastric acid suppressant.

Nutritional management is an important component of treatment and diets should be chosen to facilitate gastric emptying and enable healing. Diets with reduced fat and fiber contents will increase the rate of gastric emptying. High-quality, highly digestible proteins should be present and the diet should provide adequate amounts of protein to reverse catabolism when present. Dietary modification should also be aimed at management of the underlying disease process. Fat restriction and modification of dietary protein (elimination type diet or hydrolyzed protein) can assist in the management of inflammatory bowel disease. In cases of advanced renal insufficiency, dietary modification typically involves feeding a moderately restricted amount of a high quality protein together with restricted phosphate. Care must be taken to provide sufficient protein to avoid endogenous protein catabolism. In cases of liver dysfunction, the protein content only requires restriction when hepatic encephalopathy is present (see Chapter 17). In such cases, protein derived from milk, soy, egg, and cottage cheese may be better tolerated than protein of animal origin. In acute liver failure, it is important to supply adequate protein to prevent malnutrition, enable hepatic regeneration, and prevent catabolism of endogenous protein. For all forms of liver disease, inclusion of antioxidants such as vitamin E and *S*-adenosyl methionine can protect against oxidative injury.

Prognosis

The prognosis for gastric ulceration is highly dependent on the severity of signs at the time of presentation, whether perforation has occurred, and the underlying cause. Surgical intervention is associated with a good outcome in dogs when the predisposing factors are controlled or eliminated.[3] Approximately 10% of dogs treated surgically or medically died from their ulcer disease compared with 37.5% of those untreated.[3,5] Cats frequently present in a critical condition and prompt stabilization prior to surgery has been associated with a good outcome. Cats with intestinal and pancreatic neoplasia that is associated with gastric ulceration can be palliated for prolonged periods.[5]

Survival time in dogs with gastric carcinoma is dependent on the size and invasiveness of the tumor at diagnosis, with advanced cases being inoperable and carrying a grave prognosis. Less-advanced cases may be treated surgically (the treatment modality of choice) and are likely to have a more favorable long-term prognosis.[66] The prognosis for gastrinoma is typically considered poor to grave given the high likelihood of metastasis at the time of presentation. Survival times of 2 years have been reported when the gastric ulceration was controlled with omeprazole monotherapy.[65] Addition of somatostatin to omeprazole may further improve survival in dogs continuing treatment with omeprazole.[58,67] The prognosis for dogs presenting with mast cell tumors will depend on tumor location, stage, and grade, together with presence of systemic paraneoplastic signs. Dogs presented with high-grade tumors, evidence of metastasis, and systemic signs carry a poorer prognosis than those presented with a localized, low-grade tumor.

Prognosis in cases associated with nonneoplastic disease will be dependent on the control of the underlying disease process. Generally, progressive disease (such as chronic liver failure and renal insufficiency) will carry a guarded to grave prognosis dependent on the rate of progression and response to treatment.

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CHAPTER 57

Small Intestine

STRUCTURE AND FUNCTION

Edward J. Hall

The small intestine (SI) is, in essence, an interface between the external environment and the body, and is both an absorptive surface and a barrier; it must digest and absorb nutrients while excluding antigens and microbes and eliminating fecal waste. It faces a frequently changing dietary and bacterial intake, and yet has to maintain a dynamic but balanced microflora within its lumen while being intermittently exposed to pathogens. All of its functions—mixing and propulsion, secretion, digestion, absorption, regulation of blood flow, immunologic reaction and tolerance, and elimination—are fully integrated through both local and remote neuroendocrine and immunologic mechanisms (see Chapter 1). It thus has a complex task and requires specialized anatomic arrangements to perform them.

Gross Structure

Anatomic Regions

The SI is basically a tube, beginning at the pylorus of the stomach and ending at the ileocolic valve. However, this tube is ultimately in continuity with the external environment, proximally from the mouth via the esophagus and stomach, and distally to the anus via the large intestine (Figure 57-1, *A*).[1-3] It is relatively short, reflecting the typical dietary intake of cats and dogs. It is approximately 1 to 1.5 meters long in adult cats and ranges from 1 to 5 meters in adult dogs, in proportion to the size of the individual. It is divided arbitrarily into three anatomic segments: the duodenum proximally, then the jejunum, and finally the ileum distally (see Figure 57-1, *A*).

Duodenum

The first part of the SI, the duodenum, comprises approximately 10% of its total length. It passes from the pylorus dorsally and to the right, at the level of the ninth intercostal space, and is immobilized by the hepatoduodenal ligament. It then turns caudally into the descending duodenum in contact with the right flank, turning again at the caudal flexure near the pelvic brim. It is in close association with the common bile duct and the head and right limb of the pancreas, which lie in its mesentery.

The common bile duct and one pancreatic duct enter the duodenum via the major papilla. In dogs an accessory pancreatic duct often enters at a minor papilla more distally and slightly more ventrally (Figure 57-2, *A*), but there is a range of variations in the actual number of ducts and their drainage pattern from the pancreas (see Chapter 60). The papillae are notable endoscopic landmarks in dogs, but may not be obvious in cats.

The distal duodenal flexure, where the duodenum courses to the left side of the abdomen (see Figure 57-2, *B*) is often at the limit of the reach of a standard 1-meter gastroscope, except in cats and small dogs. In dogs the antimesenteric side of the duodenum is marked by a line of whitish, mucosal depressions signifying the presence of specialized lymphoid areas, the Peyer patches (see Figure 57-2, *C*). Secretory Brunner glands and annular mucosal folds are features of the human proximal duodenum, but are not present in dogs and cats. After the distal duodenal flexure, the ascending limb of the duodenum crosses the midline and ends at the level of L6 close to the root of the mesentery near the left kidney, with a mesenteric attachment to the colon, the duodenocolic ligament.

Jejunum

The middle part of the SI, the jejunum, arises as an indistinct structural and functional transition from the duodenum and forms the majority of the SI. The jejunum is loosely suspended in the middle of the peritoneal cavity in a dorsal mesentery, forming mobile loops, and is potentially palpable throughout its length in cooperative and nonobese patients. The mesentery is normally a continuous sheet that is folded to allow the SI to loop within the peritoneal cavity, unlike in humans where segments of the duodenum (and colon) are retroperitoneal. The mesentery carries the vascular, lymphatic, and nervous connections between the SI and the rest of the body.

Defects in the mesentery, most often traumatic in origin, can allow internal hernia formation and small intestinal incarceration. An outpouching of the dorsal mesentery of the stomach forms the greater omentum. This structure functions as a protective, immunologic organ, having the ability to migrate to sites of intraperitoneal inflammation and potentially prevent leakage from an intestinal perforation and seal off pockets of infection.

Ileum

Approximately the last 30 cm of the SI comprises the ileum. The transition from jejunum to ileum in humans is based on changes in diameter, color, and the presence of Peyer patches; in dogs and cats the distinction has been arbitrarily based on the extent of attachment of the ileocolic ligament. In fact the basic structure of the ileum is no different from the rest of the SI and it is not clearly demarcated microscopically from the jejunum. However, it does have some unique functional characteristics, such as the absorption of bile salts and cobalamin. It is also a site of dense lymphoid follicle expression. Meckel diverticulum, a remnant of the embryonic omphalomesenteric duct, found in the ileum of approximately 2% of people and a potential source of bleeding, obstruction,

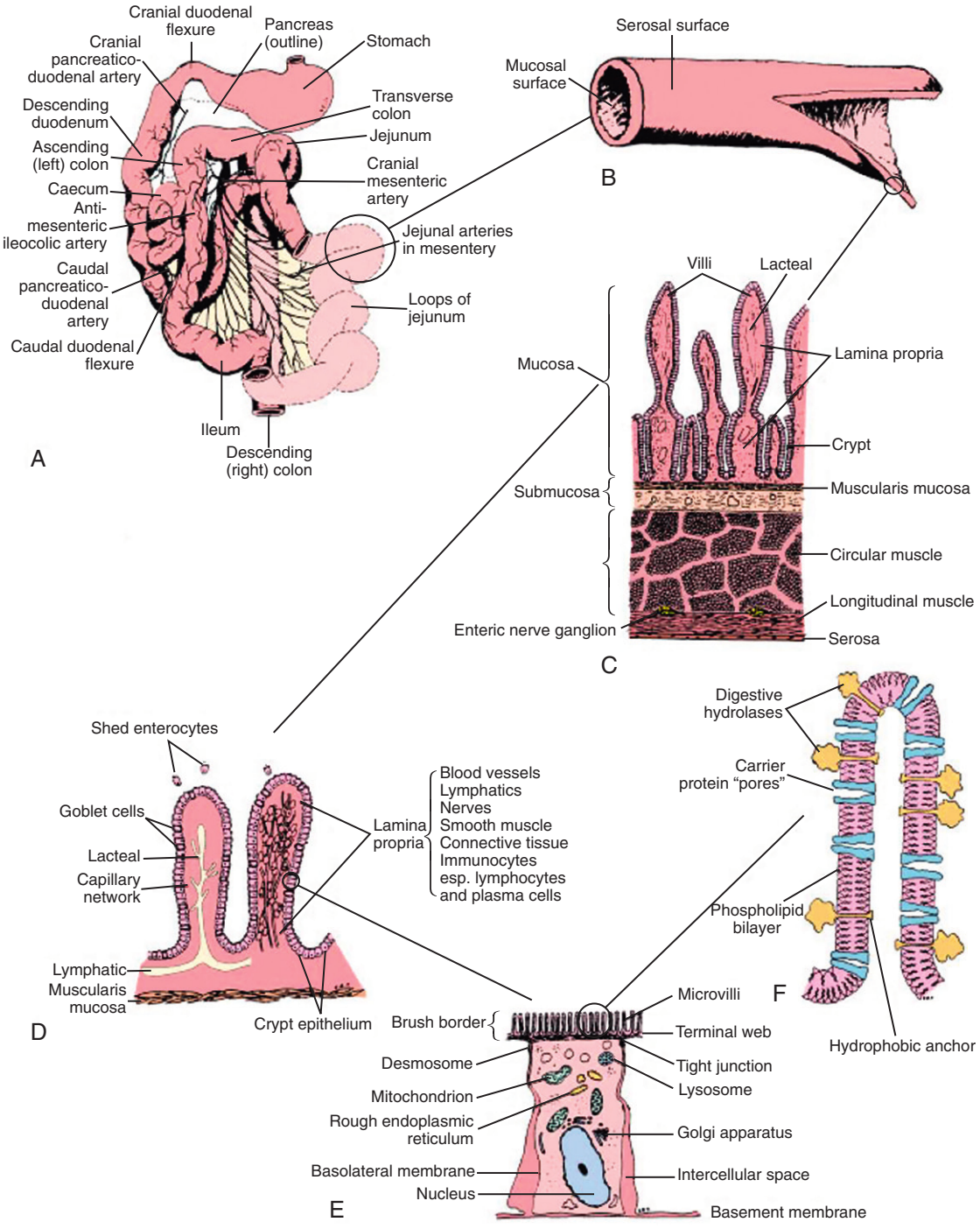

Figure 57-1 Functional anatomy of the small intestine. A, Anatomic arrangement of the small intestine. **B,** The small intestine is basically a tube with a serosal surface covered by visceral peritoneum and an inner absorptive and digestive surface, the mucosa. **C,** Beneath the outer serosa, longitudinal and circular muscle layers produce peristaltic and segmental contractions for propelling and mixing the luminal contents. The submucosa is rich in blood and lymphatic vessels. The mucosa comprises the thin muscularis mucosa, the lamina propria, and the columnar epithelium; it is thrown into folds and is covered by finger-like villi to increase the digestive and absorptive surface area. **D,** Enterocytes, which are shed from the villus tip but are continually replaced through division of crypt cells, are the site of nutrient digestion and absorption. Goblet cells secrete protective mucus. Water-soluble nutrients pass into the rich capillary network of the lamina propria, and fat is passed as chylomicrons into the lacteals. Immunocytes in the lamina propria are involved in maintaining tolerance to luminal antigens. **E,** The luminal membrane of the enterocyte is thrown into processes called *microvilli*, which increase the luminal surface area. Tight junctions between enterocytes maintain epithelial integrity. Absorbed nutrients are passed from the enterocyte into the intercellular space for distribution to the body. **F,** Schematic of a microvillus showing digestive hydrolases anchored in the phospholipid cell membrane and protruding into the intestinal lumen. Carrier proteins in the membrane are believed to act as "pores," shuttling nutrients across the membrane by means of conformational changes in their structure often induced by sodium influx at the expense of energy utilization through Na/K-adenosine triphosphatase (ATPase) on the basolateral membrane. (From Hall EJ: Small intestinal disease. In: Gorman NT, editor: *Canine Medicine and Therapeutics*, ed 4, Oxford, UK, 1998, Blackwell Science, p 488.)

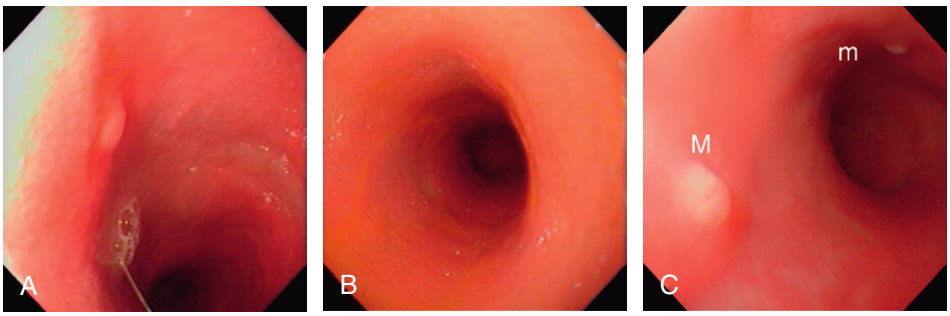

Figure 57-2 **Videoendoscopic appearance of the normal upper small intestine. A,** The major duodenal papilla (M) in the duodenum of the dog is the site of entry of the common bile duct and major pancreatic duct. The minor duodenal papilla (*m*) is seen in some but not all dogs distal to the major papilla and approximately 100 degrees clockwise from it. **B,** Normal descending duodenum in a dog; the distal flexure is visible in the distance. **C,** Peyer patches (lymphoid aggregates) in the duodenum appear as pale oval depressions along the antimesenteric border of the descending duodenum. (Reprinted with permission from Lhermette P, Sobel D: *BSAVA Manual of Canine and Feline Endoscopy and Endosurgery*. Gloucester, UK, 2008, BSAVA Publications.)

intussusception, and volvulus, is not reported in dogs and cats. The ileum ends at the ileocolic valve in close association with the cecocolic junction.

Blood Supply, Lymphatic Drainage, and Innervation

The blood supply to the proximal duodenum is from the celiac artery. Its cranio-pancreatico-duodenal branch anastomoses with the caudo-pancreatico-duodenal branch of the cranial mesenteric artery. The latter is the major blood supply to the remainder of the SI and proximal colon, anastomosing distally with the caudal mesenteric artery. It forms an arcade along the mesenteric border of the jejunum and ileum, with a short antimesenteric ileal branch. Its branching nature is an important consideration when assessing the viability of lengths of SI during surgical resection and end-to-end anastomosis.

The venous drainage of the whole SI is ultimately to the liver via the hepatic portal vein. Multiple embryonic vessels linking portal venous drainage and the systemic venous system (i.e., via ovarian veins, caudal vena cava, and esophageal veins) exist but only become functional shunting vessels if there is chronic portal hypertension as a consequence of liver disease.

Lacteals in the villi drain via intestinal lymphatics in the mesentery to the mesenteric lymph nodes and then the cisterna chyli and on to the thoracic duct. Vagal and sympathetic innervation coordinate with the intrinsic enteric nervous system and enteric hormones to regulate SI motility and function.

Intestinal Compartments

Microflora

The microflora of the SI is an integral part of its structure and function. There is a gradual increase in bacterial numbers and a shift from aerobic to anaerobic organisms progressing distally down the SI. Chapter 2 provides a more detailed description of the composition of the microflora and its interaction with the mucosa.

Mucosa

The SI mucosa performs the intestinal barrier and absorptive functions, and is comprised of an intestinal epithelium covering the lamina propria that hosts the local mucosal immune system, and is surrounded by the submucosa and the outer muscle layers.

One of the most important structural modifications of the mucosa is a vast increase in its surface area relative to the size of the animal, with an almost 600-fold increase compared with the basic tubular structure of the intestine. The surface area of the human intestine has been estimated at 175 m^2, and although the adult human intestine is longer than in even the largest dog, the villi in cats and dogs are almost twice as long (approximately 1 mm) compared with those of humans. The increase in surface area is created by folds in the mucosal wall (tripling the surface area), villus projections into the intestinal lumen (providing an approximate 10-fold increase), and microvilli on the surface of each epithelial cell (providing a further 20-fold increase in area) (see Figure 57-1, C). Diseases causing villus atrophy or even just microvillus damage are likely to produce profound malabsorption and diarrhea.

Gut-Associated Lymphoid Tissue

The GI tract is the largest immunologic organ in the body, and the SI comprises a large component of the mucosal immune system. Within the SI, the Peyer patches (see Figure 57-2, C) act as inductive sites and are covered with a specialized epithelium containing microfold (M) cells, which sample luminal antigens. Activated lymphocytes migrate via mesenteric lymph nodes to the circulation, from where they home to their effector sites, the lamina propria and epithelium. Chapter 3 details the structure and role of the gut-associated lymphoid tissue.

Microstructure

An identical, basic, tubular, cross-sectional structure is present throughout the length of the SI (see Figure 57-1, C): the external serosa surrounds the muscularis, submucosal and mucosal layers which are present throughout, and can be detected ultrasonographically (Figure 57-3).[4-10] A very narrow hyperechoic interface between the lumen and mucosal surface is usually visible above the four true layers: (a) a slightly hypoechoic mucosa, (b) hyperechoic submucosa, (c) hypoechoic muscularis, and (d) brightly hyperechoic serosa.

Regional variations in the relative proportions of each layer reflect differences in the functions of the proximal, middle, and distal regions. The mucosa is thickest in the duodenum (normal dog ≤6 mm) and thinnest in the ileum (normal dog ≤4.7 mm). Variations in the microstructure also occur with species and age and within individual animals depending on their dietary intake, as well as disease. Submucosal Brunner glands are found in the human duodenum but not in dogs and cats. Loss of normal ultrasonographic layering is suggestive of neoplastic infiltration, and echogenic mucosal striations may indicate lymphatic dilation.

The mucosal layer is responsible for secretion and absorption as well as being a barrier to the luminal environment. The submucosa, between the muscularis mucosa and muscularis, provides

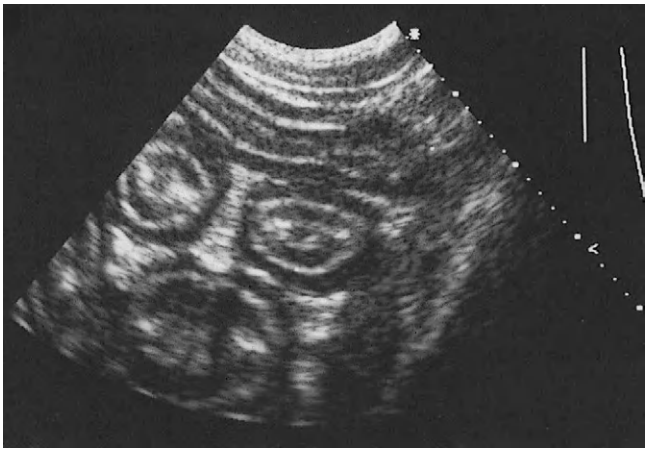

Figure 57-3 Ultrasound Image of the Small Intestine. Abdominal ultrasound image showing transverse image of three loops of bowel in a dog, with normal layering of the small intestinal wall. (From Ettinger SJ and Feldman EC, editors: *Textbook of Veterinary Internal Medicine*, ed 7, Philadelphia. 2010, Saunders, p 1541.)

connective tissue support and delivers blood vessels, nerves, and lymphatics. Within the muscularis, the outer longitudinal and inner circular muscular layers provide propulsive and segmental peristaltic contractions that mix chyme and ultimately propel it aborally. Neural plexuses are found between the muscle layers (the myenteric or Auerbach plexus) and in the submucosa (Meissner plexus), and communicate with all layers of the intestinal wall. They help coordinate intestinal motility and secretory activity, and even mucosal immune responses (see Chapters 1 and 3).

Mucosa

This is the most important layer of the intestine clinically. It is comprised of the epithelium and lamina propria overlying the muscularis mucosa, and is modified by gross folds and the villi (see Figure 57-1, C). The muscularis mucosa is a thin sheet of smooth muscle, from three to 10 cells thick, separating the mucosa from the submucosa. Smooth muscle branches within the villus lamina propria enable shortening and lengthening movements of the villi.

The lamina propria is a continuous connective tissue space bounded by the muscularis mucosa below and the epithelium above, and contains aggregates of lymphoid tissue, and nonaggregated immunocytes (see Chapter 3), enteric neurons, and blood and lymphatic vessels. A central lymphatic vessel (lacteal) within each villus drains chylomicrons into intestinal lymphatics and ultimately to the cisterna chyli.

Blood flow to a villus is provided by an arteriole that passes to the tip of the villus where it arborizes and forms a subepithelial capillary network that drains into veins. Crypts are supplied by separate arterioles and blood flow in the two regions can be controlled independently. Mucosal capillaries are fenestrated, and in conjunction with the lacteal, carry away protein-rich tissue fluid. Loss of epithelial integrity permits leakage of the protein-rich fluid and the development of a protein-losing enteropathy (PLE).

Crypt-Villus Unit

A group of crypts and their associated villus comprise the functional unit of the SI (see Figure 57-1, D).[11] Crypts are continually replenished by cell division, producing undifferentiated epithelial cells. It is estimated that there are between four and 40 stem cells per crypt in the adult intestine, with further division of daughter cells occurring as the cells pass up the crypt. As the crypt cells pass through a maturation zone they undergo a final division and differentiate into immature epithelial cells. The predominant epithelial cell type is the enterocyte, but as a number of crypts may supply the enterocytes to one villus, each villus epithelium may consequently represent a polyclonal cell population.

Box 57-1 Components of the Intestinal Mucosal Barrier

Protein denaturation by gastric acid
Protein degradation by proteolytic enzymes and bacteria
Clearance of waste by peristalsis
Unstirred water layer
Surface mucus layer
Secretory immunoglobulin A
Enterocyte microvillus membrane
Epithelial tight junctions
Mucosa-associated lymphoid tissue

Mucosal Epithelium

The intestinal surface is covered by a monolayer of polarized epithelial cells; their luminal surface is structurally and functionally distinct from their basolateral membrane.[12-18] The epithelial basement membrane is readily permeable to nutrients, but has an important role as the structural matrix on which the epithelium grows. It expresses glycoproteins, called laminins, that interact with integrins, transmembrane recognition molecules expressed by epithelial cells. These interactions promote cell adhesion, growth, polarization, and differentiation. Enterocyte differentiation during migration up the villus may be programmed, but is likely also to be modulated by the expression of different integrins at different sites on the crypt–villus axis. Communication between epithelial cells is mediated by E-cadherin, a transmembrane molecule, linked to intracellular catenins, proteins that transmit signals to the actin cytoskeleton and to intracellular growth control pathways.

A mucosal barrier is formed by the intestinal epithelium (Box 57-1). This barrier depends on intercellular tight junctions between enterocytes, encircling their lateral aspects and excluding antigens and bacteria. Effete enterocytes are shed from the villus tip by a mechanism that maintains the mucosal barrier (see Figure 57-1, D). Studies in rodents suggest intercellular bridges develop between neighboring enterocytes below the effete cell before it is shed, thus maintaining mucosal integrity. However, epithelial integrity is likely to be altered in some intestinal diseases, and the integrity of the tight junctions is actually least in the crypts, where fluid secretion occurs. There is an association of cryptal lesions with the development of PLEs.

Crypt cells have a potent secretory capacity and the crypts are the site of most mucosal fluid secretion. As enterocytes migrate to the villus tip, maturation involves loss of secretory activity and the expression of digestive and absorptive molecules in the apical (luminal) cell membrane. Some enterocytes undergo stochastic (random) cell death, but the majority undergoes apoptosis via a caspase-dependent process, and exfoliates at the tips of the villi. The duration of migration from crypt to villus tip is believed to be 3 to 5 days in dogs and cats. More rapid transit may occur in diseases where cells are lost and compensatory crypt activity occurs, but the new enterocytes tend to be functionally immature.

Enterocytes predominate in the epithelium, representing approximately 80% of all cells, with interspersed mucus-secreting goblet

cells. Goblet cell density in the SI mucosa varies, being highest in the ileum. These cells secrete protective mucus and some novel clover leaf–shaped peptides (trefoil peptides) that act as growth factors. Paneth cells, a population of cells found in some species below the proliferation zone in crypts and that secrete antibacterial peptides, are not recognized in dogs or cats. Endocrine- and paracrine-secreting cells (*synonyms:* enteroendocrine, enterochromaffin, argentaffin, argyrophil cells) are also present in the mucosal surface layer, and have important trophic and functional activities.

In addition to locally produced growth factors, a variety of luminal and humoral factors act as physiologically active growth regulators. Receptors for epidermal growth factor (EGF) are found on the luminal and basolateral surfaces of enterocytes, suggesting that they may respond to bloodborne EGF and to EGF secreted into the lumen by salivary and pancreatic tissue or delivered in milk. Transforming growth factor (TGF)-α, a polypeptide related to EGF and expressed throughout the mucosa, has growth regulatory properties. However, EGF and TGF-α are also probably important in repair of damaged epithelium as they stimulate repair without fibroblast activity, unlike TGF-β, which inhibits epithelialization and stimulates fibroplasia, and is important in deeper wound repair.

In the Peyer patches, enterocytes overlying lymphoid aggregates are modified into follicle epithelium and M cells, probably in response to signals from underlying lymphoid cells. The M cells sample the luminal contents and help present antigen to the mucosal immune system (see Chapter 3).

Enterocytes

Enterocytes contain the intracellular organelles, such as mitochondria, lysosomes, and endoplasmic reticulum, common to all cells, and which support normal cellular functions. However, enterocytes also perform specific digestive and absorptive functions.[19,20] Enzymes expressed on the surface of enterocytes perform terminal digestion of polysaccharides and peptides in conjunction with luminal hydrolysis of food polymers by pancreatic enzymes. The enterocytes then absorb the simple nutrients. These functions depend on the polarity of the enterocyte, involving a specialized portion of the cell membrane on the luminal surface, the microvillar membrane (MVM). The microscopic appearance of the MVM is the basis of its alternative name, the "brush-border" (see Figure 57-1, *E* and *F*). It consists of thousands of parallel cylindrical processes (microvilli) bearing the digestive enzymes and specific carrier proteins.

The MVM is a phospholipid bilayer that has specific proteins inserted into it. Enzymes responsible for the terminal stages of carbohydrate and protein digestion are usually anchored in the MVM by a small hydrophobic terminal and have an active site exposed to the intestinal lumen (see Figure 57-1, *F*). Specific carrier proteins traverse the MVM or basolateral membrane and, through conformational changes, shuttle nutrients into and out of the enterocyte across the cell membrane. The maximal brush-border enzyme and transport activities are expressed in the mid-villus region. Diseases damaging enterocytes often accelerate cell production and the more immature enterocytes are not as effective functionally.

Brush-border enzyme activities are highest in the proximal SI and decline in an aborad gradient. Digestive enzymes, especially disaccharidases and transport proteins, may be inducible in response to changes in the composition of the diet. This has been shown in dogs but not in cats, perhaps reflecting the obligate carnivore status of cats. Indeed dogs, which are omnivorous, show increased sucrase and maltase in response to increased dietary carbohydrate and, conversely, when fed a cereal-free diet develop reduced activities of brush-border sucrase and maltase but not lactase. Thus a sudden change in diet in dogs may cause diarrhea through transient intolerance until either existing enterocytes upregulate expression of specific enzymes and carriers, or new enterocytes expressing induced proteins differentiate, thus rendering the diarrhea self-limiting.

Enterocyte metabolism is geared toward the production of brush-border proteins and the transfer of nutrients and water from the lumen to the blood. Basolateral cell membranes export sodium from the cell via an energy-dependent N^+-K^+-ATPase. Water can follow osmotically, or compensatory sodium influx at the luminal surface can drive carrier-mediated nutrient absorption. Natural inhibition of glycolysis through expression of an alternate phosphofructokinase isoenzyme in enterocytes facilitates the transfer of glucose from the lumen to the blood. Gluconeogenesis is also inhibited, and so enterocytes can utilize ketone bodies. However their major energy source is actually glutamine (Figure 57-4). A surge in enterocyte glutamine metabolism during digestion is probably partly responsible for the postprandial rise in blood ammonia seen in some patients with hepatic dysfunction.

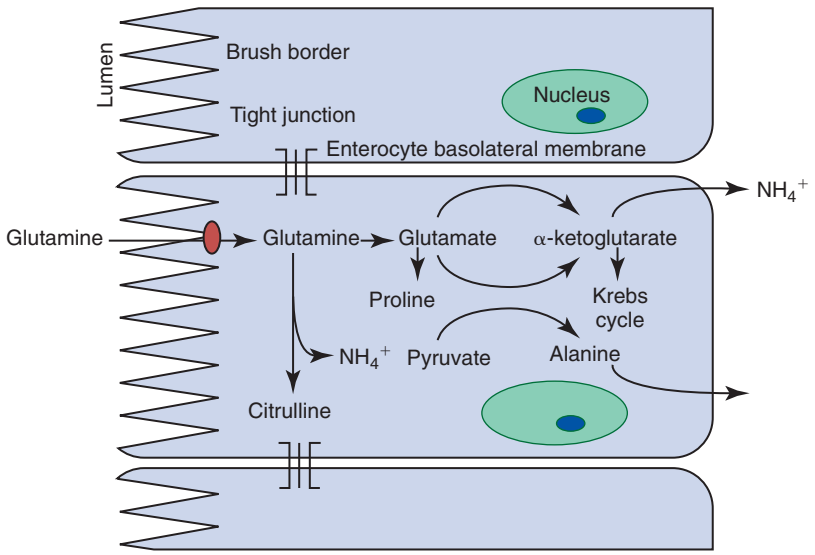

Figure 57-4 Metabolism of glutamine by enterocytes, and one potential mechanism for postprandial increases in endogenous ammonia.

Both major nutrients for enterocytes (glutamine and ketone bodies) are largely derived from the lumen, which helps explain the decline in villus structure, epithelial integrity, immune function, and absorptive function in starvation and anorexia. Consequently, attempting to maintain enteral nutrition, often by using glutamine-containing products, may be of clinical benefit.

Digestive and carrier proteins are synthesized by enterocytes and inserted in the MVM. This mechanism has been demonstrated for the synthesis of the enzyme complex of sucrase–isomaltase in pigs, but a similar process is likely to occur for this and other enzymes in dogs and cats. The sucrase–isomaltase complex is synthesized as a single polypeptide by ribosomal translation of its messenger RNA (mRNA). A terminal signal peptide extension that is ultimately cleaved, directs the intracellular trafficking of the protein from the ribosome to the endoplasmic reticulum and Golgi apparatus, where glycosylation of the protein backbone occurs. The glycosylated polypeptide is directed to the brush-border where it is inserted. It then "flips" across the apical membrane so that the active sites are on the luminal surface, and the polypeptide is anchored in the membrane by an N-terminal hydrophobic chain. The parts of the exteriorized polypeptide containing the sucrase and isomaltase activity are cleaved by pancreatic proteases but remain in close association, and form a dimer with another sucrose–isomaltase molecule.

As enterocytes migrate to the villus tip, enzymes are cleaved from the brush-border by bacterial and pancreatic proteases and are released into the lumen where they comprise solubilized enzyme activities, commonly called *digestive juice*. However, this liquid, the succus entericus, is not a true intestinal secretion.

Submucosa

Beneath the muscularis mucosa, the submucosa contains a heterogeneous population of cells: lymphocytes, plasma cells, macrophages, eosinophils, fibroblasts, and mast cells within a connective tissue matrix. An intricate network of blood vessels, nerve fibers, ganglia and interstitial cells of Cajal (Meissner plexus), and lymphatics supply the mucosa and muscularis.

Muscularis

Two muscle layers, the outer longitudinal and inner circular layers, encircle the submucosa. The intermuscular plane is a connective tissue layer bearing the myenteric (Auerbach) neural plexus. Ring contractions by the circular muscle and sleeve contractions by the longitudinal muscle may be tonic or rhythmic, and intestinal movements may be standing or migrating, allowing mixing and propulsion. Contraction of the muscle layers is coordinated by the enteric nervous system to produce peristaltic and segmental movements, with interstitial cells of Cajal acting as pacemakers. Chapter 1 details how intestinal motility is integrated with other functions of the SI.

Serosa

This is a single layer of mesothelial cells surrounding the intestine, and forms the visceral peritoneum.

Small Intestinal Function

The basic functions of the SI, that is digestion, absorption, and elimination, occur as a result of complex intercellular interactions between epithelial cells, immune cells, mesenchymal and neuronal cells and with luminal nutrients and microbes.[21] The SI is also the largest immunologic organ in the body, interacting with the intestinal microbial flora and a diverse range of food antigens (see Chapters 2 and 3, respectively).

Digestion

To be transported across the MVM, major dietary constituents must be hydrolyzed from their initial polymeric structure into monomers. This digestive process is achieved within the SI lumen by mechanical disruption (in conjunction with bile salt emulsification of fats) that allows enzymatic hydrolysis of polysaccharides, proteins, and triglycerides.[22]

The SI provides the optimum environment in terms of solute, temperature, pH, and mixing for the actions of bile salts and digestive enzymes, but most enzymes are secreted by the pancreas, and exocrine pancreatic insufficiency (EPI) is a major cause of malabsorption. The brush-border peptidase enterokinase (enteropeptidase) is important in the initial activation of pancreatic trypsin from trypsinogen by cleaving a terminal octapeptide, trypsinogen activation peptide, from the native protein.

Only terminal digestion of oligomers need normally be performed by brush-border enzymes. However, brush-border activities can partially compensate for the lack of secreted proteases and amylase in EPI, with at least 40% of dietary protein still being hydrolyzed, although severe fat maldigestion persists. Even with significant diffuse SI mucosal disease there is usually sufficient reserve capacity to enable adequate digestion of starch. However, early estimates of a 10-fold reserve capacity of digestive and absorptive activity have been refuted. The "reserve capacity" that is called into action after intestinal resection probably represents not only increases of brush-border protein expression, but also compensatory hypertrophy of the remaining tissue, as it is known to take months to reach maximal effect (see "Short Bowel Syndrome" section). Capacity appears to be regulated according to physiologic demand, and probably does not normally exceed twofold, but it is relevant that it can be modified in response to dietary change.

Carbohydrate

Starch and glycogen are the major carbohydrates in the diet and must be hydrolyzed completely to glucose for absorption (Figure 57-5, *A*). There is no salivary amylase activity in dogs and cats, and these complex carbohydrates are hydrolyzed by pancreatic α-amylase. Straight-chain starch molecules (amylose) are split to maltose, maltotriose, and some glucose. Branched-chain starch molecules (amylopectin) and glycogen are also hydrolyzed to the same products, except that the branched parts of their molecules remain as α-limit dextrins as their 1,6-glycosidic bond cannot be hydrolyzed by α-amylase. The digestion products of α-amylase are subsequently hydrolyzed, particularly by brush-border maltase (glucoamylase) and isomaltase (α-dextrinase). The brush-border enzyme trehalase hydrolyzes the 1,1 link in the fungal sugar trehalose, but is not expressed in cats.

Sucrose is an unusual constituent of canine and feline diets unless semimoist pet foods or human foods are fed. It is hydrolyzed directly at the brush-border to glucose by sucrase, part of the sucrase–isomaltase brush-border enzyme complex. Congenital sucrase–isomaltase deficiency is a rare genetic defect of man, but has not been recorded in small animals. Sucrase activity in cats is lower than dogs (Table 57-1), probably reflecting the average composition of their diets.

Lactose is found almost exclusively in dairy products and its hydrolysis to glucose and galactose by brush-border lactase is nutritionally most important in the nursing animal. At weaning, activities of lactase begin to decline, especially in cats, and adult animals may exhibit lactose intolerance if fed excess milk. This mirrors the age-related downregulation of lactase expression seen in certain human races. If animals have underlying SI disease, dairy products

should be avoided as marginal lactase activities will be reduced even further. Absolute congenital lactase deficiency, as seen rarely in humans, has not been demonstrated in cats or dogs.

Protein

Digestion of proteins follows a similar overall pattern to carbohydrate digestion (see Figure 57-5, *B*), and the amounts of pancreatic enzyme secreted and mucosal peptidases expressed are influenced by the protein content of the diet. Digestion is initiated by acidic denaturation and the proteolytic activity of pepsin in the stomach. Luminal digestion under a more neutral pH is continued in the SI by pancreatic proteases (trypsin, chymotrypsin, elastase, and carboxypeptidase), which are initially secreted as inactive proforms, and are subsequently activated by enterokinase and trypsin. Luminal proteolysis results in a mixture of oligo-, tri-, and dipeptides as well as free amino acids. Oligopeptides are subsequently hydrolyzed by brush-border peptidases, which have some selectivity for particular amino acid residues. However, there is considerable overlap in specificity, and a selective deficiency of aminopeptidase N reported in dogs is of no clinical consequence. Furthermore, any tri- and dipeptides can still be absorbed on a brush-border carrier. Theoretically a deficiency of enterokinase could cause protein malabsorption through failure of trypsin activation, but this has never been documented in dogs and cats, and trypsin autoactivation would probably still occur.

Table 57-1 Jejunal Brush-Border Disaccharidase Activities (U/mg Protein) Reported in Dogs and Cats

Reference	Sucrase	Maltase	Lactase
Cats			
Hore, Messer 1968[37]	2.8	20	0.6 to 1.2 (U/mg wet weight)
Kienzle 1993[38]	17 ± 23	102 ± 58	7 ± 8
Dogs			
Hore, Messer 1968[37]	0.87	4.2	0.33 (U/mg wet weight)
Levanti et al. 1978[39]	~80	~400	~30
Noon et al. 1977[40]	57 ± 2	240 ± 13	26 ± 1
Kienzle 1988[41]			33
Batt et al. 1984[42]	67 ± 5	329 ± 25	33.5 ± 4
Hall, Batt 1990[43]			
normal diet	78 ± 7	398 ± 26	23 ± 1
cereal-free diet	50 ± 8	252 ± 32	20 ± 2

Lipid

Fat digestion is completed entirely within the GI lumen by secreted enzymes and bile salts. Partial digestion is begun in the stomach by the action of gastric lipase secreted by gastric epithelial mucus cells. Subsequent mixing of the fat emulsifies it into small droplets. Further mixing with bile and pancreatic juice results in the formation of mixed micelles, which are approximately $1/100$ the size of the smallest fat droplet and solubilize approximately 1000 times more fatty acids. At the surface of mixed micelles, triglyceride is hydrolyzed by pancreatic lipase to di- and monoglycerides and free fatty acids (Figure 57-6). Maximal lipase activity in the gut lumen is dependent on a protein cofactor, colipase, which is secreted by the pancreas as inactive procolipase. There is some reserve capacity for fat digestion if pancreatic function is normal, and a fat-rich diet, especially one rich in unsaturated fatty acids, also stimulates increased pancreatic lipase secretion. However, neuroendocrine mechanisms initiated by the presence of fat in the duodenum and ileum, control the rate of gastric emptying and hence the rate of fat delivery. Thus a fat-rich diet or intestinal fat malabsorption delays gastric emptying.

Pancreatic phospholipase A_2 is secreted in an inactive form, and once activated in the intestinal lumen hydrolyzes phospholipid to lysophospholipids. Finally, pancreatic cholesterol esterase deesterifies cholesterol. After fat absorption, the bile salts may form further mixed micelles, but ultimately are reabsorbed by a specific

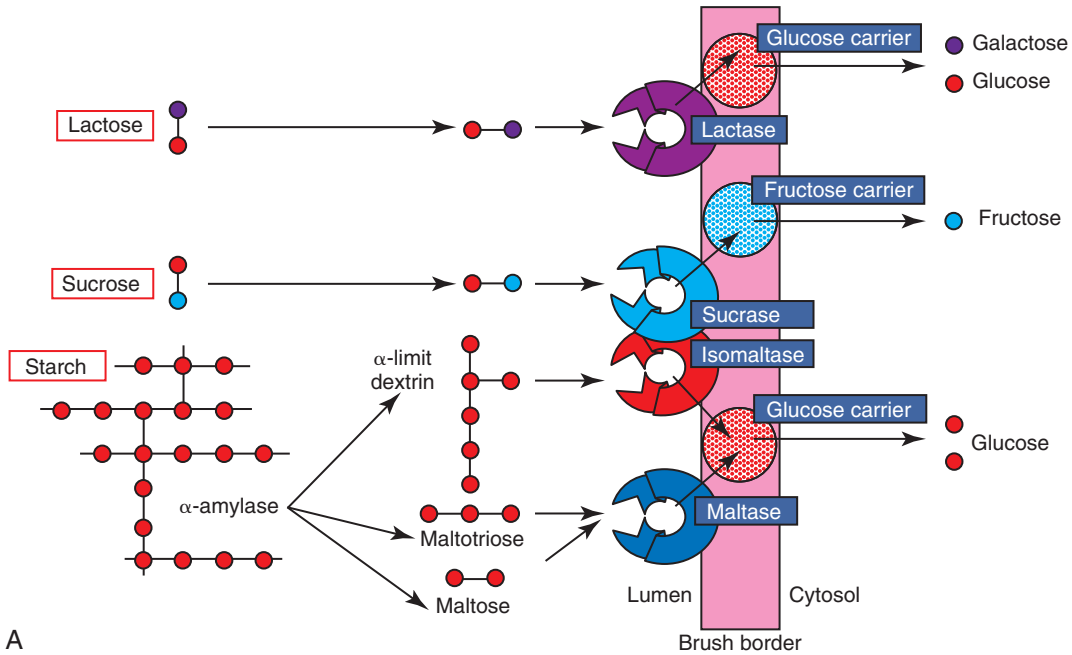

Figure 57-5 Diagram of the digestion and absorption of (**A**) carbohydrate, (**B**) protein, and (**C**) fat. (Adapted from Batt RM: The molecular basis of malabsorption. *J Small Anim Pract* 21:555, 1980.)

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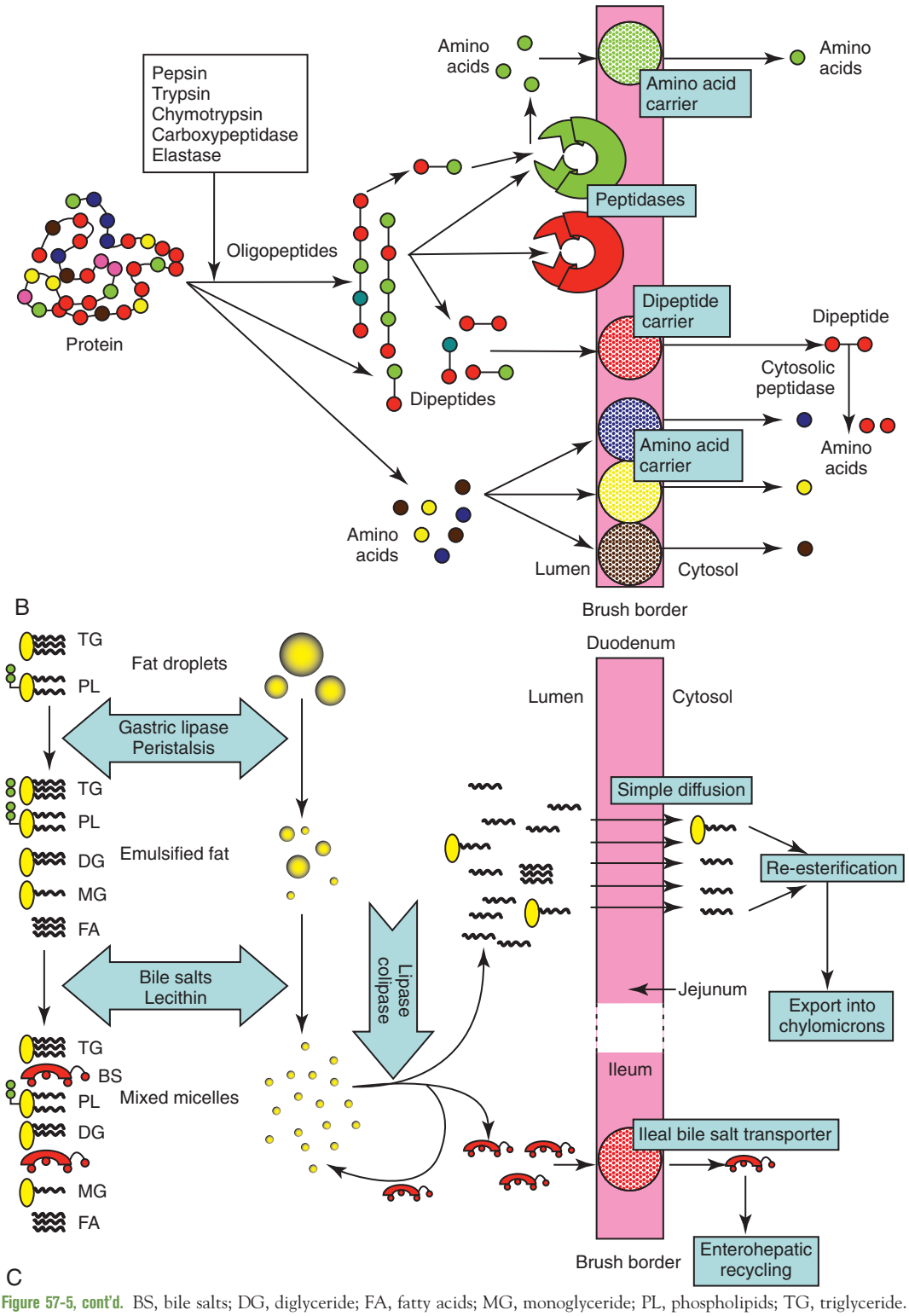

Figure 57-5, cont'd. BS, bile salts; DG, diglyceride; FA, fatty acids; MG, monoglyceride; PL, phospholipids; TG, triglyceride.

sodium-linked cotransporter in the ileum and recycled from the portal blood back into bile.

Nucleotides

Little is known of the digestion of dietary nucleotides and hydrolysis of nucleic acids released from exfoliated enterocytes. Ribonuclease and deoxyribonuclease are present in pancreatic secretions, and there is a common sodium-dependent brush-border carrier for the uptake of purines and pyrimidines.

Absorption

Digested Nutrients

Simple sugars, amino acids and oligopeptides, and fatty acids and other lipids are delivered to the body across the mucosal barrier and

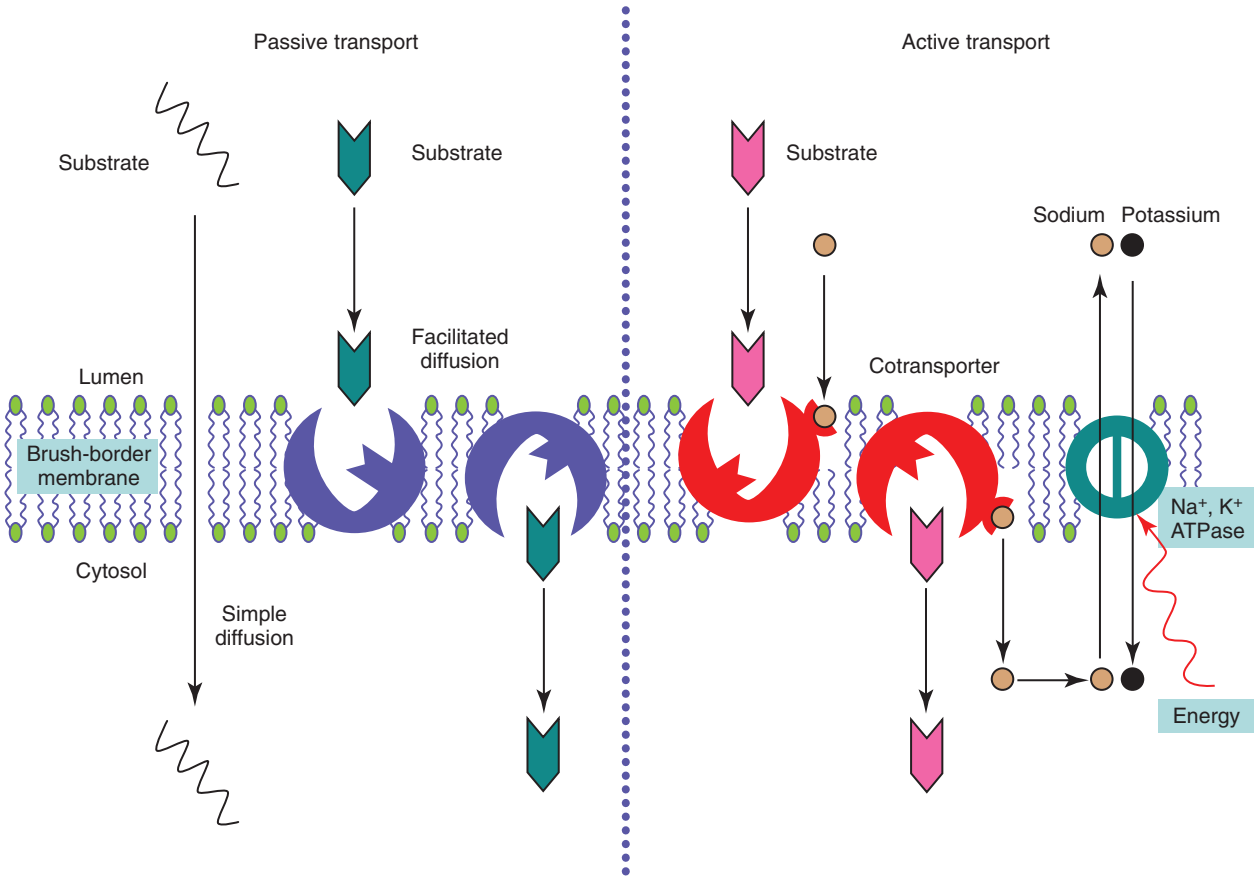

Figure 57-6 Mechanisms of diffusion.

then via the lymphatics or bloodstream.[23,24] Uptake occurs by passive diffusion or by active or facilitated carrier-mediated transport mechanisms (see Figure 57-6). Endocytosis of small, antigenic peptides is of no nutritional significance, but is involved in the neonatal absorption of colostral antibodies, and is crucial to the mucosal immune response.

The products of fat digestion are absorbed by passive diffusion from mixed micelles across the MVM and ultimately lipoproteins are passed into lacteals. The limiting factors, assuming normal pancreatic function, are the intestinal surface area and lymphatic functionality, and so villus atrophy and lymphangiectasia are likely to cause malabsorption of fat.

Mechanisms of Absorption

Passive Diffusion

Lipid-soluble products of digestion do not need a specific carrier mechanism to be absorbed across the mucosal barrier, and can bypass passive diffusion by "dissolving" in the brush-border membrane. This absorptive process obeys the Graham Law of Diffusion, being proportional to the concentration gradient across the membrane, nonsaturable, and limited only by the surface area of the membrane. Diffusion back across the brush-border is prevented by reesterification of free fatty acids within the enterocyte.

Carrier-Mediated Transport

Some small, nonpolar, water-soluble molecules (and perhaps water molecules) also appear to be absorbed by passive diffusion through "pores" in the mucosal membrane. The structure of these hypothetical pores is likened to that of ion channels in other membranes (i.e., small fixed channels through the membrane that function without a conformational change). Molecules with a molecular radius greater than 0.4 nm appear to be excluded, but larger, although numerically fewer pores may traverse tight junctions. Debate remains as to whether the predominant route is via an intracellular or paracellular route through tight junctions.

Water-soluble nutrient molecules that are too large to diffuse via the "pore route" and are insoluble in the lipid MVM must cross the brush-border on specific carrier proteins that bridge the membrane. Conformational changes in the carriers are thought to shuttle the substrate molecule across. The products of carbohydrate and protein digestion enter by this process. Transport proteins are usually highly specific and may only carry the L or D isomer of a molecule, but competitive inhibition with related solutes may occur. The number of carrier molecules in the mucosa is finite, so that the process is saturable, and although the expression of the carriers may be inducible, dietary overload is likely to cause transient intolerance and diarrhea.

Active transport of substrates across the MVM into the enterocyte is usually against a concentration gradient and energy must be expended to drive the process (see Figure 57-6). Usually the uptake of the nutrient is linked to the entry of sodium down its electrochemical gradient, with energy expenditure by a N^+-K^+-ATPase on the basolateral membrane of the enterocyte pumping sodium back out of the cell.

Facilitated transport is the carriage of substrates by a transport protein across the MVM, down a concentration gradient without energy expenditure (see Figure 57-6). Some sugars, oligopeptides,

and folate are absorbed by this process. The number of carriers is finite, and the process saturable and subject to competitive inhibition.

Endocytosis

Small antigenic peptides may be engulfed nonspecifically within endocytotic vesicles of epithelial cells. The amounts absorbed by this route are negligible from a nutritional standpoint, but this sampling of luminal contents is crucial to the mucosal immune response (see Chapter 3). Receptor-mediated endocytosis enables the uptake of small amounts of a specific intact nutrient and is the mechanism of cobalamin absorption.

Nutrient Absorption

Carbohydrate

The main product of carbohydrate digestion, glucose, is absorbed by active transport on a stereo-specific carrier that recognizes a D-pyranose structure with a C-2 hydroxyl group. Glucose is cotransported with sodium; the energy required for the coupling is provided through the entry of sodium down a concentration gradient but with the basolateral N^+-K^+-ATPase reexporting sodium against the concentration gradient. The carrier molecule in the brush-border has been identified in many species, including dogs and cats, as the sodium-glucose cotransporter protein (SGLT1; Figure 57-7). This molecule has the highest affinity for glucose, but it is also the carrier for galactose. Indirect evidence for this is shown by the inability to absorb either sugar in people with glucose–galactose malabsorption in whom a single amino acid mutation ($Asp_{28} \rightarrow Asn_{28}$) in the SGLT1 protein has been identified. Glucose and galactose thus may exhibit competitive inhibition, but glucose is the major substrate. There is circumstantial evidence for another aldohexose carrier in cats.

Facilitated transport of glucose across mammalian cell membranes is performed by a family of facilitated glucose transporters (GLUTs) with different isoforms found in different tissues. One member of this family, GLUT2, is found on the basolateral membrane of enterocytes, where it shuttles glucose, galactose, and fructose out of the enterocyte by facilitated diffusion (see Figure 57-7). GLUT2 is absent from the brush-border, and so a mechanism exists for active transport of glucose across the MVM into the enterocyte by SGLT1 and facilitated transport into the body by GLUT2. Most of the glucose is not used within the enterocyte, because of expression of a phosphofructokinase isomer that directs metabolism away from glycolysis.

Another member of the facilitated glucose transporter family, GLUT5, is found on the brush-border. It shares homology with other family members but actually allows facilitated diffusion of fructose; it is not even competitively inhibited by glucose. In humans, GLUT5 is also probably the site of D-xylose absorption, as both fructose and xylose absorption are unaffected in glucose–galactose malabsorption. However, the mechanism of D-xylose uptake is species dependent, and evidence for facilitated diffusion in dogs and cats has largely been extrapolated from humans. Nevertheless, fructose uptake in cats is low, and D-xylose absorption is equally low. This may be one reason why the xylose absorption test is unhelpful in cats. However, potential fructose malabsorption has little clinical relevance in cats as the feline diet likely contains little fructose.

Although dietary carbohydrates must be hydrolyzed to monosaccharides to be absorbed and be nutritionally useful, a small but measurable amount of disaccharide can cross the brush-border, probably through leaky tight junctions. This is of no nutritional significance, but increased uptake and subsequent urinary excretion of disaccharides can be a marker of increased intestinal permeability when damaged.

Protein

The products of protein digestion are absorbed on carriers that are stereo-specific for L-amino acids (Figure 57-8; also see Figure 57-5, *B*).[25] Sodium-linked active transport is responsible for free amino acid uptake via one of four different carriers that have a variable degree of selectivity for neutral (Gly, Ala), acidic (Asp, Glu), basic (Arg, Lys), and imino (Pro, HO-Pro) amino acids. The cat has the highest rate of uptake of basic amino acids perhaps because it has an essential requirement for arginine.

Traditionally, peptide uptake has been considered to be facilitated diffusion, with the concentration gradient being maintained by intracellular peptide hydrolysis, and only free amino acids being exported from enterocytes into the portal blood (see Figure 57-8). A single carrier for di- and tripeptides with no selectivity for their amino acid content has been demonstrated. However, in people this

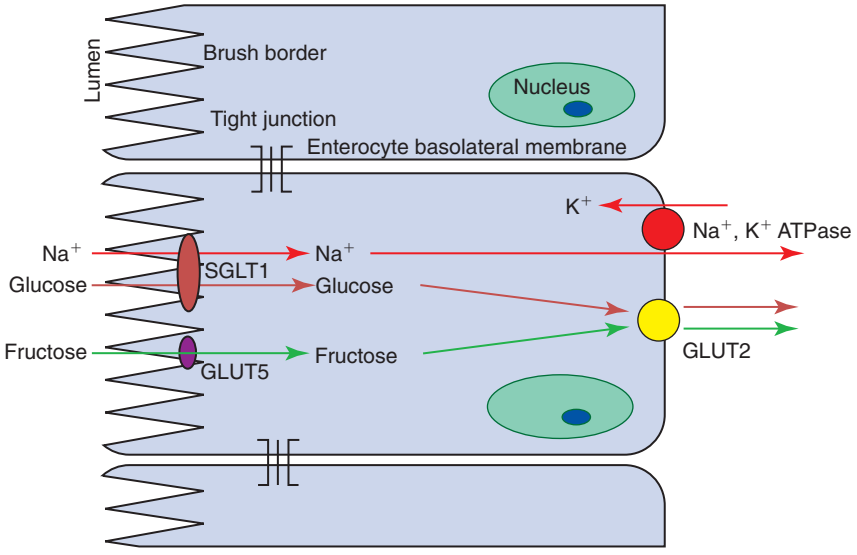

Figure 57-7 Diagram of the absorption of monosaccharides by enterocytes. GLUT, Glucose transporter; SGLT, sodium-glucose co-transporter protein.

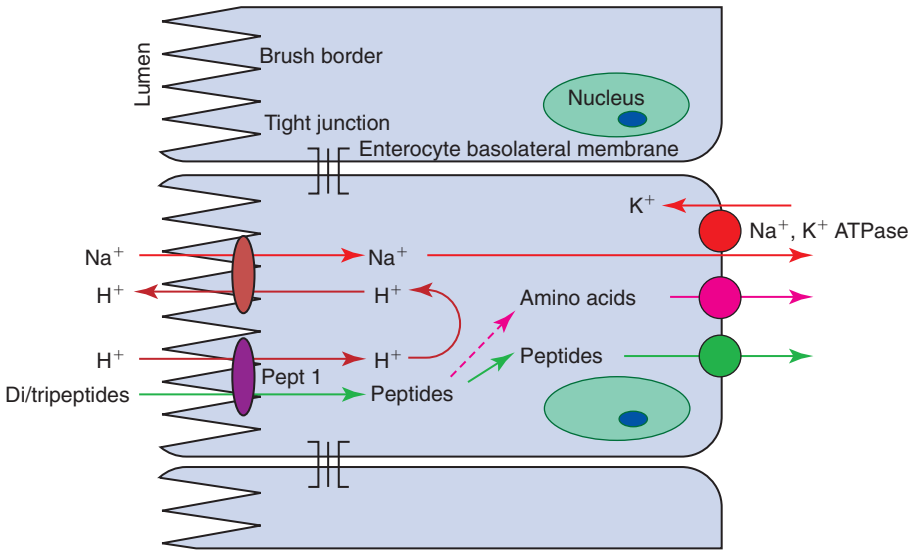

Figure 57-8 Diagram of the absorption of di- and tripeptides by enterocytes. Pept 1, a peptide carrier.

peptide carrier, Pept-1, is involved in the active influx of peptides, being linked to the influx of H^+ down an electrochemical gradient. The protons are exchanged across the MVM with sodium, which is pumped out by the basolateral N^+, K^+ ATPase. A mixture of peptides and free amino acids is exported to the blood, but it appears that peptides are absorbed more readily than free amino acids. This has clinical significance as the inclusion of dipeptides in elemental diets has a theoretical advantage over simple amino acid solutions. This transport protein is also the carrier for peptidomimetic drugs such as β-lactams and angiotensin-converting enzyme inhibitors.

Lipid

The products of fat digestion are absorbed by passive diffusion from mixed micelles into lacteals (see Figure 57-5, C). The limiting factors, assuming normal pancreatic function, are the intestinal surface area and lymphatic functionality, and so villus atrophy and lymphangiectasia are likely to cause malabsorption of fat.

Generally, the products of fat digestion are reassembled within enterocytes to prevent rediffusion back out of the enterocyte. They are combined with synthesized lipoproteins for passage into the lymphatics as chylomicrons. However, medium-chain triglycerides (length = 8-12 carbon atoms) can be absorbed directly into the portal blood, and provide an alternative route for fat uptake when lymphatic flow is impaired, as in lymphangiectasia. However, evidence exists that a proportion of medium-chain triglycerides are absorbed into the lacteals as they can be found within the thoracic duct.

Fat-Soluble Vitamins

Dietary fat-soluble vitamins A, D, E, and K are solubilized in mixed micelles before passive diffusion across the brush-border. Fat malabsorption associated with inadequate amounts of bile salts (e.g., bile duct obstruction), lymphangiectasia, or severe villus atrophy is also likely to result in vitamin deficiency. This is clinically most relevant for vitamin K as its body stores are not large and, particularly in cats, can lead to vitamin K–dependent coagulation factor deficiencies.

Vitamin A (retinol) is ingested either as a dimer (beta-carotene) or as an ester that must be hydrolyzed by pancreatic esterases. Beta-carotene is absorbed directly from micelles, but retinol is insoluble and must be anchored by a binding protein before absorption. Subnormal serum vitamin A concentrations have been observed in dogs with EPI but no associated signs of deficiency have been reported. However, vitamin A supplementation has been recommended following surgery in animals subsequently treated with corticosteroids to aid wound healing, and would be particularly relevant in animals that have had surgical intestinal biopsies.

Vitamin D is absorbed from mixed micelles. It is important for calcium homeostasis, controlling calcium absorption from the gut, as well as renal excretion. Vitamin D malabsorption may be (partly) responsible for the reductions in serum ionized calcium and magnesium that are reported in protein-losing enteropathies, which cannot be due to reduced protein binding because of hypoalbuminemia.

Vitamin E (α-tocopherol) is absorbed from mixed micelles by passive diffusion, and passes into the lymphatics unchanged. Vitamin E deficiency has been reported in Beagles with severe malabsorption, and is associated with EPI and bacterial overgrowth in German Shepherd dogs.

Vitamin K is derived from dietary sources (K_1) and synthesis by the enteric flora (K_2). Vitamin K_2 is probably absorbed in the ileum and colon. As well as bile salt deficiency, prolonged antibiotic usage may result in vitamin K deficiency.

Water-Soluble Vitamins

Water-soluble vitamins B and C are absorbed by a mixture of passive diffusion (e.g., pyridoxine [B_6] and C), saturable facilitated transport (e.g., riboflavin [B_2]), or active and facilitated transport (e.g., thiamine [B_1]) in other species, but the mechanisms in cats and dogs are uncertain. The absorptive mechanisms for folic acid and vitamin B_{12} are more complex and important clinically as they may be helpful in determining the site and nature of intestinal disease.

Folic acid is present in adequate amounts in most commercial foods, but is also produced by the enteric flora. It is usually conjugated in a poorly absorbable polyglutamate form and must be hydrolyzed by folate deconjugase, a brush-border enzyme, before absorption. Folate (pteroyl monoglutamate) is absorbed by a carrier-mediated process at low luminal concentrations and by passive diffusion at high concentrations (Figure 57-9). After absorption folate is methylated in the cell to form methyltetrahydrofolate.

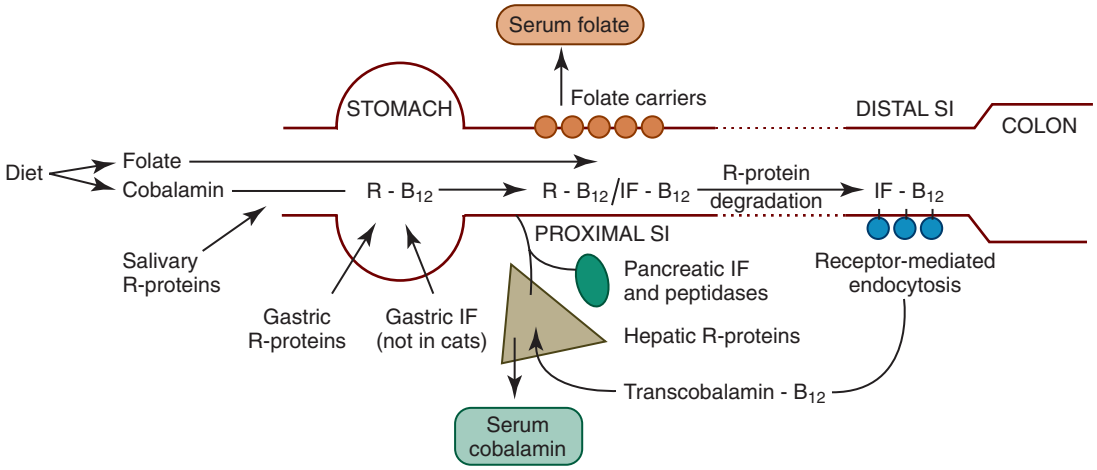

Figure 57-9 Diagram of the absorption of folate and cobalamin. Folate is absorbed in the proximal SI by means of carrier-mediated diffusion. Dietary cobalamin is initially protected from digestion by R proteins, and is then absorbed in the ileum through receptor-mediated endocytosis bound to intrinsic factor (IF). (From Ettinger SJ, Feldman EC, editors: *Textbook of Veterinary Internal Medicine*, ed 7, Philadelphia, 2010, Saunders, p 1528, Figure 270-1A.)

Vitamin B_{12} (cobalamin) is absorbed by receptor-mediated endocytosis in the ileum (see Figure 57-9), but the process is complex so that intact cobalamin is absorbed and potentially harmful analogues are excluded. Following ingestion, cobalamin is released from food in the stomach and then bound by R proteins (haptocorrins), which are nonspecific binding proteins of salivary and gastric origin. At acidic pH, cobalamin has high affinity for R proteins, but on entering the more alkaline environment of the SI, R proteins bind cobalamin less avidly and undergo proteolysis. Thus cobalamin is transferred to another binding protein, intrinsic factor, which promotes cobalamin absorption in the ileum. The source of intrinsic factor is the stomach and pancreas in dogs and solely the pancreas in cats. Intrinsic factor–bound cobalamin complexes pass to the ileum until they bind specific receptors and are endocytosed. Cobalamin is passed into the portal blood where it is bound to a protein, transcobalamin 2, enabling it to enter tissues and to be reexcreted in bile. Inherited abnormalities of the cobalamin–intrinsic factor receptor in breeds such as the Giant Schnauzer and Border Collie cause selective cobalamin deficiency.

Minerals

Zinc and copper are absorbed via divalent cation transporters. There is competition for binding, while intracellular binding of copper by metallothionein is also part of the normal homeostatic mechanism, as the copper is trapped within effete enterocytes and shed.

Iron is absorbed by the duodenum and proximal jejunum both as heme and nonheme iron. Heme, found largely in meat, is better absorbed as it is unaffected by other dietary constituents or intraluminal factors. Gastric acid and chelation with mucopolysaccharide, ascorbate, and citrate help maintain iron in solution for absorption, and ferrous forms of nonheme iron are better absorbed than ferric forms. Ferrous iron is absorbed by an energy-dependent carrier mechanism, and is carried out of the enterocyte bound to transferrin. However, absorption is regulated, and if the body is iron-replete, crypt cells synthesize apoferritin, which traps iron in enterocytes as ferritin. When the enterocyte is exfoliated at the villus tip, the trapped iron is excreted back into the lumen.

Calcium absorption is complex and is modulated by systemic control mechanisms. In particular, vitamin D stimulates the activity of calcium-binding protein within enterocytes. However, uptake of calcium at the brush-border is an active process and is markedly influenced by the intraluminal pH and other substances such as organic and inorganic phosphates.

Motility

Slow wave, segmental, and peristaltic contractions of the SI are generated by the coordinated contraction of smooth muscle in response to spontaneous electrical activity.[26-34] Interstitial cells of Cajal are considered coordinating/pacemaker cells and smooth muscle contraction is also modulated by coordinated neurohumoral and neurochemical molecule release. Many of these molecules are also involved in the regulation of intestinal secretion and absorption and the mucosal immune response, producing a complex coordinated process for the digestion of food.

Intestinal motility in the fasted state in dogs is characterized by three phases. A cycle comprising a quiescent phase (lasting approximately 1 hour), phase two comprising minor contractile activity (15 to 40 minutes), and then migrating myoelectric (motor) complexes (MMCs) (4 to 8 minutes), and is repeated approximately every 3 hours. The short MMC phase is a period of intense contractile activity that sweeps undigested food, secretions, desquamated cells, and bacteria down the intestine. This process is known as the *intestinal housekeeper* wave and is induced by motilin secretion. Erythromycin can stimulate motilin receptors and at low doses it can be prokinetic mimicking the MMC; higher doses overstimulate and may cause emesis. The pattern of intestinal motility in cats is somewhat different, but a migrating spike complex correlates with the MMC.

In the fed state, the pattern of motility is most similar to phase two fasting motility. Its duration is determined by the nature of the diet, with fats and fiber prolonging it. The presence of unabsorbed fat in the distal SI reflexly inhibits gastric emptying by neurohormonal mechanisms. This "ileal brake" mechanism may be the cause of the delayed gastric emptying that is typically seen in malabsorption. Feeding a patient with SI disease more than four times a day is unlikely to be helpful as the stomach will be trickle-feeding it anyway.

Segmental contractions slow intestinal transit and ensure mixing and digestion of nutrients, until peristalsis propels the ingesta onwards. Reduced segmental motility may lead to rapid transit, and decreased peristalsis delays transit, conditions manifesting clinically as diarrhea and ileus, respectively.

Secretion and Absorption of Water and Electrolytes

Intestinal secretion, a function of villus crypt cells, is believed to occur by passive flux of water osmotically following active transcellular chloride secretion into the intestinal lumen. Bacterial toxins can cause hypersecretion.

The ability of the intestine to absorb fluid and electrolytes varies according to the site, with water absorption becoming increasingly efficient distally. The net amount of fluid and electrolytes in the GI tract reflects a balance between absorption and secretion, with net absorption in health. However the daily fluxes are massive (approximately 2.7 L/day in a 20-kg dog) and the consequences of net loss is not only diarrhea but also rapid dehydration.

The absorption of water is passive and follows transport of solutes across the GI epithelium by one of three processes: passive absorption, active absorption, or solvent drag. The jejunum absorbs approximately 50%, the ileum approximately 75%, and the colon approximately 90% of the fluid volume presented to it, leaving approximately 2% in feces. This gradient in absorptive ability is a function of enterocyte pore size, membrane potential difference, and the type of transport processes associated with each intestinal segment. The site of the enterocyte on the villus is also important; villus enterocytes absorb, whereas crypt cells secrete.

Colonic absorption is important in SI disease because it helps to compensate for fluid losses and diarrhea will only occur if the colonic reserve capacity is overwhelmed. SI dysfunction may then present with signs of dysfunction of the large intestine because products from the SI, such as hydroxylated fatty acids and deconjugated bile acids, stimulate colonic secretion.

Control of Fluid Balance

Intestinal fluid balance is regulated by the neurocrine systems in the submucosal plexus as a largely autonomous process.[35,36] Acetylcholine and vasoactive intestinal polypeptide are major mediators of secretion, increasing intracellular calcium and cyclic adenosine monophosphate (cAMP), inhibiting neutral sodium and chloride absorption, and facilitating transcellular chloride efflux. Many bacterial agents exert their diarrheagenic effects by increasing cAMP in enterocytes. The principal regulators of absorption—noradrenaline, somatostatin, and opioids—lower intracellular cAMP and calcium concentrations and stimulate neutral NaCl absorption and thereby can have therapeutic antidiarrheal effects.

Mucosal Immunity

The mucosal immune system is a large and complex organ and is critical to the health of not only the intestine but the whole animal. Chapter 3 describes its structure and function in detail.

DIAGNOSTIC EVALUATION

Edward J. Hall

General Approach

As most cases of small intestinal disease are acute, self-limiting, and nonfatal, they require only symptomatic support and not necessarily a definitive diagnosis. Medical investigation is more necessary if acute diarrhea is hemorrhagic, accompanied by systemic signs, and unresponsive to symptomatic treatment, although the extent of the medical workup may still be a balance between the severity of the illness and the cost of investigation. By definition, chronic diarrhea is not self-limiting, and an etiologic or histopathologic diagnosis is usually required to allow specific treatment.

The history and physical examination are crucial steps toward reaching a diagnosis and in some cases may be all that is required. Preliminary laboratory investigation may include collection of baseline data (e.g., hematology, serum biochemistry, urinalysis, and fecal examination), and are performed before more specific laboratory tests, imaging, and biopsy with histopathologic investigations are undertaken.

History

Background

Information about the recent activity of a patient is helpful in acute small intestinal disease as it may follow an episode of dietary indiscretion, particularly if the animal is allowed to roam or has contact with other animals with infectious gastroenteritis. A full dietary history is helpful when investigating chronic disease, especially when trying to formulate an exclusion diet. Travel information is important as regional infectious diseases, such as histoplasmosis, may move from one geographic site to another.

Clinical Signs

The presence of dehydration should be ascertained by clinical signs (e.g., skin tenting, tachycardia, dry mucous membranes, and depression) and addressed therapeutically, as dehydration can rapidly become life-threatening through profuse diarrhea. Metabolic acidosis and hypokalemia are common acid–base and electrolyte abnormalities, and a balanced electrolyte solution containing potassium can be administered while the medical investigation is being pursued.

The cardinal sign of small intestinal disease is diarrhea, but other signs (Box 57-2) may occur in the absence of diarrhea. Vomiting may be stimulated by intestinal distention or inflammation, and, indeed, vomiting is the most common manifestation of inflammatory bowel

Box 57-2 Clinical Signs of Small Intestinal Disease

Cardinal sign
- Diarrhea
- Increase in frequency, volume, and consistency of stool

Other signs
- Vomiting
- Weight loss and/or failure to thrive
- Hematemesis
- Melena
- Altered appetite
- Inappetence/dysorexia
- Anorexia
- Polyphagia
- Coprophagia
- Pica
- Abdominal discomfort, pain
- Abdominal distention
- Borborygmi and flatus
- Halitosis
- Dehydration
- Polydipsia (compensatory)
- Ascites and edema
- Shock

disease (IBD) in cats. Vomiting of blood may indicate gastric and/or upper GI bleeding, and copious volumes of bilious vomit are suggestive of upper GI obstruction. More distal obstructions of the SI may cause infrequent vomiting of a fecal-like material.

Anorexia can be a feature of intestinal disease, especially if there is sepsis, severe inflammatory, or extensive neoplastic disease. Some weight loss is expected in anorexic patients, but losses in the face of an increased appetite (or very rapid losses) are often an indication of malabsorption, and/or PLE. Severe SI disease is sometimes observed despite the absence of any diarrhea, which is testament to the colon's reserve capacity for the absorption of water (see Chapter 1).

Diarrhea caused by SI disease is usually of large volume and watery, but passed only a few times each day. Urgency and tenesmus are rare findings unless there is colonic involvement in a more diffuse disease process, or if colitis has developed secondary to the chronic passage of undigested food. Diarrhea associated with SI disease may contain undigested food, especially fat (steatorrhea), and may be malodorous; patient breath may have a characteristic odor, as well. The diarrhea can be a bizarre color, such as yellow or green, indicative of incomplete intestinal bacterial metabolism of excreted bile pigments that normally impart a brown color to the feces.

If there is bleeding, the blood is usually partially digested, and if in sufficient volume, will be recognized as melena; at least 1 mL blood/kg/day must be lost before it becomes grossly visible.

Physical Examination

Nonspecific signs of SI disease, such as dehydration and weight loss, are readily apparent, and fever is sometimes present with infectious enteritis. Weight and body condition score should be recorded in all patients.

Direct, noninvasive examination of the SI is impossible, but examination of the mouth for a linear foreign body and rectal examination should be performed. Abdominal palpation is best performed with gradual, gentle, manual pressure on the abdomen. In larger dogs pressure is applied between the hands placed on either flank, but in cats and small dogs the thumb and fingers of one hand may be used. Elevating the cranial abdomen may allow masses normally within the rib cage to fall back to where they can be detected. Masses, foreign bodies, or distended or thickened loops of bowel may be readily palpated. However, the success of palpation depends not only on the skill and patience of the examiner, but also on the body condition and patient compliance. Abdominal palpation should be repeated at least daily in hospitalized patients, and the opportunity should be taken to repeat palpation if the patient is sedated or anesthetized when the abdominal wall will be relaxed.

Free fluid within the peritoneal cavity should be detected by ballottement; tapping on one side of the abdomen allows detection of a fluid wave on the opposite flank. Detection of abdominal pain may be more difficult, depending on how the patient responds. Specific localization is rarely possible as abdominal visceral sensory output is not segmental and decussates within the spinal cord. Localized peritonitis may be detected as the parietal peritoneal sensory output is segmental.

Minimum Database

Results of the hemogram, serum biochemistry, and urinalysis are rarely diagnostic of any specific SI disease. Indeed they are often more reflective of hydration status, and are largely undertaken to rule out diseases in other organ systems that may manifest with SI signs. Some changes can help assess dehydration (e.g., packed cell volume, total solids/proteins, azotemia) and secondary electrolyte abnormalities, but changes seen in SI disease are often quite nonspecific.

Hemogram

Elevation of the packed cell volume can be indicative of dehydration, whereas extreme erythrocytosis is a hallmark of hemorrhagic gastroenteritis or paraneoplastic syndrome. Paraneoplastic production of erythropoietin by intestinal stromal cell tumors causing erythrocytosis has been reported in rare cases.

Anemia can reflect chronic illness or intestinal blood loss. Mild normocytic normochromic anemia is the most common abnormality, but a regenerative anemia may be seen if there is blood loss. Hypochromic, microcytic anemia (and thrombocytosis) is indicative of iron deficiency, which can occur through chronic SI blood loss.

A stress leukogram is often associated with significant SI disease, but an inflammatory leukogram is unusual, even in the presence of marked intestinal inflammation. Neutrophilia, left shift, and sometimes toxic neutrophils can indicate incipient sepsis or SI perforation and peritonitis. Eosinophilia can be a result of parasitism, but is an unreliable marker of intestinal parasites and eosinophilic enteritis. Marked eosinophilia may be seen as a paraneoplastic effect in lymphoma and mastocytosis.

Serum Biochemistry

Total serum proteins will be increased if there is dehydration and decreased by chronic blood loss. If a PLE exists, panhypoproteinemia typically develops, as both albumin and globulin are lost through the leaky gut wall. This can usually be differentiated from protein-losing nephropathy (low albumin, normal globulin, proteinuria) and hepatic failure (low albumin, raised globulin, and hyperbilirubinemia). Occasionally hyperglobulinemia is found in severe IBD, and a monoclonal gammopathy is seen rarely in alimentary lymphoma and plasmacytoma.

Liver enzymes may be elevated secondarily in SI disease because of portal venous transport of toxins and/or bacteria from a compromised SI, but overall liver function (as assessed by serum bile acids) will usually be normal. Hypocholesterolemia is a crude indicator of malabsorption.

Hypoglycemia is a complication found in perinatal patients that have reduced nutritional intake during SI disease. Paraneoplastic hypoglycemia is occasionally found with SI stromal cell tumors that produce insulin-like factors.

Prerenal azotemia (i.e., increased urea and creatinine) will develop if the patient is dehydrated, but an increased urea-to-creatinine ratio in a fasted animal is suggestive of GI bleeding, with conversion of blood proteins to ammonia by intestinal bacteria, and hence urea formation by the liver.

Hypokalemia is common in SI disease as a result of decreased intake and intestinal losses. The finding of an abnormal sodium-to-potassium ratio may identify cases of hypoadrenocorticism, but is sometimes seen in primary SI disease, notably salmonellosis and whipworm infection,[1] or if ascites and third-space effects are associated with PLE.

Fecal Examination

Fecal examinations[2] are an important component in the investigation of SI disease. Tests such as quantification of fecal fat excretion are unsuitable for most practice settings, and bacteriologic culture

is sometimes of questionable value, but identification of endoparasites is important.

Direct Smear

Fecal smears can be stained for undigested starch granules (Lugol iodine solution), fat globules (Sudan stain), and muscle fibers (Wright or Diff-Quik stain). Positive findings may indicate maldigestion and malabsorption but are generally unreliable and completely nonspecific. The presence of fungal elements is of uncertain significance, but rectal cytology may be useful, with fecal leukocytes being suggestive of intestinal inflammation.

Unstained wet mounts may be used to identify protozoal trophozoites of *Giardia* (dogs and cats) or *Tritrichomonas* (cats). Clostridial endospores and fungal elements (*Histoplasma*, *Aspergillus*, *Pythium*, and *Candida* spp.) may be identified. Enterotoxin production by *Clostridium perfringens* is a potential cause of diarrhea. The presence of a large number of clostridial endospores (more than 5 per oil field) on Diff-Quik–stained smears may be significant, but a positive fecal enterotoxin assay (enzyme-linked immunosorbent assay [ELISA] or reverse passive latex agglutination) is likely more significant. However the correlation of sporulation, toxin production, and diarrhea is unclear.[3]

Rectal Cytology

Although probably more relevant for large intestinal disease, the rectal wall can be very mildly abraded at the end of a rectal examination, and the gloved finger rolled on a microscope slide for special staining. Cytologic examination is often negative, showing only bacteria and fecal debris, but when positive it can provide some useful information. Although the test is fast and simple, in all cases confirmatory tests are indicated. An increased number of neutrophils may be suggestive of a bacterial problem, indicating the need for fecal culture, and malignant lymphocytes may exfoliate if lymphoma is present. *Histoplasma* and *Prototheca* organisms may be visualized.

Fecal Concentration Techniques

For detection of most parasites, fecal concentration techniques are more rewarding. Examination of three fecal samples by zinc sulfate flotation is recommended to detect *Giardia* oocysts. A direct smear, sedimentation, or the Baermann technique can identify larvae of *Strongyloides* spp.

Bacteriologic Examination

Routine Culture

The culture of all bacteria from a fecal sample in vitro is of little value, but targeted evaluation for potential pathogens may be helpful, although molecular techniques may be needed to identify pathogenic strains. For example *Escherichia coli* can be cultured from most fecal samples, but only certain strains are pathogenic, and polymerase chain reaction (PCR) probes are needed to detect genetic pathogenicity markers.

Culture of feces is indicated in animals with acute hemorrhagic diarrhea, with fever, and an inflammatory leukogram, and/or with neutrophils on rectal cytology. Identification of *Salmonella* spp., *Campylobacter jejuni*, and *Clostridium difficile* may be helpful, although the significance of a positive isolate should be interpreted in the light of the clinical history, because these organisms can be present in the feces of clinically healthy animals. Furthermore, the fecal flora does not necessarily reflect the SI flora and cannot be used to diagnose small intestinal bacterial overgrowth, but may be representative of colonic bacterial populations.

The significance of a positive result needs further evaluation, because potential pathogens can be isolated from feces from both healthy and ill dogs. Failure to speciate *Campylobacter* isolates may lead to erroneous conclusions, as the relatively nonpathogenic, and potentially commensal, *Campylobacter upsaliensis* is a more common isolate from dog feces than the pathogenic *C. jejuni*. Testing by PCR may aid speciation, but still does not overcome the fact that isolation does not necessarily indicate the cause of the diarrhea. Feces can be cultured for fungi, such as *Histoplasma capsulatum*, but isolation is difficult and slow.

Molecular Fingerprinting[4]

Many intestinal bacteria cannot be cultured in vitro. Identification can be performed by comparative gene sequencing of the bacterial 16S ribosomal RNA (rRNA) derived from mucosal brushings or fecal samples. This method can be used to identify a single species using degrading gradient gel electrophoresis or to look at the pattern of the flora in both mucosal brushings and feces by the high-throughput pyrosequencing metagenomic approach (see Chapters 2 and "Infection" section in this chapter).

Virologic Examination[5]

Viral diarrhea is usually acute and self-limiting and does not require a positive diagnosis. Electron microscopy can be used to identify the characteristic viral particles of rotavirus, coronavirus, and parvovirus. Fecal ELISA tests for parvovirus are also available.

Examination for Protozoa

Coccidia

Oocysts are best detected by fecal flotation methods.

Giardia

Zinc sulfate flotation in the hands of an experienced technician remains the diagnostic method of choice. A commercially available ELISA can be used to detect *Giardia* antigen in feces and may be more sensitive. PCR is also likely to be more sensitive.

Tritrichomonas fetus[6]

Infection with this organism, which can be an important pathogen in young cats,[6] and may complicate canine diarrhea, can be diagnosed by direct evaluation of a fresh fecal smear, although experience is needed to distinguish it from *Giardia*. In vitro culture in pouches, developed to identify cattle infections, can be used but needs to be examined every 2 days for the presence of the organism. A fecal PCR is available, but can be problematic because of inhibitors of the PCR reaction in feces, and the intermittent excretion of the organism; false negatives are less likely if diarrheic feces or colonic washings are used.

Occult Blood

At least 1 mL of blood per kilogram of patient body weight is needed to recognize overt melena.[7] The occult blood test is used to test for intestinal bleeding from ulcerated mucosa and benign or malignant tumors before melena is observed grossly. Unfortunately, it is very sensitive and tests nonspecifically for hemoglobin from any mammalian species, thus reacting with any dietary meat as well as patient blood. Consequently the patient must be fed a meat-free diet for at least 72 hours for a positive result to have any significance.

α_1-Protease Inhibitor[8]

α_1-Protease inhibitor (α_1-PI; synonym: α_1-antitrypsin) is a naturally occurring endogenous serum antiprotease. If lost into the intestinal

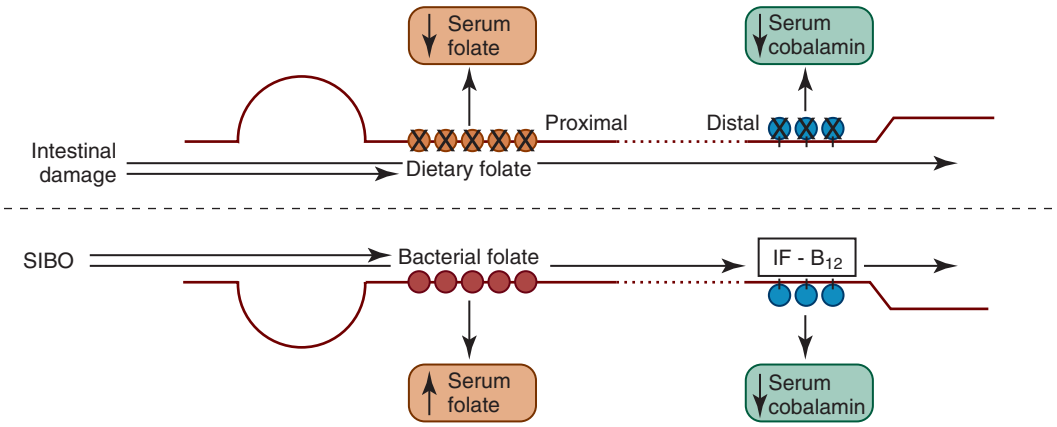

Figure 57-10 Diagram of the absorption of folate and cobalamin. In diseased intestine, proximal and distal mucosal damage causes folate and cobalamin malabsorption, respectively. Reduced serum folate and/or cobalamin are markers for proximal and/or distal SI damage. Classically, small intestinal bacterial overgrowth (SIBO) causes increased folate uptake because of bacterial folate synthesis and decreased cobalamin uptake because of bacterial incorporation. However, these changes are poorly sensitive, and cannot be used to reliably diagnose SIBO: they do not correlate with antibiotic responsiveness. IF, Intrinsic factor. (From Ettinger SJ, Feldman EC, editors: *Textbook of Veterinary Internal Medicine*, ed 7, Philadelphia, 2010, Saunders, p 1528.)

lumen because of PLE, it can be found in feces as it resists bacterial degradation. The α_1-PI test originally assayed the presence of α_1-PI in feces by ELISA, but has been replaced by a validated radioimmunoassay.

To improve the diagnostic accuracy of the test, three fresh fecal samples should be sampled. The assay is only valid when used on fecal samples collected following spontaneous defecation, as abrasion of the colonic wall during digital evacuation is enough to elevate α_1-PI concentrations. The test is less useful in patients with GI blood loss. The test appears to be of value for the diagnosis of PLE, correlating well with historical testing by fecal radioactive ^{51}chromium-labeled albumin excretion. Fecal α_1-PI may prove to be more sensitive than the finding of reduced serum albumin for the detection of early disease.

Fecal Calprotectin

Calprotectin has been characterized as a marker of neutrophil elastase activity.[9] Assay of fecal calprotectin is a useful marker of inflammation in human IBD, and a dog-specific assay has been developed, but the clinical utility, sensitivity, and specificity are unknown.

Special Tests

In cases of malabsorption, intestinal biopsy is usually necessary to obtain a definitive diagnosis. However, exocrine pancreatic insufficiency should be ruled out before biopsy, because signs of malabsorption are nonspecific and not easily differentiated from maldigestive disorders.[10,11] Thus serum trypsin-like immunoreactivity (TLI) measurement must be performed in all cases (see Chapters 25 and 60). It is also well-recognized that biopsies from up to 50% of malabsorption patients are considered normal by light microscopy. Therefore before biopsy, a number of indirect tests are performed to assess for intestinal damage, altered permeability, and dysfunction. Indeed, empirical treatments, such as administration of fenbendazole or an exclusion diet trial, may be indicated before biopsy.

Serum Folate and Cobalamin Concentrations

The assay of serum folate and cobalamin concentrations[12] can be performed on the same serum sample taken for the TLI test (see Chapter 25). This assay has limited value in the diagnosis of specific SI diseases and is not recommended for the diagnosis of canine small intestinal bacterial overgrowth (SIBO). However, subnormal folate and cobalamin concentrations are markers of GI disease as well as indicators for the need for vitamin supplementation (see Figures 57-9 and 57-10).

Tests of Intestinal Absorption

Attempts to assess intestinal function by measuring the absorption of numerous substrates (e.g., lactose, glucose, starch, triglyceride, and vitamin A) are no longer performed because of a lack of sensitivity and specificity. Even the D-xylose test has been abandoned because it is insensitive in dogs and nondiscriminatory in cats. GLUT5 on the MVM allows facilitated diffusion of both fructose and D-xylose, and as fructose uptake in cats is low, the xylose absorption test is particularly unhelpful in this species. The differential absorption of two sugars (xylose and 3-*O*-methyl-D-glucose) eliminates the nonmucosal effects that blight the xylose test, and initial results suggest that the test may be of more value in dogs and cats.[13]

Intestinal Permeability

Intestinal permeability[13-15] is an index of mucosal integrity and is assessed by measuring noncarrier mediated uptake of nondigestible probe markers. These tests use a nonmetabolizable probe that is measurable in plasma and/or excreted in the urine. The permeability probe ^{51}chromium-labeled ethylenediaminetetraacetic acid (^{51}Cr-EDTA) was used in original studies, but the need for a γ-emitter limited its safe use.

Errors related to nonmucosal factors (including the gastric emptying rate, intestinal transit time, and completeness of urine collection) can be eliminated by concurrently measuring the absorption of two probes with different pathways of absorption (Figure 57-11). Calculation of their excretion ratio eliminates errors from extramucosal factors because both probes should be affected equally. The ratio, which is altered by villus atrophy or epithelial damage or both, offers a simple, sensitive diagnostic test.

A 5-hour urine collection is performed after oral administration of two sugars. A number of candidates can be used for the probe molecules, and a mixture of one large simple sugar (e.g., lactulose, cellobiose, raffinose) and one small one (e.g., rhamnose, arabinose,

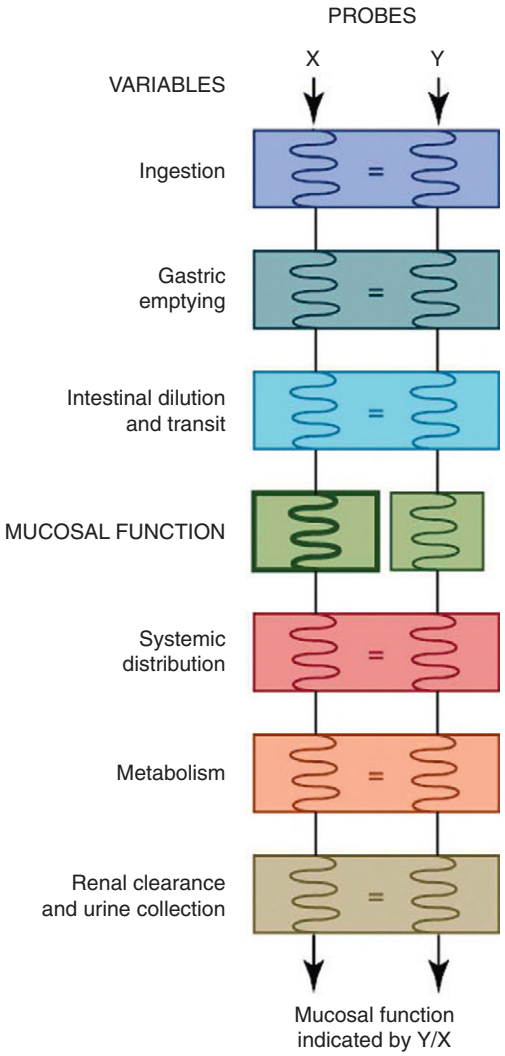

Figure 57-11 Principle of differential permeability testing. Simultaneous administration of two probes selected to respond identically to each variable except mucosal permeability. The Y-to-X ratio provides a specific index of mucosal permeability. (From Hall EJ: Small intestinal disease: is endoscopic biopsy the answer? *J Small Anim Pract* 35:408, 1994.)

mannitol) can be chosen. The cellobiose-to-mannitol excretion ratio and lactulose/mannitol ratio have been used in companion animals, but with advances in the high-performance liquid chromatography assay of these sugars in blood and urine, the lactulose/rhamnose ratio test has become the standard test of SI permeability.

Tests for Protein-Losing Enteropathy

Historically, intestinal protein loss has been detected by measuring the fecal loss of radiolabeled molecules such as ^{51}Cr-labeled albumin and ^{67}Cu-labeled ceruloplasmin. These tests are difficult to perform, potentially hazardous, and have largely been discarded, although they remain the standard by which other tests, such as the assay of fecal α_1-PI (see previous), are judged.

Breath Tests

Breath tests[12,16] have been used to assess bacterial metabolism in the GI tract. Intestinal bacteria synthesize hydrogen and volatile gases (e.g., methane), which are partially absorbed and excreted in breath where they can be measured. Breath hydrogen tests have been used most extensively because mammalian cells cannot produce hydrogen, and therefore any H_2 gas that is measured must be of bacterial origin. Such tests can assess carbohydrate malabsorption and orocecal transit time, when most of the hydrogen is produced by colonic bacteria. Theoretically breath hydrogen can detect increased bacterial colonization of the SI, that is, bacterial overgrowth, but as colonic bacterial numbers are massive, the test is unlikely to be discriminatory.

A variety of protocols has been used, including giving xylose to assess malabsorption, lactulose to assess orocecal transit, and a test meal to assess SI bacterial fermentation. A number of studies have attempted to standardize the techniques for companion animals, and use of substrates labeled with stable isotopes has increased. However, these techniques are not widely used, even in referral centers, because of technical difficulties, and lack of specificity.

Unconjugated Bile Salts

The hypothesis behind the test to measure serum unconjugated bile acids (SUBAs) is that conjugated bile acids are excreted into the intestine via the biliary tract where some SI bacterial species carry out deconjugation reactions.[17] Unconjugated bile acids are then absorbed passively by the SI, poorly cleared from portal blood, and measured in peripheral blood. Therefore, in theory, increases in SI bacterial numbers might result in an increase in SUBAs. Preliminary work suggesting that the test was sensitive and specific for canine SIBO has since been contradicted. Its utility has been questioned as there is a marked postprandial rise in healthy animals, deconjugation is partly a function of *Lactobacillus* activity, and results do not correlate with the diagnosis.

Miscellaneous Tests

A number of tests for intestinal bacterial metabolites have been devised to detect bacterial metabolic activity or SIBO, or to assess orocecal transit time. These include the nitrosonaphthol test, urinary indican excretion, bacterial release of sulfapyridine from sulfasalazine, and bacterial release of paraaminobenzoic acid (PABA) from a bile salt conjugate (PABA-UDCA [ursodeoxycholic acid]).[18] However, none of these tests are widely used in companion animals. Evaluation of the volatile gases emitted by feces can give a profile that is characteristic of specific infections, but has not been evaluated in small animals.

Assessment of Intestinal Motility

Methods to measure intestinal transit time include barium studies with and without food, ultrasonography (including pulsed Doppler measurements), breath hydrogen following carbohydrate administration, and using visual (e.g., carmine red dye, chromic oxide) or chemical markers that are excreted in the urine after absorption (e.g., sulfasalazine, acetaminophen, nitrofurantoin, PABA-UDCA).[19] Results are quite variable and often the methodologies do not correlate well as results are variable with both the composition of the test diet and stress affecting transit rates as much as disease. Intestinal transit is best studied with wireless motility capsule system and scintigraphy, but again the diet composition and stress affect the result. Measurement of myoelectrical activity either in vivo or in vitro is impractical in clinical practice.

Imaging

With the development of ultrasound, advanced imaging techniques, and endoscopy, imaging of the intestinal tract is no longer limited

Box 57-3 Differential Diagnosis of Ileus

- Gas ileus
  - Generalized
  - Aerophagia
  - Smooth muscle paralyzing drugs
  - Generalized peritonitis
  - Enteritis
  - Localized
  - Localized peritonitis (e.g., pancreatitis)
  - Early stage bowel obstruction
  - Disruption of mesenteric arterial supply
- Fluid ileus
  - Generalized
  - Enteritis
  - Diffuse intestinal neoplasia
  - Localized
  - Foreign body
  - Tumor causing obstruction
  - Intussusception or other mechanical obstruction, e.g., incarceration

to plain and contrast radiography. Scintigraphy, computed tomography (CT), and magnetic resonance imaging are now being adopted, and "virtual endoscopy" by helical CT is becoming available.

Plain Radiography

Survey, plain radiographs[20] are most useful in the investigation of diarrhea associated with vomiting, abdominal pain, and palpable abnormalities. The diagnostic yield is enhanced if orthogonal views are taken, although a single lateral radiograph may be adequate if combined with ultrasonography. The utility of plain radiographs in malabsorption is minimal, especially if ascites is present, as detail is obscured by fluid and lack of fat contrast, respectively. Generally the aim of plain, survey radiographs is the detection of (acute) surgical disease (e.g., foreign bodies, free gas, displacement, masses, obstructions), decreased serosal detail suggestive of effusion, and ileus, an abnormal dilation of an immotile segment of intestine. The differential diagnosis of ileus depends on whether it is localized or generalized and whether an accumulation of gas or fluid is present (Box 57-3). Interpretation should be cautious if the patient has been treated with drugs that affect the GI tract.

Contrast Radiography

Since the introduction of alternative imaging techniques, especially endoscopy, contrast radiographic studies are of limited value in the assessment of SI disease.

Follow-through Examinations

Studies using microfine barium suspensions can identify ulcers and irregular mucosal detail. Although they may confirm the presence of radiolucent foreign bodies, they are of limited use in identifying mural masses and partial obstructions, and rarely provide more information than good quality survey radiographs.

Although contrast studies theoretically can be used to assess the rate of intestinal transit, results do not correlate closely to movement of ingesta as assessed by scintigraphy. Furthermore, dysmotility may occur secondary to other causes and studies provide limited etiologic information. Administration of barium may delay endoscopy for at least 24 hours. If perforation is suspected an iodine-based contrast is used if confirmation is required, although the presence of free abdominal gas on survey films is adequate for a diagnosis in most cases.

Barium-Impregnated Polyethylene Spheres

These are solid-phase radiopaque markers that provide information on gastric emptying, intestinal transit, and obstructive disorders. Given that the transit time of barium-impregnated polyethylene spheres (BIPS)[21] is highly variable, their use for transit studies is limited. They may be most helpful in the detection of partial obstructions, as the larger BIPS are held up by partial obstructions that are seen clinically significant, but may not be identified by barium suspension transit.

Ultrasonography

Transabdominal ultrasound examination is now a routine part of the investigation of SI disease.[22,23] In the future, endoscopic ultrasound will allow the mucosal wall and adjacent viscera (e.g., pancreas) to be examined in more detail.

A conventional examination can detect layering of the wall, peristalsis, ileus, and luminal contents, and can measure SI wall thickness. It has excellent sensitivity for the detection of lesions such as intussusceptions, masses, radiolucent foreign bodies, and intestinal wall thickening and lymphadenopathy in chronic inflammatory, lymphatic, and neoplastic enteropathies. Intussusceptions are usually recognized in the transverse plane as multiple concentric rings and longitudinally as a thick, multilayered segment.

Values for normal SI wall thickness have been reported for dogs and cats; thickness decreases from proximal (5 to 6 mm) to distal (4 to 5 mm), but depends on body size, with the thickest seen in the large- and giant-breed dogs. Disruption of the normal five-layered sonographic appearance (mucosal surface–mucosa–submucosa–muscularis–serosa) is typical of neoplasia, whereas wall thickening can result from other infiltrative disorders and edema, as well as neoplasia. Ultrasound-guided fine-needle aspiration for cytologic examination is possible.

Duodenal Fluid Examination

Duodenal fluid[17,24-26] can be collected either by needle aspiration through the intestinal wall at laparotomy, or during duodenoscopy through a sterile polyethylene tube passed down the biopsy channel. Collection of sufficient sample without blood and tissue contamination can be difficult.

The sample can be examined for motile *Giardia* trophozoites, although this has not proved reliable for diagnosis. Quantitative and qualitative aerobic and anaerobic cultures can be performed. This is considered the gold standard for diagnosis of SIBO, although there are major problems in interpretation and routine diagnostic use of duodenal fluid bacterial culture is not recommended.

Intestinal Biopsy

In most cases of acute diarrhea, a histologic diagnosis is not needed, and intestinal biopsy is very rarely performed. However, in chronic diarrhea a definitive diagnosis often depends on histologic examination of intestinal tissue, although this has major limitations. Biopsy specimens are collected either endoscopically or surgically.

Best practice is to perform endoscopic biopsy first unless there is evidence that the disease is beyond the reach of the endoscopy; the surgical option is preferred if there is any possibility of extraintestinal disease or focal intestinal pathology, or if endoscopic biopsy has

failed to reveal a diagnosis. Thus the client should always be made aware that surgical biopsies may ultimately be required.

Endoscopic biopsies should always be taken, even in the absence of gross abnormalities, because microscopic changes may be present but only the duodenum (and proximal jejunum, if accessible) are biopsied routinely via gastroscopy, while ileal biopsies may be obtained via colonoscopy. Multiple specimens (a minimum of six from each area) should be collected, because small size, artifacts, and fragmentation can make interpretation difficult. The size and quality of endoscopic biopsies depends not just on the equipment available, but also on the pressure exerted by the forceps, which is in part dependent on the operator's experience. At laparotomy, full-thickness biopsies are usually taken from at least three sites, the duodenum, the jejunum, and the ileum. Intestinal biopsies can also be obtained laparoscopically, but evidence of a greater diagnostic utility than endoscopy or greater safety than surgery has yet to be proven.

Tissue handling and processing also affect the diagnostic quality of the sample. Careful orientation of the sample so that the tissue is flattened with the mucosa uppermost theoretically improves the likelihood of optimal sectioning, but must be weighed against the increased time needed to lay out the tissue and the attendant development of artifacts through handling and delayed fixation.

Examination of Biopsies

Histopathology

Although histopathologic assessment of intestinal biopsies remains the gold standard for diagnosis of intestinal disease, it too has limitations.[27-33] Biopsies may be normal by light microscopy, which suggests that many diseases have a functional rather than a morphologic abnormality or that sampling or interpretation problems have occurred. Histopathology may be satisfactory when there are pathognomonic changes, for example, neoplasia, but it has become evident that it may be difficult to diagnose intestinal inflammatory diseases reliably because of a lack of standardized sample preparation and staining practices and agreed upon histologic criteria.

Agreement between histopathologists often is poor, especially when examining endoscopic biopsies and a standardized approach is required. Histopathologic scoring schemes and standardized criteria have been suggested by the World Small Animal Veterinary Association (WSAVA) GI Standardization Group as a means of improving agreement. However, Group members also have shown that the experience of the endoscopist, as well as simply the quality and numbers of biopsies, can influence the reliability of the histologic interpretation. Furthermore there is emerging evidence that ileal biopsies are more likely to be diagnostic than duodenal. As expected, fewer biopsies are needed to reliably detect architectural changes the better their quality (i.e., better size, depth, and integrity) and more specimens are needed the deeper the lesion. Therefore the clinician should always interpret endoscopic biopsy results cautiously; results should be questioned if the tissue diagnosis does not fit the clinical picture, or if the response to apparently appropriate therapy is poor. In some cases, repeat biopsy (e.g., by exploratory laparotomy) may be required. Cytologic examination of endoscopic biopsy squash preparations or mucosal brushings are only an adjunct to histopathologic examination.

Even if intestinal inflammation can be diagnosed reliably, there remains the difficulty that the histologic pattern in intestinal inflammation seen is likely a common final pathway caused by a number of potential causes. Thus unless an etiologic agent is evident on microscopic (e.g., visible protozoa) biopsy alone, it may not be possible to determine the cause of any intestinal inflammation. Although different histologic patterns, for example, eosinophilic and lymphoplasmacytic, are recognized, their specificity in indicating the etiology is poor.

Box 57-4 Research Methods beyond Routine Histopathology Used for Examining Intestinal Biopsies

- Electron microscopy
- Biochemical assay of brush-border enzymes
- Immunocytochemical characterization of B cells, T cells, and their subsets (e.g., CD4 and CD8 cells) and major histocompatibility complex expression by immunohistochemistry and flow cytometry
- PCR for cytokine and receptor (nucleotide-binding oligomerization domain, Toll-like receptors) mRNA expression
- Assessment of T-cell clonality—PCR for antigen receptor rearrangement (PARR)
- Fluorescence in-situ hybridization to demonstrate bacteria in biopsies

Alternative Examinations

A number of research tools have been applied to the investigation of intestinal biopsies. However they are largely research tools, limited by availability and/or cost.[34-36] Box 57-4 outlines more specific examinations.

Empirical Treatment

If a specific diagnosis is made, specific treatment(s) can be given. Yet often the diagnosis is not obvious, usually because of a lack of specific or marked histopathologic changes, and it may be appropriate to perform empirical treatment(s). It is logical and safest to do this sequentially, starting with the treatment least likely to do harm. Therefore parasiticides, followed by an exclusion diet trial, and then an antibacterial trial should be considered before finally attempting immunosuppression. This empirical approach may identify occult parasitism, diet-responsive conditions, and antibiotic-responsive diarrhea, respectively. However, because treatments lack specificity, caution should be exercised in using such trials to make a diagnosis without investigation.

INFLAMMATION

Alexander J. German

In companion animal gastroenterology, IBD is the term used to describe patients affected by persistent or recurrent GI signs, and that have histopathologic evidence of inflammation in intestinal tissues.[1] It is only appropriate to use the term *idiopathic* IBD if no underlying cause for the inflammation can be found. Although there are recent studies into pathogenesis, diagnosis, and treatment, much controversy remains. To make a diagnosis of IBD, detailed investigations must be undertaken to exclude other potential causes of intestinal inflammation; nevertheless, the likelihood is that IBD represents a syndrome comprising a group of disorders with similar characteristics, rather than a single disease entity. It should be noted that canine and feline IBD bear little resemblance histologically or

Table 57-2 Histopathologic Classification of Idiopathic Inflammatory Bowel Disease

Histopathologic Description	Comment
Lymphocytic-plasmacytic enteritis (LPE)	Most common
Basenji enteropathy	A variant of LPE?
Familial PLE and protein-losing nephropathy in soft-coated Wheaten Terriers	A variant of LPE?
Eosinophilic enteritis	Second most common form; marked increase in eosinophils
Granulomatous enteritis	Rare; due to feline infectious peritonitis in cats
Regional enteritis	Rare, a variant of granulomatous enteritis?
Neutrophilic enteritis	Rare in dogs, uncommon in cats

clinically to either of the main IBD variants in humans (i.e., Crohn disease and ulcerative colitis).

Companion animal IBD is further subdivided based on the predominant inflammatory cell type present as judged by histopathologic examination of intestinal biopsy samples (Table 57-2). However, such classification is often arbitrary, and depends upon the opinion of the pathologist concerned. Indeed, many cases have a generalized increase in several cell subsets and cannot easily be classified. The WSAVA GI Standardization Group has undertaken the task of reviewing both collection of biopsy material (endoscopy) and subsequent histopathologic interpretation.[2] It is hoped that such standardization will improve the reliability and diagnostic yield from this procedure.

Types of Small Intestinal Inflammatory Bowel Disease

Forms of small intestinal IBD include lymphocytic-plasmacytic enteritis (LPE), eosinophilic enteritis (EE), granulomatous enteritis, regional enteritis, and neutrophilic enteritis (see Table 57-2). Furthermore, certain breed-specific patterns of disease are recognized, including Basenji enteropathy and the PLE/protein-losing nephropathy (PLN) syndrome of soft-coated Wheaten Terriers. Although the histopathologic findings of these disorders may differ, the etiopathogenesis is thought to be broadly similar.

Lymphocytic-Plasmacytic Enteritis

LPE is the most common histopathological form of SI IBD, and is characterized by mucosal infiltration of lymphocytes and plasma cells (Figure 57-12). LPE can be associated with lymphocytic-plasmacytic inflammation in other regions of the GI tract (e.g., lymphocytic-plasmacytic gastritis [see Chapter 56] and lymphocytic-plasmacytic colitis [see Chapter 58]). LPE in cats can be associated with inflammatory disease in the pancreas (see Chapter 10) and/or liver (see Chapter 61) as part of the "triaditis" syndrome.

Clinical signs of LPE are similar to other forms of IBD and are not pathognomonic. Severe LPE is reportedly prevalent in German Shepherd dogs, Shar-Peis, and pure-bred cats. The approach to diagnosing LPE is the same as for any other form of IBD. However, in both cats and dogs, it can be difficult to differentiate severe LPE from alimentary lymphoma. Exploratory celiotomy may be a preferable means of collecting biopsy material in cats, given both concerns over differentiation of LPE from GI lymphoma on endoscopic biopsy, and the concurrence of pathologic change in other organs. Given these diagnostic dilemmas, clonality studies assessing T-cell receptor rearrangements may assist in identifying low-grade lymphoma.[3]

Eosinophilic Enteritis

EE is reportedly the second most common form of IBD and can be associated with disease elsewhere in the GI tract. On histopathologic examination, mucosal architectural disturbances (e.g., villus atrophy) are present in conjunction with a mixed infiltrate of inflammatory cells with eosinophils predominating (Figure 57-13). The diagnosis has been problematic in the past because diagnostic criteria (e.g., degree of eosinophil infiltration) varied amongst pathologists. However, the WSAVA standards suggest clear diagnostic criteria (e.g., mild 5 to 10 eosinophils per ×40 field; moderate 10 to 20 per ×40 field; marked eosinophils dominate the tissue population).[2] A diagnosis of EE should only be made once other causes of eosinophilic infiltration (e.g., endoparasitism and hypersensitivity disorders) have been eliminated. EE also may be associated with systemic eosinophilic disorders (e.g., hypereosinophilic syndrome) in both cats and dogs.

The condition can be seen in dogs and cats of any breed and age, although it is more common in younger adult animals. Boxers, German Shepherds, and Dobermans may be predisposed. The clinical signs reported are similar to other forms of IBD, although mucosal erosion and/or ulceration may occur more frequently and lead to hematemesis and melena. Concurrent PLE is also recognized, and severe eosinophilic gastroenteritis is also associated with spontaneous perforation of the GI tract.[4]

Basenji Enteropathy

Basenji enteropathy is a severe, hereditary form of LPE that has been well characterized in Basenjis, although the mode of inheritance remains unclear. Vomiting and small intestinal diarrhea are the main clinical signs. A progressive PLE is often noted, and some severe cases develop spontaneous intestinal perforation. Intestinal lesions in Basenjis are characterized by increases in $CD4^+$ and $CD8^+$ T cells.[5,6] In addition to lymphocytic-plasmacytic gastritis, mucosal hyperplasia occur, and this is thought to be secondary to hypergastrinemia. Treatment is usually unrewarding, with progressive clinical signs and dogs dying within months of diagnosis. However, early aggressive combination treatment with glucocorticoids, antibacterials, and dietary modification may achieve remission in some cases.

Familial Protein-Losing Enteropathy and Protein-Losing Nephropathy In Soft-Coated Wheaten Terriers

A unique clinical syndrome has been reported in soft-coated Wheaten Terriers.[7] Affected dogs may present with signs of PLE, PLN, or both. A genetic basis is likely and, although the mode of inheritance is not yet clear, a common male ancestor has been identified. An immune-mediated pathogenesis is likely and dietary hypersensitivity might be involved, as suggested by alterations in antigen-specific fecal immunoglobulin (Ig) E concentrations.[8,9] Signs of PLE tend to develop at a younger age than PLN, and clinical signs include vomiting, diarrhea, weight loss, and pleural and peritoneal effusions. Affected dogs are at risk of thromboembolic disease.[10] Treatment is similar to that described for general IBD.

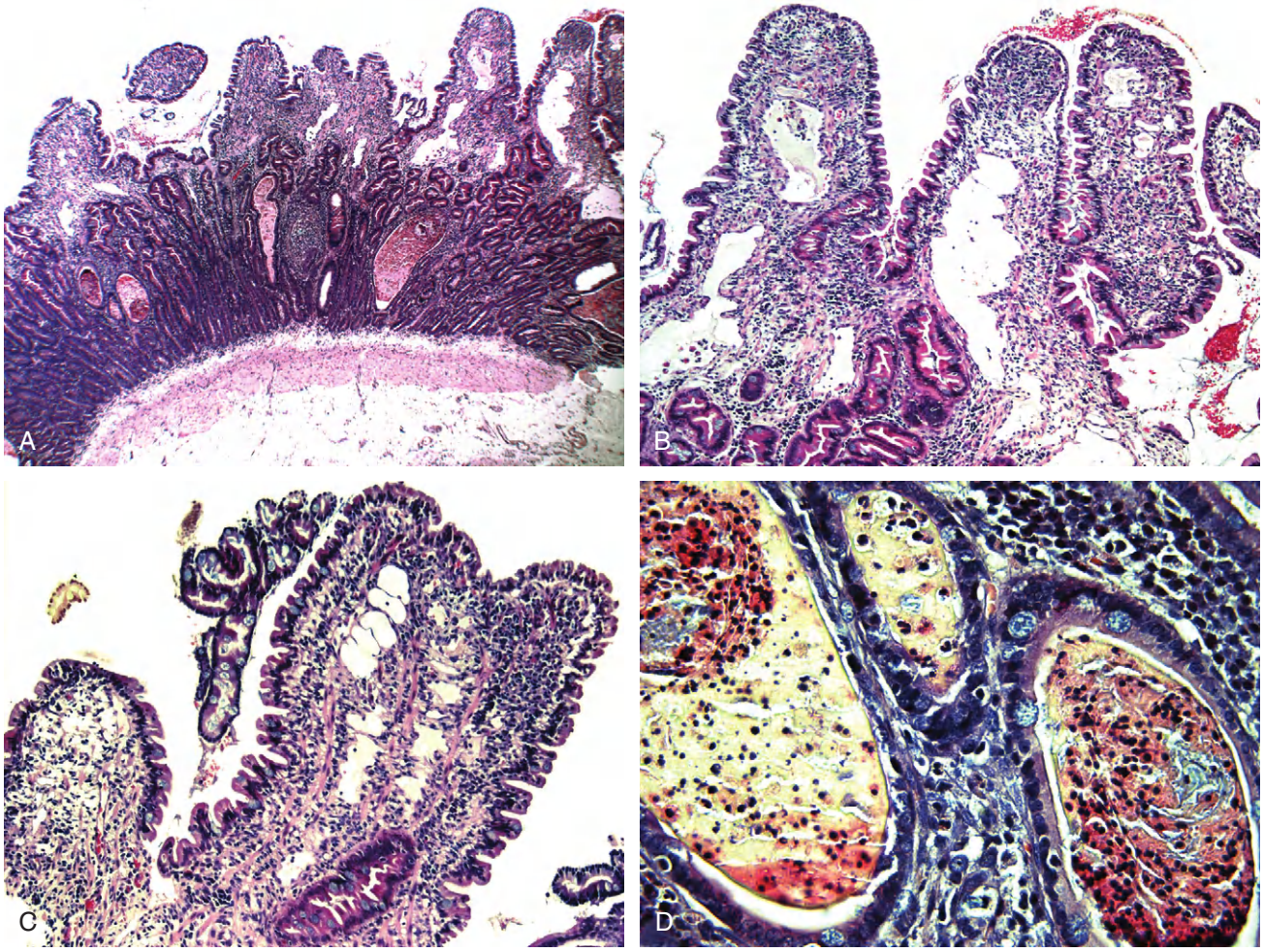

Figure 57-12 **A,** Low-power photomicrograph of the histologic appearance of a duodenal biopsy specimen taken from a dog with lymphocytic-plasmacytic enteritis. Hematoxylin and eosin stain, original magnification ×10. **B** to **D,** Higher-power views showing architectural characteristics of IBD, including villus stunting (**B**), villous fusion (**C**), and crypt distention (**D**). Hematoxylin and eosin stain, original magnifications ×40.

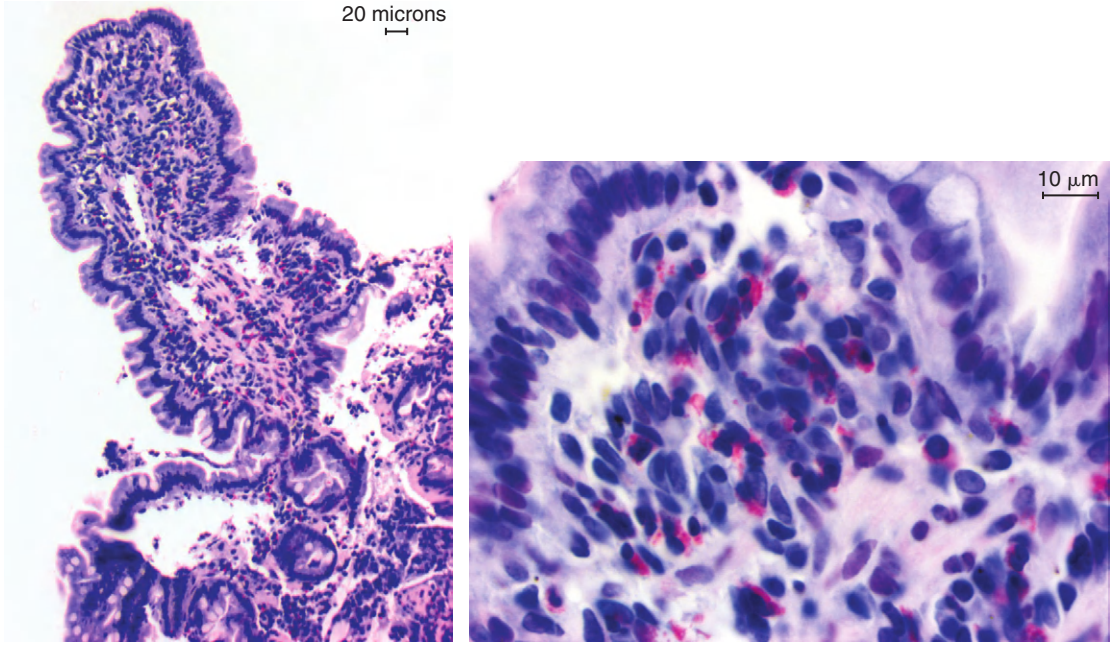

Figure 57-13 Histologic appearance of duodenal biopsy specimens taken from a dog with eosinophilic enteritis. Sirius red stain.

Granulomatous Enteritis

This rare form of IBD is characterized by the development of granulomas and mucosal infiltration with macrophages. This condition is likely to be the same as regional enteritis where ileal granulomas are reported.[11,12] Potential causes of granulomatous inflammation include *Yersinia* and mycobacterial infections, foreign-body reactions, and fungal diseases. In cats a pyogranulomatous transmural inflammation has been associated with feline infectious peritonitis (FIP) virus infection. Although there are similarities between this condition and human Crohn disease, intestinal obstruction and fistula formation are not observed. Conventional therapy for IBD is usually not effective and the prognosis is guarded, although a combination of surgical resection and antiinflammatory treatment was reported to be successful in one case.

Neutrophilic Enteritis

Some inflammatory diseases may be characterized by infiltrates of neutrophils or by granulomatous inflammation, although these patterns are rare. If neutrophils are evident, an underlying bacterial infection should be considered. Alternatively, the neutrophilic infiltrate may have arisen from bacterial invasion secondary to mucosal barrier disruption from erosive or ulcerative lesions. Glucocorticoids are generally not recommended for such cases, unless they fail to respond to all other therapeutic modalities.

Proliferative Enteritis

Proliferative enteritis is characterized by segmental mucosal hypertrophy of the intestine. It is most common in pigs, but a similar although very rare condition has been reported in dogs.[13] There may be an underlying infectious etiology and *Lawsonia intracellularis* infection has been implicated but not yet been proven. Other potential infectious causes include *Campylobacter* spp. and *Chlamydia*.

Etiology and Pathogenesis

Reportedly, IBD has an immune-mediated etiology and thus the GI associated lymphoid tissue likely plays a critical part in pathogenesis.[14] Full details of the mucosal immune system are found in Chapter 3, while intestinal inflammation is reviewed in Chapter 4. Briefly, the intestinal mucosa has a barrier function ("immune exclusion"), and controls exposure of antigens to the gut-associated lymphoid tissue, which must generate protective immune responses against pathogens while remaining "tolerant" of harmless environmental antigens such as commensal bacteria and food. IBD develops when the normal decision-making process breaks down, leading to inappropriate immune responses and uncontrolled inflammation. Critical to the development of inflammation is a breakdown in tolerance to normal luminal antigens (particularly endogenous bacterial species). This loss of tolerance may result from disruption of the mucosal barrier leading to excessive antigen exposure to the underlying immune system, from dysregulation of normal mucosal immune system function, or from a combination of these processes. The end effect is uncontrolled inflammation, which is the result of activation of the many effector pathways. The inflammation can then lead to architectural disruption, resulting in adverse effects on function, which depend upon the part of the bowel affected.

Unfortunately, data that directly assess the pathogenesis of canine small intestinal IBD are limited, and many gaps in our understanding remain. Many studies have used histochemical and immunohistochemical techniques to quantify immune cell populations within the intestinal mucosa with variable results.[14] For canine IBD, recent studies have suggested an increase in cells expressing Toll-like receptors-2, -4, and -9.[15] Other studies have shown a decrease in certain lymphocyte populations (total T cells and IgG^+ plasma cells), while others have shown increases ($\alpha\beta$ T cells, $CD4^+$ T cells, IgG^+ plasma cells) as well as increased macrophage and granulocyte numbers.[14] The confusion is compounded by the fact that in feline IBD, a disease with similar histopathologic changes to the canine form, the only reported difference from control samples was an increase in cells expressing major histocompatibility complex class II.[16]

Inconsistent results have also been seen with the studies conducted to date on soluble immunologic factors. Increased concentrations of acute phase proteins (e.g., C-reactive protein) have been documented in canine IBD in some,[17] but not all studies.[18,19] Recent studies suggest decreased acute-phase proteins in feline IBD.[20] Initial semiquantitative reverse transcriptase PCR (RT-PCR) studies suggested increased cytokine gene expression in canine chronic enteropathies,[21] and this has been confirmed in one,[22] but not all,[23] more recent studies that have used real-time PCR methodology. Again, these results differ from feline studies, where histopathologic evidence on mucosal inflammation correlated with increases in a range of cytokines.[24] Unfortunately, in all of these studies, gene expression alone was assessed, and not the functional protein. However, in a recent study, tumor necrosis factor (TNF)-γ protein was not detected in the serum of 15 dogs with IBD.[16]

The reasons for such discrepancies are not known but may relate to the fact that the chosen gold standard throughout was histopathology, which itself is variable and lacks consensus among pathologists.[2] An alternative possibility is that the many studies have assessed patients in various stages of disease, and it may be that immunologic responses differ, and this lead some researchers to suggest the alternate name of "chronic enteropathy."[18]

Clinical Presentation

Historical Findings

Many clinicians consider small intestinal IBD to be the most common cause of chronic vomiting and diarrhea in dogs and cats; however, given that large scale epidemiologic studies have hitherto not been conducted, the true prevalence of the condition is unknown. In reality, the condition may be overdiagnosed as a result of the ease with which endoscopic biopsy samples of the intestine can be collected, the current difficulties in interpretation of histopathologic specimens, and because alternative reasons for the clinical signs are inadequately eliminated during the diagnostic workup.

The studies that have been published to date suggest that canine SI IBD is most common in middle-aged animals and is uncommon in dogs younger than 12 months of age. Young and growing animals are most likely to suffer from either infectious causes of chronic diarrhea or adverse reactions to food components. No apparent gender predisposition has been reported. IBD can potentially occur in any breed of dog, although predispositions are reported for certain breeds (discussed previously). IBD can affect cats of any age or gender, although middle-aged animals are most commonly affected. Some pure breeds (e.g., Siamese) are said to be predisposed to IBD; the pattern of disease also differs in that concurrent histopathologic changes can be seen the intestine, pancreas, and liver (often termed *triaditis*) (Figure 57-14). For instance, there may be concurrent LPE, lymphocytic cholangitis, and chronic lymphocytic pancreatitis.[2] Interestingly, concurrence of IBD and pancreatitis has been reported in dogs,[25] suggesting that the distinction between species may be less clear than previously thought.

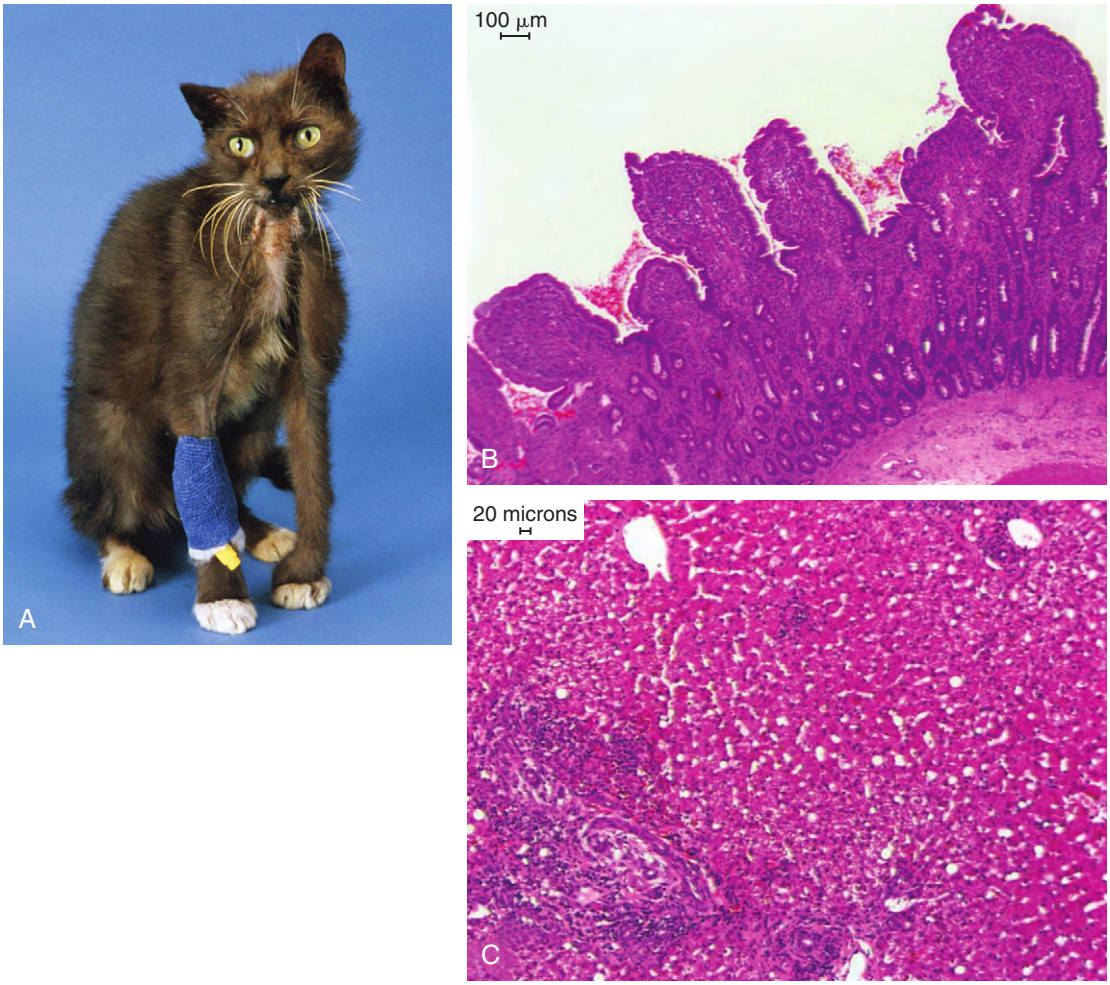

Figure 57-14 **A,** Eight-year-old, neutered female, domestic shorthair cat with severe cachexia, diarrhea, and *Malassezia* dermatitis. **B,** Histologic appearance of a jejunal biopsy specimen taken from the cat in **(A)**, showing evidence of LPE. Hematoxylin and eosin stain; bar, 100 µm. **C,** Histologic appearance of a liver biopsy specimen taken from the cat in (A), showing evidence of mild lymphocytic-cholangitis. Hematoxylin and eosin stain; bar, 20 µm.

A range of possible clinical signs is associated with both canine and feline SI IBD, but none are pathognomonic for the condition. Not surprisingly, a "small intestinal pattern" diarrhea is most commonly seen (e.g., increased volume, watery, altered color). However, mixed-pattern diarrhea can be seen if the IBD also involves the large intestine and, in occasional cases, a large intestinal pattern diarrhea occurs, most likely the result of prolonged SI diarrhea or the presence of agents that stimulate colonic secretion (e.g., bacteria, bacterial toxins, deconjugated bile acids, or hydroxylated fatty acids).

In cats, vomiting is often the predominant clinical sign of small intestinal IBD, and diarrhea may be only occasional or absent. This may, in part, be related to the fact that some cats do not use a litter tray and thus owners may be unaware of toileting habits. Vomiting is also seen in canine SI IBD although, in the author's experience, almost invariably accompanies, and is less severe than, diarrhea. Hematemesis or melena is usually associated with more severe disease, which has caused mucosal ulceration or erosion; although it can occur in any form of IBD, it appears to occur more often with EE.

Appetite changes can be variable in SI with some cases demonstrating polyphagia, others show differing severities of anorexia, or there may be no appetite change observed. If marked inflammation is present within the SI, significant malabsorption may result, and this can lead to weight loss. Such cases may also develop panhypoproteinemia, and two studies demonstrated that hypoalbuminemia is a poor prognostic indicator in IBD.[18,26] If marked hypoalbuminemia is present (e.g., serum albumin concentrations below approximately 1.5 g/dL), associated signs such as ascites and subcutaneous edema may develop. Thromboembolism and remote organ failure is seen in some patients with PLE. Other systemic consequences of IBD include thrombocytopenia and arthropathies and typical signs may be noted. However, such reports are rare,[27] and in my opinion these are uncommon findings in both canine and feline IBD. Progression of disease is variable and, in some cases, signs may wax and wane.

Physical Examination

General physical examination findings may include dehydration, alterations in demeanor, poor body condition, and signs of anemia if associated blood loss is severe. Abdominal palpation is an important component of the examination, and associated findings include (mild) abdominal discomfort, thickened intestines, turgid or thickened intestinal loops, and ascites (fluid thrill). Although rectal examination does not directly investigate the SI, it may reveal evidence of changes in fecal characteristics (e.g., melena).

Determining Clinical Severity

In humans, activity indices are used to quantify disease severity in IBD, aiding the assessment of the response to treatment and allowing comparisons between published studies in the literature. Recently, an activity index was suggested for canine IBD (canine IBD activity index [CIBDAI]; Table 57-3),[17] and its use in the clinical setting provides a more objective measure of therapeutic response.[18,28] In one study, CIBDAI correlated with serum acute phase protein concentrations,[17] although this was not confirmed by recent work.[19] Clinicians must understand that increases in CIBDAI simply suggest an increase in severity of GI signs, and that high values do not confirm the diagnosis of IBD. For example, increased CIBDAI has been seen in dogs with food-responsive conditions, and values decreased on successful treatment.[29] More recently, a variation of CIBDAI, the canine chronic enteropathy activity index (CCEAI; see Table 57-3) was proposed.[18] All of the same signs are scored as for the CIBDAI, but additional characteristics are also assessed (e.g., presence of ascites and/or peripheral edema, pruritus, and serum protein concentrations). A recent study shows that this correlates better with prognosis than the CIBDAI[18]; however, the advantage of improved performance may be offset by the requirement for blood sampling and serum albumin measurement. Time will tell which system is preferred by clinicians and researchers. Finally, an activity index for feline IBD (FIBDAI) was proposed, which makes use of histology, GI signs, serum total protein and phosphorous concentrations, serum alkaline phosphatase concentration, and endoscopic lesions.[30]

Approach to Diagnosis

Given that none of the clinical signs and physical examination findings that are seen with IBD are pathognomonic, further investigations are essential in order to make a diagnosis. Because the term *idiopathic IBD* should be restricted to use in cases in which intestinal inflammation is found without an obvious underlying cause, all other etiologies must first be excluded. Therefore detailed preliminary diagnostic investigations must be performed, prior to acquisition of GI biopsy samples, to ensure that other etiologies are

Table 57-3 Criteria for Assessment of Severity of Canine Inflammatory Bowel Disease

Characteristic	CIBDAI	CCEAI
Attitude/activity	0. Normal 1. Slight decrease 2. Moderate decrease 3. Severe decrease	0. Normal 1. Slight decrease 2. Moderate decrease 3. Severe decrease
Appetite	0. Normal 1. Slight decrease 2. Moderate decrease 3. Severe decrease	0. Normal 1. Slight decrease 2. Moderate decrease 3. Severe decrease
Vomiting	0. None 1. Mild (once/wk) 2. Moderate (2 to 3/wk) 3. Severe (>3/wk)	0. None 1. Mild (once/wk) 2. Moderate (2 to 3/wk) 3. Severe (>3/wk)
Stool consistency	0. Normal 1. Slightly soft feces, fecal blood mucus, or both 2. Very soft feces 3. Watery diarrhea	0. Normal 1. Slightly soft feces, fecal blood mucus, or both 2. Very soft feces 3. Watery diarrhea
Stool frequency	0. Normal 1. Mild increase (2 to 3/day) 2. Moderate increase (4 to 5/day) 3. Severe increase (>5/day)	0. Normal 1. Mild increase (2 to 3/day) 2. Moderate increase (4 to 5/day) 3. Severe increase (>5/day)
Weight loss	0. None 1. Mild (<5%) 2. Moderate (5% to 10%) 3. Severe (>10%)	0. None 1. Mild (<5%) 2. Moderate (5% to 10%) 3. Severe (>10%)
Serum albumin		0. Albumin >2.0 g/dL 1. Albumin 1.5 to 1.99 g/dL 2. Albumin 1.2 to 1.49 g/dL 3. Albumin <1.2 g/dL
Ascites and peripheral edema		0. None 1. Mild ascites or peripheral edema 2. Moderate ascites/peripheral edema 3. Severe ascites/pleural effusion and peripheral edema
Pruritus		0. No pruritus 1. Occasional episodes of itching 2. Regular episodes, but stops when asleep 3. Dog regularly wakes up due to itching
Final score	0 to 3. Clinically insignificant disease 4 to 5. Mild IBD 6 to 8. Moderate IBD ≥9. Severe IBD	0 to 3. Clinically insignificant disease 4 to 5. Mild IBD 6 to 8. Moderate IBD ≥9. Severe IBD

CIBDAI, Canine inflammatory bowel disease activity index; CCEAI, canine chronic enteropathy activity index.

excluded. Investigations include fecal analyses, routine hematologic analysis, clinical chemistry, urinalysis, assay of serum TLI, pancreatic lipase immunoreactivity, and diagnostic imaging. Although none of these tests is diagnostic for IBD, they help to eliminate the possibility of extraintestinal disease (e.g., pancreatitis, hypoadrenocorticism, renal failure, and hepatic failure), anatomic intestinal disease (e.g., tumor or intussusception), and other known causes of intestinal inflammation. Diagnostic imaging in particular allows the clinician to determine whether focal or diffuse intestinal disease is present, allowing selection of the most appropriate method of intestinal biopsy. In many cases, standardized therapeutic trials can help to confirm the diagnosis, by eliminating other possible causes of intestinal inflammation.

Hematology

In companion animals with SI IBD, hematologic examination is frequently unremarkable. Changes in white blood cells that are occasionally observed include mature neutrophilia, neutrophilia and left shift, and eosinophilia, but none are pathognomonic. Reactive "atypical" lymphocytes may be seen in patients with LPE, and lymphopenia can occur if lymphangiectasia is present. If anemia is present, it may be a reflection of either chronic inflammation or chronic blood loss. Iron-deficiency anemia, with a microcytic hypochromic pattern, also has been reported in IBD,[31] and thrombocytosis also may be seen.[31]

Clinical Biochemistry

In many patients with SI IBD, clinical biochemistry is unremarkable. If PLE is present, serum concentrations of both albumin and globulin can be decreased. Confirmation of PLE requires the absence of significant liver changes (e.g., marked enzyme elevations, low urea, low glucose) on clinical chemistry, or the absence of anemia on complete blood cell count, and of proteinuria on urinalysis. However, fecal α_1-PI measurement may help. Hypocholesterolemia may suggest malabsorption, but this finding is not pathognomonic. Ionized hypocalcemia and hypomagnesemia are also reported.[32,33] Intestinal inflammation in dogs may cause a reactive hepatopathy with mild to moderate (two- to fourfold increases) in liver enzyme (i.e., alanine transaminase [ALT] and alkaline phosphatase) activities. In contrast, as a consequence of their shorter half-lives, liver enzyme increases are less common in feline IBD, and marked elevations in ALT more commonly occur secondary to alimentary lymphoma than feline IBD.[34]

Fecal Examination

Fecal flotation is very important in eliminating parasitic causes of mucosal inflammation. In most cases of SI IBD, these tests yield negative results. When occasional positives do occur, determining the significance can be problematic, as these organisms can be found in the stool of healthy animals. Although trial therapy may be considered, clinicians should exercise caution given concerns over the development of therapeutic resistance.

Serum Folate and Cobalamin

Measurement of serum folate and cobalamin is available for both dogs and cats, and deficiency of these substances is associated with IBD. Recent work has highlighted the importance of hypocobalaminemia in cats,[35] and hypocobalaminemia is also a negative prognostic indicator in chronic enteropathy in dogs[18] as well as other alimentary tract diseases such as EPI.[36] Although such alterations are not pathognomonic, deficiencies in IBD suggest the need for more aggressive therapy against the primary disease, and also the need for parenteral supplementation. This is particularly important, because cobalamin deficiency may itself have systemic metabolic consequences and cause intestinal dysfunction,[37] and anecdotal evidence suggests that the response to immunosuppressive therapy for IBD may be suboptimal until cobalamin deficiency is resolved.

Diagnostic Imaging

Radiographic and ultrasonographic studies are most commonly used to eliminate other possible diseases rather than to make a diagnosis of SI IBD. However, when used in conjunction with specific clinical signs and laboratory testing, the information from imaging studies enables an appropriate choice of a biopsy method (e.g., upper or lower GI endoscopy, or exploratory celiotomy). Ultrasonography in IBD patients can help to document mesenteric lymphadenopathy.[38,39] Although intestinal wall thickness can be measured, one study suggests that this measure is of limited value in the diagnosis of SI IBD.[40] In fact, the only occasions when the bowel wall was notably thickened was when edema was present secondary to marked hypoproteinemia. A recent study suggests that different ultrasonographic patterns can help to differentiate chronic enteropathies with different etiologies.[41] Loss of normal intestinal layering is more commonly seen with neoplasia than IBD.

Intestinal Biopsy

Intestinal biopsy is essential to prove the presence of intestinal inflammation and confirm a diagnosis of SI IBD; either endoscopy or exploratory celiotomy can be used. During endoscopy, the gross appearance of the intestinal mucosa can also be observed. Intestinal inflammation may be indicated by findings such as increased granularity, irregularity, and friability with the presence of erosions, ulceration, and spontaneous hemorrhage. However, these findings are not pathognomonic, and correlation between gross inspection and histopathology is poor.[18,28] Limitations of endoscopy include small sample size, superficial and often fragmented samples, and the fact that tissue can only be collected from proximal regions and (occasionally) the distal ileum. Exploratory celiotomy and full-thickness biopsy may be necessary, although this is more invasive and wound healing can be problematic if severe hypoproteinemia is present.[42] Nonetheless, the approach may be more suitable for cats, given the tendency for concurrent hepatic and pancreatic involvement,[43] the difficulties in differentiating IBD from small-cell lymphoma in endoscopic duodenal biopsies,[34] and the reliability of the small size of endoscopic biopsies that are often collected in this species.

Histopathologic Assessment of Biopsy Samples

The pattern of histopathologic changes in biopsy specimens depends upon the type of IBD. Histopathologic assessment of intestinal biopsies remains the gold standard for diagnosis of many intestinal diseases, but has marked limitations, most notably variable quality of tissue specimens obtained endoscopically[44] and poor agreement between histopathologists.[45] The latter may be a result of the subjective nature of interpretation of the degree of inflammation, the patchiness of inflammation, or the presence of edema (caused by hypoproteinemia) leading to difficulties in assessing cell density.

It can be difficult to distinguish severe LPE from lymphoma, particularly when endoscopic biopsy samples are examined. This may be a result of the fact that infiltration of malignant lymphocytes is patchy, that inflammatory change may accompany alimentary lymphoma (and predominate in some areas), or that lymphocytic infiltration is deep to the area sampled. Cases of feline alimentary lymphoma can be missed if duodenal endoscopic biopsy samples are used in histopathologic assessment, rather than full-thickness

specimens.[34] Hence, it may be preferable to collect surgical specimens in this species, and this approach gives the added advantage that other organs can be sampled (e.g., liver and pancreas) when checking for "triaditis."

The standards published by the WSAVA GI Standardization Group[2] hopefully will improve the reliability of IBD diagnosis.[18,28] Ultimately, the primary clinician should interpret histopathology results cautiously and try to relate them to the clinical presentation. Results should be questioned if the histopathologic diagnosis does not fit the clinical picture or the response to apparently appropriate therapy is poor. In some cases repeat biopsy (e.g., by exploratory celiotomy) may be required.

Diagnostic Horizons

Many research techniques have been developed to assess alterations of the immune system that occur in IBD. Examples include immunohistochemical characterization of immune cell populations,[46-49] measurement of gene expression for cytokines by RT-PCR,[21-23] assessment of T-cell clonality,[3] measurement of mucosal perinuclear antineutrophilic antibody (pANCA),[50] and measurement of mucosal P-selectin expression.[51] Although these techniques have not been widely adopted for clinical diagnosis, there may be potential for future application. In particular, assessment of T-cell clonality may prove to be a useful tool to differentiate LPE from low-grade lymphoma.[3] In addition, there may be benefit in development of mucosal pANCA and P-glycoprotein expression for helping to predict response to therapy.[50,51]

Treatment as a Diagnostic Tool

In many cases, clinicians can use an organized therapeutic plan to help confirm the diagnosis, and determine the optimal therapy for a particular case. Unless the animal is debilitated, single therapeutic modalities are instigated sequentially, and the owner is asked to record precisely in an event diary the frequency and nature of clinical signs. The clinician can then review the diary and calculate disease severity using one of the recognized scoring schemes (see Table 57-3). Although response to treatment can inevitably be judged more objectively, clinicians should still be cautious that therapy might have only invoked a placebo effect. My favored order of treatment trials is anthelmintic/antiparasitic medication, dietary modification, antibacterial trials, and, finally, trial immunosuppressive therapy.

Approach to Therapy

Regardless of the histologic type of IBD, treatment usually involves a combination of dietary modification, antibacterials, and immunosuppressive therapy. Most recommendations are based upon individual experience because objective information of efficacy is generally lacking, and no randomized controlled clinical trials have been conducted. A staged approach to therapy is recommended whenever possible, but may not be appropriate in seriously ill patients (e.g., those with severe hypoproteinemia) where immediate intervention with combination therapy may be essential. Where sequential therapeutic trials are used, initial treatment should be with antiparasitic agents to eliminate occult endoparasite infection. I most commonly use fenbendazole at 50 mg/kg q24h PO for 3 to 5 days. However, not all parasites are sensitive to this drug (e.g., *Trichomonas* in cats) and resistance may be present in other organisms (e.g., *Giardia*). Subsequently, an exclusion diet and antibacterials should also be employed, before the use of immunosuppressive medication is considered. Some authors no longer bother with antibacterial medication, as one study suggested that it is not beneficial in canine IBD.[52]

As mentioned above, a diary record can be maintained by the owner, and used to determine success of each therapy. Where partial responses are noted to single agents, multimodality therapy can be justified. The treatment trial approach is labor intensive, but is the best way of achieving successful resolution of the clinical signs. Clients appreciate the interest shown by the clinician, and are more accepting of the advice, than when communication is poor subsequent to diagnosis.

Therapeutic Options

Intravenous Fluid Therapy

Crystalloid therapy is usually only necessary if the patient is dehydrated, but is not required for most patients. If hypoproteinemia is present, intravenous colloid therapy may be required, and options include synthetic colloids (e.g., hydroxyl-ethyl starch), and plasma transfusion. Infusions of human albumin can be considered, but this approach is controversial. First, the half-life is shorter than for synthetic colloids such as hydroxyl-ethyl starch so that any benefit may be short-lived; second, recent work has demonstrated rapid development of immune responses to the human albumin molecule, which can lead to anaphylactic reactions[53]; importantly, some dogs developed anaphylaxis even on first administration of albumin, perhaps because prior exposure had occurred (e.g., during vaccination or intradermal skin testing). Finally, because the human albumin molecule will crossreact in the serum albumin assay, this parameter cannot be used as a means of monitoring response to therapy.

Dietary Management

Most clinicians agree that dietary management is a key component in the successful treatment of IBD, and in support of this, dietary modification was recently shown to play a critical part in long-term therapy for cats with chronic GI disease,[54] and dogs with chronic enteropathy.[50] Two main approaches exist for dietary management of SI IBD: switching to a highly digestible diet or to an exclusion diet. In reality, these strategies need not be mutually exclusive because most commercial exclusion diets are also formulated to be highly digestible.

High digestibility ensures that components can be readily assimilated in the face of suboptimal digestive function. Protein should be of high biologic value. Gluten is perceived to be a common food allergen, largely because of its known association with gluten-sensitive enteropathy in Irish Setters.[55,56] As a result, most formulated diets avoid the use of gluten. However, although undoubtedly responsible for some adverse reactions to food, there is no evidence that gluten is any more antigenic to other commonly fed proteins. Fat restriction was traditionally recommended because of concerns over malabsorption, meaning that unassimilated fatty acids could be available for hydroxylation, thus stimulating electrolyte secretion. However, the need for fat restriction has recently been challenged as most cases can tolerate a higher dietary fat content, and fat restriction may exacerbate existing weight loss. Modification of the n3:n6 fatty acid ratio may also modulate the inflammatory response and have some benefit in treatment and maintenance of remission.[57,58] However, there have been no studies done to prove a benefit of such modification in canine IBD.

An exclusion diet trial should be considered in all cases of unexplained intestinal inflammation to exclude the possibility of an adverse food reaction. Most clients are willing to try this first, given concerns over the side effects of immunosuppressive drugs, but this may not be feasible in severely ill animals. The choice of diet

depends upon prior dietary exposure, and the preference of both owner and clinician, and options include home-prepared recipes or commercial single-source protein diets. Although, no GI-specific data exist to recommend one approach over the other, recent work in canine atopic dermatitis demonstrates improved efficacy of commercial rations over home-cooked rations.[59]

The main recent advance in this field has been the availability of hydrolyzed protein diets, where a native chicken or soy protein has undergone chemical or enzymatic treatment, producing low-molecular-weight protein derivatives. In theory, such diets should be less antigenic; this supposition is supported by recent work, in an experimental model of canine food-allergic skin disease, demonstrating reduced in vitro antigenicity compared with the native molecule.[59] The other major advantage of utilizing protein hydrolysates is the improved digestibility of the protein components, which may be superior to traditional single-source protein exclusion diets. Thus they are now the exclusion diet of choice for many clinicians, and a recent clinical trial was encouraging.[60]

Whichever type of diet is chosen, it must be palatable and should be introduced in gradually increasing amounts over 4 to 7 days. It is best to feed the chosen diet exclusively, and in small, frequent meals (e.g., 4 to 5 per day). Finally, parenteral nutrition is occasionally required for cases of severe, debilitating IBD.

Vitamin Supplementation

Cobalamin malabsorption is relatively common in SI IBD, especially if distal regions are involved, and this can have significant metabolic consequences, including ill-thrift and poor appetite. As mentioned previously, cobalamin deficiency is a negative prognostic sign in canine chronic enteropathy[18] and is associated with more severe feline alimentary tract disorders.[35] When hypocobalaminemia is identified, therapy is recommended. Oral administration of cobalamin is ineffective and it must be given by subcutaneous injection (e.g., 20 μg/kg q7days for 4 weeks and then the same dose q28days for a further 3 months). Serum cobalamin concentration should be rechecked a month after the last dose and should be supranormal at that time, indicating that cobalamin supplementation can be discontinued. Less commonly, folate malabsorption may accompany severe and prolonged SI IBD, and oral supplementation is easily achieved with administration of approximately 1 mg of folic acid per day. Although such therapy is well-tolerated, no published studies are available to support the therapeutic benefit of such an approach.

Antibacterial Therapy

The use of antimicrobials in IBD can partly be justified by the potential to treat any undiagnosed enteropathogens, and partly by the fact that it is bacterial antigens which are thought to drive the pathogenetic pathways. However, this approach is not universally accepted and a recent study suggests that antibacterial therapy is of limited benefit in canine IBD.[52] Metronidazole remains the preferred antibacterial for SI IBD, and it has long been suggested to have immunomodulatory properties in addition to an antimicrobial action. Tylosin also may have immunomodulatory effects and may have some efficacy in canine IBD. Although there are few studies demonstrating the efficacy of these drugs in companion animal IBD, a recent study in a rat model of IBD (colitis induced by 2,4,6-trinitrobenzene sulfonic acid) suggests that tylosin is effective at decreasing inflammation.[61] This work is particularly interesting in light of the recent report of a series of dogs with diarrhea that responded to tylosin therapy.[62] However, the relationship between this condition and the IBD syndrome is not well understood.

Immunosuppressive Drugs

Undoubtedly, the most important therapy for idiopathic IBD is immunosuppression, although this should only be considered a last resort. In human IBD, glucocorticoids and thiopurines (e.g., azathioprine, 6-mercaptopurine) are the most widely used.[63]

In dogs and cats, glucocorticoids are most frequently used for immunosuppressive therapy in SI IBD, and prednisolone (or prednisone) is the drug of choice. The standard initial dosage in dogs is 1 mg/kg PO q12h, given for 2 to 4 weeks, and then tapered slowly over the subsequent weeks to months. In most cases therapy can be only be reduced to a low maintenance dose given q48h, and in the minority of cases can be completely withdrawn. Cats are usually treated with higher doses, typically twice those of dogs (2 mg/kg q12h PO initially, then tapering).

If severe malabsorption is present, prednisolone can be administered parenterally and oral therapy instigated once signs have improved. In some cases an initial response to steroids is followed by a relapse and lack of further response even when dosages are increased. This may be either a result of transformation to lymphoma or an incorrect initial diagnosis. However, it is feasible that resistance to steroids may have developed, because of induction of the multiple-drug resistance gene and expression of P-glycoprotein.[51] Despite the widespread use of these drugs in companion animal gastroenterology, controlled clinical trials demonstrating efficacy are lacking. A recent study in dogs suggests that CIBDAI decreases upon successful treatment with steroids,[29] although neither mucosal permeability nor histopathologic abnormalities change significantly. This further supports the supposition that the condition is controlled rather than cured with such therapy.

In some dogs, high doses of conventional glucocorticoid therapy are poorly tolerated. In this circumstance, options include adding a drug to provide a "steroid-sparing" effect, or using a novel steroid with fewer side effects. Budesonide is a glucocorticoid with high first-pass metabolism, and an enteric-coated formulation of this drug has been successful in maintaining remission in human IBD. The use of this drug has been reported for canine IBD,[13] although there is no evidence to suggest it is more efficacious than prednisolone. Interestingly, both suppression of the hypothalamic–pituitary–adrenal axis and development of glucocorticoid hepatopathy have been demonstrated in dogs, but minimal systemic effects are noted.[13,64] The optimal dose has not yet been determined, although, anecdotally, a dose of 1 to 3 mg/m^2 q24h PO has been used. A delayed-release formulation is most often used, but the main concern in SI IBD is that the drug may not become active until after it reaches the large intestine. Further work is required before clinicians can be confident in the use of this drug.

Azathioprine at 2 mg/kg PO q24h is commonly used in dogs in combination with prednisolone/prednisone when the initial response to steroid therapy is poor or side effects are marked. However, its activity may show a delayed onset (up to 3 weeks) and, given its myelosuppressive potential, regular hematologic monitoring is necessary. Azathioprine is not recommended for cats, largely because cats have very low activities of thiopurine methyltransferase (TPMT), the major enzyme involved in the degradation of 6-mercaptopurine (6-MP), the active metabolite of azathioprine. Chlorambucil (2 to 6 mg/m^2 PO q24h until remission, then tapering) is a better choice of a cytotoxic immunosuppressive agent in cats. A combination of prednisolone and chlorambucil can also be effective for alimentary lymphoma in cats, and is particularly suitable for use when differentiation of severe IBD from lymphoma has been problematic.

Cyclosporine binds to the cytosolic protein cyclophilin (immunophilin) of immunocompetent lymphocytes (especially T

lymphocytes); the resulting complex then inhibits calcineurin, which itself is responsible for activating interleukin-2 transcription, thereby leading to a reduced function of effector T cells. As a result, it has been proven to be useful as an immunomodulator in human gastroenterology.[65] Efficacy has been demonstrated in immune-mediated conditions such as anal furunculosis and atopic dermatitis. A recent uncontrolled study also shows that cyclosporine (5 mg/kg q24h PO) may be effective in IBD, which is refractory to steroid therapy.[66] Most dogs achieved either complete or partial remission, and response correlated with reductions in both CIBDAI and mucosal T-lymphocyte numbers; however, no change in histopathology score was noted. The favorable response came at a cost, with side effects (including vomiting, gingival ulceration, alopecia) occurring in almost half of the dogs.

This drug is most commonly used in refractory cases of IBD, when other immunosuppressive therapy has failed, but widespread use may be limited by cost of therapy. Furthermore, given the marked immunosuppressive effect, it is vital that all possible infectious etiologies have first been eliminated; thus the drug should be used with caution in areas where fungal infections are endemic, and it may be prudent to screen for occult infectious diseases (e.g., *Toxoplasma*, feline leukemia virus [FeLV], and feline immunodeficiency virus in cats), prior to instigating therapy.

Other immunosuppressive cytotoxic drugs include methotrexate and cyclophosphamide. Methotrexate is effective in the treatment of human Crohn disease,[67] but it is not widely used in companion animals. A single case report has reported a response of severe IBD, with concurrent hypoproteinemia and lymphangiectasia, to methotrexate after a combination of prednisolone and cyclosporine were ineffective.[68] This observation should be confirmed with larger case series and, preferably, evidence-based medicine before the routine use of this drug is recommended. Cyclophosphamide has few advantages over azathioprine and is rarely used.

Mycophenolate mofetil has been used to treat human IBD, although its efficacy is variable.[69] Its use is reported for the treatment of canine myasthenia gravis,[70] but to my knowledge there are no published studies on its use for SI IBD in dogs or cats. Drugs that target TNF-α (e.g., thalidomide, oxpentifylline) are used in human IBD, but have not been used in dogs. Anti–TNF-α monoclonal antibody therapy is also beneficial in human IBD, but will only be suitable for canine and feline IBD if species-specific monoclonal antibodies are developed for therapeutic use.[71-73]

Prebiotics and Probiotics

Modulation of the enteric flora with probiotics or prebiotics included in the food may have benefits in IBD. Nondigestible carbohydrates, such as lactulose, inulin, fructooligosaccharides, and mannanoligosaccharides are the most frequently used prebiotics. However, there is little evidence that they modify the bacterial flora of the SI.[73] These agents are frequently incorporated in diets formulated for therapy of SI IBD. Probiotics can directly antagonize pathogenic bacteria, but they also modulate mucosal immune responses. Probiotics are suggested to be beneficial for human IBD,[74] although no truly objective data (e.g., double-blind placebo-controlled trials) exist, despite promising initial reports. More work is required before probiotic use becomes commonplace in companion animal IBD therapy.

Miscellaneous Therapies

Diuretics may reduce ascites: spironolactone at 1 to 2 mg/kg PO BID may be more effective than furosemide for treating ascites. Thromboembolism is a feature of some patients with PLE, and prophylactic low-dose aspirin at 0.5 mg/kg BID has been advocated in PLE. Some dogs with SI IBD present with severe microcytic anemia[31] and these may require intravenous blood replacement (whole blood or packed red cells). Furthermore, oral ferrous sulfate (at 200 mg/dog) may be required for a prolonged period (often months).

Predicting Response to Therapy

Some studies have examined ways of predicting response to future therapy. For example, high mucosal pANCA expression prior to treatment correlates with response to dietary therapy, while those that did not respond (and required glucocorticoids) had lower levels of expression.[50] P-glycoprotein is a transmembrane protein that functions as a drug-efflux pump in the intestinal epithelium. In human IBD, high lymphocyte P-glycoprotein expression is seen in patients who fail to respond to treatment with steroids. Recent work in canine IBD demonstrates that low pretreatment mucosal lymphocyte P-glycoprotein expression correlates with a favorable response to treatment.[51] The lowest levels of expression were found in dogs that responded to a dietary trial, moderate levels in steroid-responders, and the highest levels in those that responded neither to steroid nor diet. However, the main limitation of this assay is the necessity for repeat endoscopy to monitor cases, given that many owners may be reluctant to allow their pet to undergo such procedures.

Prognosis and Prognostic Indicators

A recent study examining prognosis in canine IBD suggests that success of therapy is variable.[26] Although many cases initially responded, only a quarter achieved complete remission; intermittent signs remained in a further half of the dogs, while response was poor in the remaining cases and many were euthanized. One negative prognostic indicator was hypoalbuminemia, a finding recently confirmed in another study, which also identified hypocobalaminemia as a negative risk factor.[18] A high disease activity index (e.g., CIBDAI, CCEAI) and a high endoscopic score were also identified as risk factors for a poor outcome in this study.

Other potential markers for IBD prognosis include serum acute-phase proteins, such as C-reactive protein; in one study, C-reactive protein was found to decline upon successful therapy[17]; however, this acute-phase protein did not correlate with outcome in two more recent studies.[18,19] Furthermore, histopathologic scoring of biopsies, prior to and after therapy, does not correlate with outcome,[18,28] although this study was conducted prior to the release of the histologic scoring scheme.[2] Mucosal pANCA expression recently was shown to be increased (prior to therapy) in cases that ultimately respond to dietary management, and expression of this marker increases posttherapy in steroid-responsive cases. Finally, low pretreatment mucosal lymphocyte P-glycoprotein expression was recently shown to predict a favorable response to therapy, and could also be of use in determining which treatments (diet or steroids were most suitable).[51]

MALABSORPTION

Michael D. Willard

Etiology

Malabsorption

Malabsorption generally connotes chronic small intestinal disease that may have one or more underlying pathophysiologic

mechanisms.[1] Malabsorption is usually, but not always, associated with diarrhea. Common causes of malabsorption include dietary-responsive disease (e.g., allergy and intolerance; see Chapter 31), antibiotic-responsive diarrhea (also referred to as SIBO and "dysbiosis"; see other sections in this chapter, Infection, Neoplasia, and IBD).

Protein-Losing Enteropathy

PLE is associated most importantly with lymphangiectasia (dogs only), lymphoma, parasites, fungal infections, ulceration/erosion, intussusception, and IBD,[2] but dietary-responsive disease and antibiotic-responsive disease may also be responsible.

Short Bowel Syndrome

Short bowel syndrome (SBS) occurs when a patient has a large resection of the SI.[3] It is almost always an iatrogenic phenomenon, and is typically caused by overly aggressive small intestinal resection as a result of diffuse malignancy, linear foreign bodies, multiple perforations, and adhesions caused by peritonitis.

Pathophysiology

Malabsorption

Malabsorption may result from reductions in absorptive surface area (e.g., villus atrophy and villus fusion), damage to enterocytes (e.g., bacterial infection), and intestinal mucosal infiltration (e.g., inflammatory or neoplastic cells).[1] Multiple pathophysiologic mechanisms may be operative in an individual patient. Villus atrophy is caused by loss of enterocytes, decreased precursors in intestinal crypts, infiltrative disease causing villus fusion, and mechanical destruction of the absorptive surface area (e.g., massive gastric acid emptying into the intestine with gastrinoma). Enterocytes can be damaged by bacteria (e.g., damage to the microvillar membrane) or can be immature and poorly functional as a result of accelerated turnover. Infiltrates of the mucosa can affect mucosal permeability, villus structure and function, and lymphatic flow; therefore the host's immune system may be integral to the ultimate severity of the intestinal lesion. Intestinal pathology from any number of causes might allow otherwise normal luminal bacteria to proliferate or persist, in turn causing worsening of enterocyte damage and/or more mucosal inflammation. Finally, animals severely malnourished and protein-deficient from the intestinal disease may have a more difficult time repairing intestinal damage. In this way malabsorptive disease may become self-perpetuating.

Dietary antigens can cause immune (types I and IV hypersensitivity) as well as non–immune-mediated (i.e., intolerance) reactions in the intestinal mucosa (see Chapter 31).

Intraluminal bacteria (discussed in more detail in Chapters 2 and in other sections of this chapter, e.g., "Infection") can elicit inflammatory responses in the intestinal mucosa, and bacterial toxins and metabolic by-products can damage enterocytes through various mechanisms such as deconjugated bile acids, alcohols, and hydroxylated fatty acids. Antibiotic-responsive disease is generally caused by nonpathogenic bacteria, hence specific toxins (as are seen with certain *E. coli* or *Campylobacter* infection) are not usually considered important.

Parasites (e.g., *Giardia*) can have direct cidal effects on enterocytes.

IBD is a syndrome in which intestinal mucosal inflammation becomes self-sustaining and recurrent (see Chapters 3, 56, and 59). Dietary and bacterial antigens play an important role in disease pathogenesis. The mechanisms are speculative, but it is believed that these antigens gain access to the mucosa, perhaps as a result of increased mucosal permeability, and then either an aberrant immune response or a constant ingress of antigens maintains the inflammatory response. Cats might have a greater incidence of IBD, which might be partially explained by their strong inflammatory response to exogenous antigens.

Protein-Losing Enteropathy

PLE occurs when serum proteins are lost into the GI tract. There are three basic mechanisms for protein loss: lymphatic obstruction or rupture, increased mucosal permeability because of mucosal infiltrates (e.g., inflammatory and neoplastic), and mechanical causes (e.g., ulcers, erosions, and congestion).[2,4]

Lymphangiectasia affects dogs only and is usually caused by lymphatic obstruction, either anatomic or physiologic.[5] Lacteals in the villi dilate as they absorb lipid and lipoprotein until they finally rupture, releasing protein and lipid back into the intestinal lumen. The severity of PLE depends mostly upon the distribution of this lesion. If only a small portion of the intestine is affected, protein loss may be offset by the ability of the healthy intestine to digest and absorb proteins and lipids, as well as the liver's ability to produce more albumin. Some PLE patients may have normal serum albumin concentrations if the obstructive process is of short duration and limited distribution but, PLE is seldom diagnosed until the discovery of hypoalbuminemia causes the clinician to look for a reason.

Lipogranulomas in the intestinal wall or mesentery (Figure 57-15) develop as a consequence of lymphatic leakage and further complicate the disorder. As lipogranulomas enlarge and coalesce, they alter tissue compliance and contribute to the obstructive lymphatic process. Some dogs with lymphangiectasia and severe hypoalbuminemia have minimal mucosal inflammation except perhaps for a few inflammatory cells around areas of lymphatic leakage or some macrophages attempting to eliminate the chyle.[2]

Inflammatory conditions (e.g., IBD, histoplasmosis) and some neoplasia (e.g., lymphoma) seemingly cause PLE because inflammatory and neoplastic cell infiltrates alter vascular and mucosal permeability, thereby permitting serum proteins and red blood cells to leak from the mucosa. *Parasites* (hookworms, whipworms) and ulcers/erosions cause mucosal bleeding that produces the PLE. Congestion in the tip of an intussusceptum can cause serum exudation and hypoalbuminemia.

Short Bowel Syndrome

Massive small bowel resection, nutrient malabsorption, and protein-calorie malnutrition define SBS.[3] There is no precision in the amount of small bowel resection that must take place before the development of SBS. Some patients tolerate large resections with minimal complication, whereas others have significant complications following lesser amounts of resection.[6] Development of SBS is influenced by the patient's preoperative nutritional status as well as postoperative pathophysiology. For example, following resection, gastric acid may cause chemical injury to the remaining unbuffered SI. Moreover, the remaining small bowel often assumes a bacterial flora more typical of the large bowel. This problem is further exacerbated with resections of the ileocolic sphincter.

Clinical Examination

Malabsorption

Weight loss or loss of body condition, small bowel-type diarrhea, and polyphagia are the primary clinical signs of malabsorptive

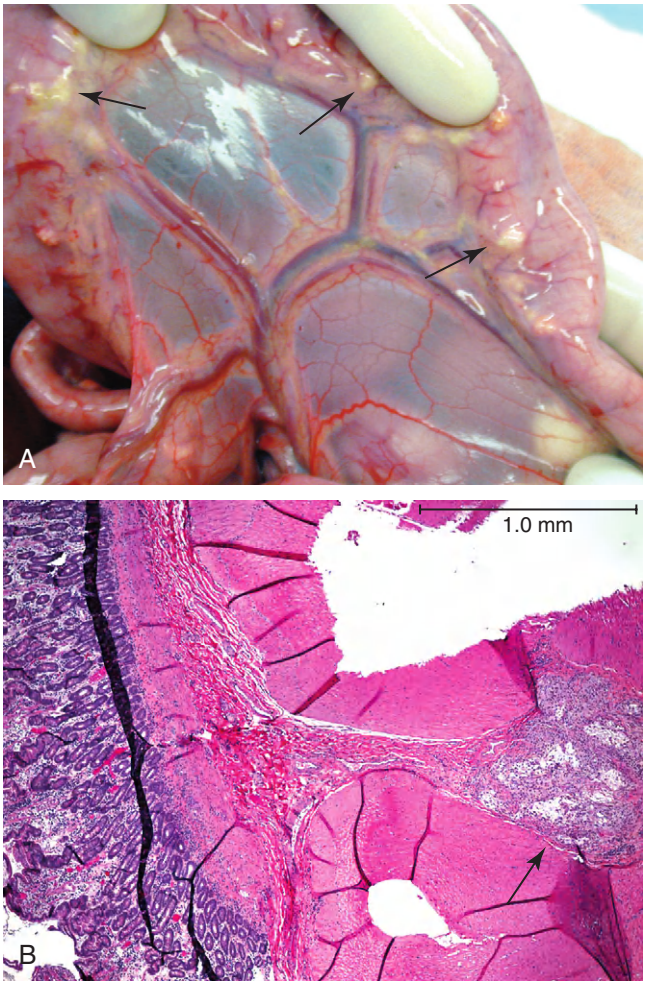

Figure 57-15 **A,** A gross picture taken at surgery of a dog with lymphangiectasia that had severe lipogranulomas (*arrows*) at the mesenteric border. **B,** A photomicrograph of an intestinal biopsy from the tissues seen in **(A).** Note the large lipogranuloma in the tunica muscularis (*arrow*).

disease, although this triad is not uniformly present in all SBS patients. Diarrhea is defined as an increase in the liquidity, frequency, or volume of feces. The colon has an abundant reserve capacity to absorb water (see Chapter 1); therefore the feces may appear "normal" to the pet owner despite severe small bowel disease. Instead these patients will have a voluminous fecal output as a result of intestinal malabsorption. If accelerated transit and hypersecretion make the patient nauseous, it may have a poor appetite instead of polyphagia.[1] The vestigial SI may seem normal or thickened on abdominal palpation. Some patients with dietary allergies also will have cutaneous manifestations consistent with allergy.

Clinical pathology testing is often not very informative, except for hypoalbuminemia, hypocholesterolemia, and hypocobalaminemia. Changes in cobalamin (vitamin B_{12}) metabolism are very specific for distal small intestinal disease, but it is a fairly insensitive biomarker; many animals with severe small intestinal disease have normal serum cobalamin concentrations.[7] Imaging of the gut is also insensitive. Ultrasonographic determination of small intestinal thickness has not been shown to clearly correlate with disease[8]; however, changes in small intestinal layering may reflect infiltrative disease. Mild to moderate mesenteric lymphadenopathy may be seen in patients with nonneoplastic disease.

Protein-Losing Enteropathy

Diarrhea as a clinical sign is inconsistently reported in many PLE patients. Intestinal lymphangiectasia patients in particular often have normal-appearing feces.[2] Ascites (low-protein transudate) and/or peripheral edema may be the only historic or physical examination findings, especially in lymphangiectasia patients. Weight loss is common but may be "hidden" by the ascites, unappreciated until palpation reveals boney prominences across the body. Two breeds at risk for PLE are the soft-coated Wheaton Terrier[9] (Wheaton Terriers may have concurrent PLN) and the Norwegian Lundehund.[10] Yorkshire Terriers have an increased risk for PLE, based upon data reported from one institution.[11,12] Chinese Shar-Pei and Basenji dogs are prone to severe IBD with concurrent PLE.[2]

Hypoalbuminemia is the key clinicopathologic finding in PLE. Panhypoproteinemia is "classic" but not invariable.[2] Patients who hyperglobulinemic prior to developing PLE (e.g., chronic inflammation caused by rickettsial, fungal, cutaneous, or heartworm infection) may lose most of their serum proteins but still have normal serum globulin concentrations. Lymphopenia sometimes occurs if the intestinal lymphatics are involved in the disease process. Hypocholesterolemia is common and expected, but is also seen in hepatic insufficiency. Hypocholesterolemia is not typically seen in PLNs (which sometimes helps distinguish between these causes). Hypocalcemia is common finding,[5] and would appear to be secondary to hypoalbuminemia in many patients, but suppression of parathyroid function[11,12] and/or decreased vitamin D[13] may be responsible in others. The hypocalcemia is seldom associated with tetany. It is more clinically useful to measure ionized serum calcium as opposed to total serum calcium. Hypomagnesemia often occurs in severe PLE and may contribute to hypocalcemia by affecting parathyroid function.[11,12] Fecal α_1-PI concentrations are generally increased in this patient population.[14] Ultrasound sometimes reveals "streaking" within the mucosa, presumably associated with the dilated lymphatics in lymphangiectasia.[15]

A thickened segment of bowel is palpated in many patients with GI intussusception, although this can be easily missed if the intussusception takes place at the root of the mesentery. Young dogs with a recent history of enteritis (e.g., parvoviral, parasitic) from which they should have recovered, but which continue to have diarrhea, is suggestive of the disorder. Finding hypoalbuminemia in these same patients strongly suggests parasites or intussusception. Abdominal ultrasound is the best way to noninvasively detect intussusceptions.

Short Bowel Syndrome

These patients have had a recent, massive, intestinal resection and are typically losing weight (or are already emaciated) with severe, profuse diarrhea.[3]

Diagnosis

Malabsorption

Malabsorptive disease is presumptively diagnosed from history, physical examination findings, clinical pathology data, and by eliminating other causes of disease (e.g., feline hyperthyroidism, hepatic insufficiency).[1] Finding small intestinal histopathology with an appropriate history and physical examination findings is confirmatory, but not all small intestinal malabsorptive diseases have concurrent histologic changes. In particular, dogs with antibiotic-responsive enteropathy or dietary-responsive disease may have minimal to no discernible histologic change in the SI. Therapeutic trials are often

the best way to diagnose these last two diseases. For most other disorders (e.g., IBD, intestinal lymphoma), biopsy is necessary.

Protein-Losing Enteropathy

PLE is often a diagnosis of exclusion.[2] Patients typically have serum albumin ≤2.0 g/dL, and other causes of hypoalbuminemia must be eliminated. PLN and hepatic insufficiency are the two major differentials for this finding. Anorexia and weight loss are inadequate explanations for a serum albumin this low. Urinalysis/urine protein-to-creatinine ratio and hepatic function tests (e.g., serum bile acid concentrations) are typically needed to eliminate these syndrome. Serum blood urea nitrogen and creatinine concentrations, ALT activity, and bilirubin concentrations will be inadequate for this purpose. It should be reemphasized that some dogs with PLE will not have diarrhea, at least as defined by an increase in the liquidity of feces.

It should also be recognized that patients with PLN or hepatic insufficiency can have concurrent PLE. If a patient with modest urinary protein loss has concurrent diarrhea and a serum albumin of 1.5 g/dL, the urinary protein is likely inadequate to explain the magnitude of the hypoalbuminemia. Such patients may require measurement of fecal α_1-PI concentrations for a definitive diagnosis.[14] This test is available through the GI laboratory at Texas A&M University. The test has many difficulties in the collection and storage of feces, making it critical to consult the laboratory before beginning the study.

In parasite-rich environments, one cannot eliminate parasitism because of one negative fecal examination. Adult animals can die of prepatent hookworm infections, and whipworm ova are often difficult to detect. Ultrasonographic imaging may be indispensable in the detection of neoplastic masses, inflammatory infiltrates (which might permit diagnosis by fine-needle aspiration), and intussusceptions. Ultrasound findings also may aid the clinician in deciding whether to do endoscopic or full-thickness intestinal biopsies. Intestinal biopsy is often crucial because there are numerous causes of PLE, and histopathology is often the only way to distinguish between the various causes.

There is considerable debate about endoscopic versus full-thickness biopsy (see Chapter 27). Advantages of endoscopy include its ease, noninvasive nature, ability to detect mucosal lesions allowing one to direct the biopsy to those areas, and ability to take multiple samples from one area.[16] The major disadvantages of endoscopy are that it does not allow access to the mid-jejunum, and nondiagnostic tissue samples may be obtained if the operator was not trained properly. Superficial samples (e.g., villus tips only) or compressed lacteals (Figure 57-16) may be obtained with all too vigorous handling of the endoscopic biopsy forceps. Surgery and laparoscopy provide ready access to the mid-jejunum (which endoscopy seldom can reach) and facilitate tissue sampling that will detect submucosal lesions. Surgery also permits biopsy of mesenteric lymph nodes. Surgical and laparoscopic biopsy are more invasive, have greater risk for morbidity and mortality from dehiscence,[17] are more expensive, do not reliably detect mucosal lesions (which means you may have biopsied the wrong site), do not guarantee a diagnosis, and generally require removal of ascites. The latter intervention has the possibility of lowering body albumin content further still, making it all the easier for ascites to quickly reform. Furthermore, untrained individuals can easily take nondiagnostic full-thickness biopsies.

It is important to be able to reliably diagnose lymphangiectasia. It may be more common than generally realized and yet can be particularly difficult to diagnose. Endoscopy allows strong presumptive diagnosis when erratic, grossly enlarged lacteals are observed (Figure 57-17).[2,4] I typically feed a small amount of a very-high-fat diet to the patient the night before the procedure to help ensure that lacteals will be filled, hopefully augmenting diagnosis.[18] Lymphangiectasia can affect the entirety of the GI tract, but more often than not is localized to one segment of the SI (which can

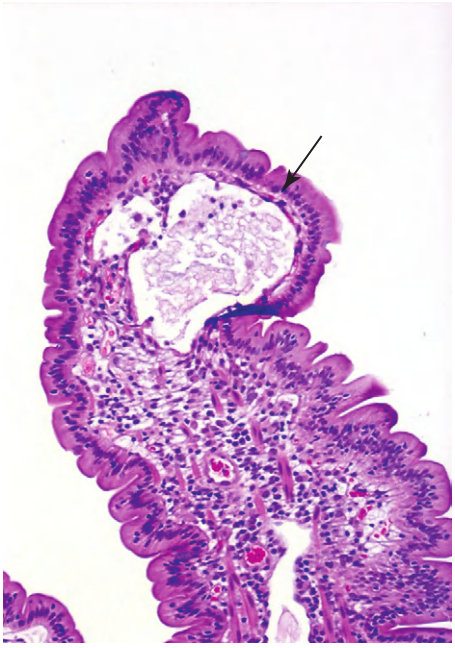

Figure 57-16 A photomicrograph of a villi with lymphangiectasia. Note how the lacteal has engorged so much that now only the epithelium (*arrow*) is holding the chyle in the lacteal. This lacteal is about to rupture and release its contents into the intestinal lumen. It would be very easy to rupture this relatively fragile "balloon" if it were compressed, as might likely happen when using endoscopic biopsy forceps.

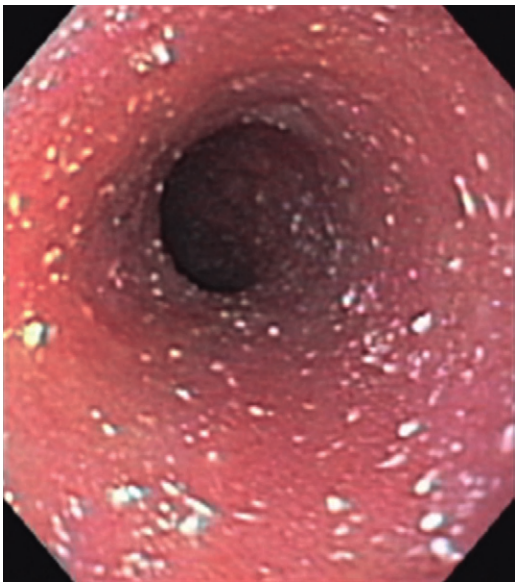

Figure 57-17 An endoscopic view of the duodenum of a dog with lymphangiectasia. The large, white spots are dilated lacteals. This dog has lymphangiectasia. Note that if a full-thickness biopsy was obtained, the likelihood of diagnosis could depend upon where the biopsy was performed, as the lesions are not uniform throughout the mucosa.

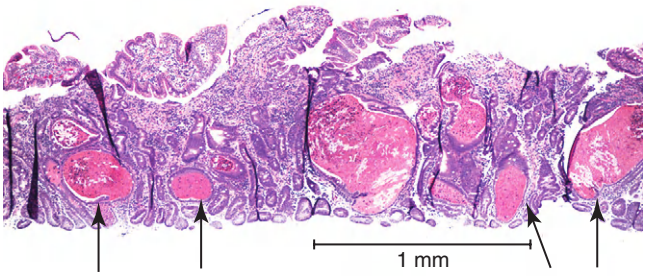

Figure 57-18 A photomicrograph of intestines from a dog with PLE. Note the crypts that are engorged and dilated with pink, proteinaceous material (*arrows*).

sometimes be ascertained by ultrasound). Sometimes an obvious white fluid is released as biopsies are taken, which is chyle being released from lacteals that are ruptured during the biopsy process.[2] There are at least two significant problems with histologic diagnosis of lymphangiectasia. First, the lesions may be localized to one section of the gut (e.g., lymphangiectasia is found in the ileum but not the duodenum). Second, lesions may be relatively localized to the deeper layers of the intestine (e.g., the border between the mucosa and the submucosa) and can only be found with full-thickness biopsies. The extent of these problems is unknown.

Intestinal crypt lesions have been reported in association with PLE (Figure 57-18).[19,20] It is not known whether this lesion is disease specific or associated with several disease entities. The need to identify lesions such as these illustrates the importance of obtaining the entire thickness of intestinal mucosa and not just the villus tips.

Some patients with severe PLE do not have discernible histologic lesions nor do they have strongly suggestive ultrasonographic or endoscopic abnormalities. In these situations, there appear to be at least two main possibilities. First, the patient may have lymphangiectasia at a site not biopsied or observed. Second, the patient may have PLE as a consequence of a disease that does not always cause severe histologic mucosal changes, such as antibiotic-responsive enteropathy or food-responsive diarrhea.

In certain cases (e.g., client monetary constraints, inability to find a histologic lesion), a rapid increase in the serum albumin concentration after the initiation of an ultralow-fat diet is suggestive of lymphangiectasia. Likewise, an increase in serum albumin after initiating antibiotic therapy or dietary therapy suggests antibiotic-responsive disease or dietary-responsive disease, respectively. It is generally preferable to do intestinal biopsy in patients with severe PLE as opposed to observing the response to therapeutic trial; however therapeutic trials are clearly necessary in some patients.

Extra-GI disease (e.g., hypoadrenocorticism, cardiac disease,[21] pulmonary disease[22]) may be associated with PLE. Hypoadrenocorticism may be suspected because of the classic electrolyte changes or lack of a stress leukogram, or because all other causes have seemingly been eliminated.

Short Bowel Syndrome

SBS is diagnosed based upon history and physical examination, as defined for example.

Treatment

Malabsorption

Successful treatment of malabsorptive disease requires that the underlying cause be determined. The reader is referred to other sections of this chapter, e.g., "Antibiotic-Responsive Diarrhea," "Dietary Responsive Disease," "IBD," "Parasitism," and "Neoplasia."

Protein-Losing Enteropathy

Treatment of PLE requires that the underlying cause (see appropriate sections in this chapter, e.g., "IBD," "Lymphoma," "Parasites," "Ulcers," "Fungal Infections," "Antibiotic Responsive Enteritis," and "Dietary Responsive Diarrhea") be resolved. Intussusception is treated by resection and anastomosis.

In general, patients with PLE do not benefit substantially from IV administration of plasma unless very large amounts are given. Even then, the subsequent rise in serum albumin tends to be transient because the administered albumin is all too quickly lost from the body. Generally ascites should not be removed unless it is causing a substantial problem (e.g., diaphragmatic compression and dyspnea). Removing ascites removes albumin as well as fluid, which ultimately lowers the total body albumin concentration, making it easier for ascites to reform. To lessen ascites, one may administer hetastarch IV (10 to 20 mL/kg), which hopefully stays in the intravascular compartment longer than albumin because of its size, thereby drawing third space fluid into the intravascular compartment. Although one may administer furosemide (2 to 4 mg/kg BID-TID) to lessen ascites, it is best to administer moderate doses. Massive doses of diuretics can deplete the intravascular compartment and cause hypovolemia. In emergency situations (e.g., severe dyspnea as a consequence of pressure on the diaphragm), an abdominocentesis can be performed but only to remove sufficient fluid to alleviate the dyspnea. Patients should be monitored for hypomagnesemia, which can complicate cases and worsen hypocalcemia. If magnesium supplementation is necessary, a continuous rate infusion of $MgSO_4$ in 5% dextrose in water (35 to 50 mg/kg/day) is preferred. Orally administered magnesium tends to act as a laxative.

Lymphangiectasia is primarily treated by feeding an ultra-low-fat diet to minimize lacteal dilation and rupture.[2] Historically, medium-chain triglyceride oil was supplemented to the diet to provide calories without causing lacteal dilation. Most ultra-low-fat diets were high in fiber and lacking in calories; hence, the supplementation. High fiber concentrations are not optimal because the patient often needs caloric support. If an ultra-low-fat diet without a lot of fiber is fed, medium-chain triglyceride oil is unnecessary (which is fortunate because the oils are expensive and not very palatable).

Antiinflammatory and/or cytotoxic drugs help some patients, possibly because they minimize or eliminate intestinal and mesenteric lipogranulomas. Glucocorticoids (at a dose of 1 to 2 mg prednisolone/kg/day) can help but have several important side effects, including fluid retention. Azathioprine (2.2 mg/kg once daily or every other day) or cyclosporine (3 to 5 mg/kg BID; adjust dose based upon therapeutic drug monitoring) appears to be useful in some cases. Monitoring the serum albumin concentration and body weight are probably the best way to monitoring the patient's response to therapy. Substantial improvement of the serum albumin concentration implies that therapeutic progress is occurring, even if diarrhea persists.

Short Bowel Syndrome

SBS is best treated by preventing it. Aggressive intestinal resections should be avoided, even if it requires second exploratory

laparotomies a few days later to ensure that additional resection is unnecessary. Many intestinal resections resulting in SBS are unnecessarily aggressive. Once SBS has occurred, it is important to aggressively treat the animal with total parenteral and enteral nutrition (e.g., elemental diets). Decreasing gastric hyperacidity with H_2-receptor antagonists (famotidine 0.5 mg/kg) or proton pump inhibitors (omeprazole 0.7 to 1.5 mg/kg daily) and suppressing the proliferation of the intestinal microflora (oral broad-spectrum antibiotics) are important components of therapy.[3] The patient should receive parenteral nutrition until it is able to maintain itself on oral nutrition, which usually means multiple, small feedings of highly digestible diets, sometimes including monomeric or polymeric elemental diets. Some SBS patients may need supplementation with vitamin B_{12} (cobalamin) and the fat-soluble vitamins (A, D, E, and K). Treatment with ursodeoxycholate improves the nutritional status of dogs with experimentally induced SBS.[23]

Prognosis

The prognosis for the various nonneoplastic causes of malabsorption and PLE is usually good, assuming that the underlying cause is accurately diagnosed, the patient is seen before the disease is too far advanced, and the client can afford treatment. There are some exceptions. Intestinal lymphangiectasia that has marked lipogranuloma development within the walls of the intestines appears to be more difficult to treat. Pythiosis has a very poor prognosis if it cannot be surgically excised. Histoplasmosis usually responds to antifungal therapy, but very advanced cases may be difficult to salvage because of the marked fungal burden in the body. Diffuse intestinal lymphoma in dogs is more difficult to manage than multicentric lymphoma. Feline intestinal lymphoma may respond well to treatment, if it is well differentiated.

INFECTION

Michael R. Lappin

Helminths

Hookworms

Etiology

Ancylostoma caninum, *Ancylostoma braziliense*, and *Uncinaria stenocephala* are common hookworm infections in dogs. Cats are commonly infected by *Ancylostoma tubaeforme* and *A. braziliense*, but rarely by *U. stenocephala*. *A. caninum* and *A. tubaeforme* are found most frequently in tropical and subtropical areas; *A. braziliense* in warm coastal areas, Central and South America; and *U. stenocephala* in cooler areas like the northern United States, Canada, and Europe. Prevalence rates of hookworm infection have changed over the years.[1-5] In one large study of 1,213,061 dogs examined at 547 private veterinary hospitals in 44 states of the United States, 4.5% of samples contained eggs of *Ancylostoma* spp.[1] In high-risk areas and animals, infection rates can be much higher. For example, in one study in Florida *A. tubaeforme* and *A. braziliense* were found in feces of 75% and 33% of tested cats, respectively.[5]

Pathophysiology

Adult hookworms live in the SI and discharge eggs into the environment in the feces. The eggs develop into infective third-stage larvae in approximately 2 to 9 days depending upon environmental conditions. Dogs are infected by ingestion of larvae in the environment, skin penetration, ingestion of larvae during nursing, or ingestion of infected paratenic hosts (usually rodents). Cats are infected similarly but do not have transmammary infection. After transmammary infection in dogs, cutaneous infection, and ingestion of larvae, some larvae migrate to the lungs via the systemic circulation and molt to fourth-stage larvae in the bronchi and trachea. The larvae are then coughed up, swallowed, and develop into adults in the SI. Some larvae invade muscle tissue where they undergo arrested development (hypobiosis) and can be maintained for months to years. Upon reactivation, during stressful events like pregnancy, these larvae resume migration and reenter the intestine or concentrate in the mammary tissues of dogs and infect subsequent litters. Ingestion of infected paratenic hosts leads only to intestinal infections in dogs or cats. Puppies infected with *A. caninum* by nursing can shed eggs as soon as 10 days after birth. The prepatent periods for *A. braziliense*, and *U. stenocephala* are 13 to 27 days. The prepatent period for *A. tubaeforme* is approximately 3 weeks after ingestion and 3 to 4 weeks after transcutaneous infection.

The primary pathogenic mechanism of disease associated with hookworms is blood loss, which can start approximately 8 days postinfection, prior to shedding of eggs. To potentiate blood ingestion, hookworms release enzymes that cause local tissue necrosis as well as anticoagulants and hookworm platelet inhibitor.[6] Hookworm feeding and reattachment causes small ulcerative areas in the intestine. Blunting of the microvillar membrane and eosinophilic infiltrates may result in malabsorption and diarrhea. Heavily infected dogs and cats can develop cough and pneumonia from lung migration, and transcutaneous infection can result in local skin disease.

Clinical Examination

Heavy infections can result in life-threatening blood loss with the clinical findings of pale mucous membranes, weakness, lethargy, and elevated heart and respiratory rates, particularly if concurrent *Ctenocephalides* spp. infestation is present. Chronic infection can lead to iron-deficiency anemia in puppies. Other clinical signs observed in young animals include small bowel diarrhea with melena and failure to thrive. Hookworm infections may induce weight loss, poor hair coat, loss of appetite, and pica. Adult dogs and cats are less likely to have clinical signs of disease; however, hookworm infection may result in eosinophilic IBD or potentiate other intestinal diseases. Cough and dyspnea can occur from heavy pulmonary infections. When skin lesions occur, they are most common in the interdigital spaces of affected animals and are characterized by pruritus, erythema, and papules.

Diagnosis

The diagnosis of hookworm infection is confirmed by microscopic visualization of eggs in feces after fecal flotation. Centrifugation techniques are more sensitive than passive flotation.[7] Hookworms can produce significant intestinal pathology prior to the shedding of eggs and so fecal flotation can be falsely negative. Adult worms can be visualized in feces and in the intestinal lumen.

Treatment

Anthelmintic drugs to treat the intestinal stages and supportive care as needed are used in the management of hookworm infected dogs or cats (Table 57-4; see Chapter 37). There are no drugs available that can eliminate larvae from the tissues however. Some heavily infected dogs and cats may require blood transfusion and iron

Table 57-4 Drugs Approved for the Treatment of Hookworm Infections of Dogs and Cats

Animal	Approved Drugs
Dogs	
Adult *Ancylostoma caninum*	Fenbendazole, milbemycin oxime, moxidectin, pyrantel pamoate
Adult *Uncinaria stenocephala*	Fenbendazole, pyrantel pamoate, moxidectin
Adult *Ancylostoma braziliense*	Pyrantel pamoate
Fourth-stage and young adult *A. caninum* and *U. stenocephala*	Moxidectin
Cats	
Adult Ancylostoma tubaeforme	Emodepside, ivermectin, milbemycin oxime, moxidectin, pyrantel, selamectin
Fourth-stage and immature adult *A. tubaeforme*	Emodepside, moxidectin

supplementation is needed in some cases with chronic iron deficiency.

Prevention

If the risk of hookworm infection is high, all puppies and kittens (and their mothers) should be treated with appropriate anthelmintics at 2, 4, 6, and 8 weeks of age (see Chapter 37). In addition, the Companion Animal Parasite Council (CAPC) recommends that all puppies and kittens should be prescribed monthly preventives as soon as label recommendations allow and that administration be continued year round (www.capcvet.org). If puppies and kittens are not evaluated until 6 to 8 weeks of age or later, CAPC recommends the administration of a monthly preventive according to label recommendations from that point forward with administration of an anthelmintic 2 weeks later. If heavy hookworm infections have occurred in dogs, fenbendazole can be administered to pregnant bitches from the fortieth day of gestation through the fourteenth day of lactation. Kennel floors and runs should consist of tarmac or concrete, be free of crevices, and be kept as clean and dry as possible. Bedding in kennels and free feces in the environment should be removed daily to lessen larval contamination. CAPC recommends fecal examinations two to four times in the first year and one to two times per year thereafter, depending on the age of the animal and its prior history of infection to assess efficacy of the initial treatments, efficacy of the monthly control product, and client compliance.

Public Health Considerations

Cutaneous larva migrans is the most common syndrome in people associated with dog and cat hookworms.[8] This syndrome results when hookworm larvae penetrate human skin at the point of contact and migrate just beneath the skin. Self-limited, serpentine lesions that are very pruritic can occur; these lesions are usually more severe following infection by *A. braziliense*. Deeper tissue penetration can occur in some people leading to muscle pain, lung disease, abdominal pain syndrome, and eosinophilic enteritis.[9,10]

Prognosis

The prognosis for hookworm infections in dogs and cats is good to excellent.

Roundworms

Etiology

The significant roundworms (ascarids) of dogs or cats include *Baylisascaris procyonis* (raccoons and occasionally dogs), *Toxascaris leonina* (dogs or cats), *Toxocara canis* (dogs), and *Toxocara cati*. *B. procyonis* resides in the SI of the raccoon in North America and Europe, with higher prevalence in northeast, midwest, and west coast U.S. states. Prevalence of *B. procyonis* can be very high; the organism was detected in 12.7% of 188 raccoons in a recent study in Tennessee.[11] Dogs occasionally are infected by *B. procyonis* and the life cycle can be completed in the canine host. *Toxocara* spp. and *T. leonina* have worldwide distribution. Prevalence rates vary by the study, region, and age of animals tested with puppies and kittens more likely to have patent infections. For example, the overall prevalence rate for ascarid infections in cats was 2.92% in one study.[2] In other studies, *T. cati* was detected in 33% of kittens,[12] 21% of feral cats, and 18% of pet cats.[13] In one large study of 1,213,061 dogs examined at 547 private veterinary hospitals in 44 states of the United States, 5.04% of samples contained eggs of *T. canis*.[1]

Pathophysiology

B. procyonis, *Toxocara* spp., and *T. leonina* eggs are passed in feces. Infective larvae then develop in the environment after varying time periods (*B. procyonis*, 2 to 4 weeks; *T. leonina*, 1 week; *Toxocara* spp., 2 to 4 weeks) and can survive in the environment for months to years depending upon environmental conditions. Once larvation has occurred, *B. procyonis*, *T. leonina*, and *Toxocara* spp. eggs are infectious for a variety of hosts, including people (*B. procyonis* and *Toxocara* spp.). All three genera are transmitted by ingestion of embryonated eggs or by ingestion of tissues from other infected vertebrate hosts. Embryonated *Toxocara* spp. eggs have been transmitted by earthworms, flies, and cockroaches, and have been found on the fur of pets.[14,15] Raccoons tend to use favored defecation sites called latrines that often include rooftops, woodpiles, decks, base of trees, barns, and outbuildings, and these sites can become heavily infected by *B. procyonis*. After ingestion of larvated eggs, the prepatent periods for *B. procyonis*, *T. leonina*, *T. canis*, and *T. cati* are 7 to 10 weeks, 8 to 10 weeks, 4 weeks, and 8 weeks, respectively. The prepatent period for *T. canis* can be as short as 2 weeks if infection is acquired by ingestion of another infected vertebrate host.

In the definitive host, *T. leonina* remains in the intestinal tract. After ingestion of infective *Toxocara* spp. eggs, the larvae are released, penetrate the bowel wall, migrate to the liver via the systemic circulation, and then migrate to the lungs of infected dogs and cats. The migrating larvae induce inflammation while migrating through the liver and lungs of puppies and kittens. Hepatic migration rarely results in measureable clinical disease, but pulmonary migration can cause extensive damage, resulting in clinical signs of disease and occasionally death. After reaching the lungs, *Toxocara* spp. larvae either undergo tracheal or somatic migration. After somatic migration, the larvae encyst in tissues. For *T. canis* and possibly *B. procyonis*, the larvae can be reactivated by a triggering mechanism like pregnancy and migrate to the placenta, resulting in infection of the puppies. Transmammary transmission of *T. canis* can occur but is not as important for ascarids as for the hookworms. In young puppies or kittens, tracheal migration is more likely to occur leading to patent infections intestinal infections. As the puppies or kittens become adults, somatic migration is more likely, which explains the lower prevalence of infections in older animals. *Toxocara* spp. infections acquired by ingestion of infected vertebrate hosts result only in intestinal infections.

Table 57-5 Drugs Approved for the Treatment of Roundworm Infections in Dogs and Cats

Animal	Approved Drugs
Dogs	
Toxocara canis, Toxascaris leonina	Fenbendazole, milbemycin oxime, moxidectin, pyrantel pamoate, piperazine
T. canis, T. leonina	Pyrantel with ivermectin or pyrantel with ivermectin and praziquantel
T. canis, T. leonina	Febantel with pyrantel and praziquantel
Cats	
Toxocara cati, T. leonina	Fenbendazole, milbemycin oxime, moxidectin, pyrantel pamoate, selamectin, piperazine
T. cati	Pyrantel, febantel, emodepside

Clinical Examination

In puppies and kittens, intestinal ascarids infection is often associated with vomiting, small bowel diarrhea, potbellied appearance, and general ill-thrift. Heavy infections can induce coughing, increased respiratory rate, and death during pulmonary migration. Animals with large ascarid worm burdens have developed intestinal obstruction, intussusceptions, and intestinal rupture. Neurologic disease has been recognized in some dogs infected with *B. procyonis*. In adult dogs and cats, ascarid infections are often subclinical.

Diagnosis

The diagnosis of ascarid infection is confirmed by microscopic visualization of eggs in feces after fecal flotation. Centrifugation techniques are more sensitive than passive flotation.[7] Adult worms can sometimes be found in the vomitus of infected animals.

Treatment

Anthelmintic drugs to treat the intestinal stages and supportive care as needed are used in the management of ascarid infected dogs or cats (Table 57-5; see Chapter 37). There are no drugs available that can eliminate larvae from tissues.

Prevention

In people, prevention of infection revolves around avoiding the ingestion of embryonated eggs in the environment, particularly those frequented by dogs, cats, or raccoons. In pets, hunting should be discouraged and areas frequented by large numbers of untreated dogs and cats should be avoided. Feces should be removed from the yard and litterboxes with some regularity. All puppies and kittens should be dewormed; if the potential for concurrent hookworm infection exists, deworming can begin at 2 weeks of age. CAPC recommends that all puppies and kittens should be prescribed monthly preventives that control ascarids as soon as label recommendations allow and that administration be continued year round (www.capcvet.org). Raccoons should not be kept as pets and should be discouraged from defecating in areas frequented by people or dogs. Transplacental transmission by infected pregnant bitches can be lessened by administering fenbendazole as described for hookworms. CAPC recommends performing a fecal examination two to four times in the first year and one to two times per year thereafter, depending on the age of the animal and its prior history of infection to assess efficacy of the initial treatments, the efficacy of the monthly control product, and client compliance.

Public Health Considerations

T. leonina has no known public health risks. *Toxocara* spp. infections of people are associated with visceral larva migrans (pulmonary disease, hepatomegaly, and eosinophilia), ocular larva migrans (unilateral granulomatous retinitis), neural larva migrans, and nonspecific clinical signs including abdominal pain. Although these syndromes are relatively rare, many people are infected by *Toxocara* spp. Sera collected between 1988 and 1994 from 30,930 people 6 years of age or older in the United States had an age adjusted *Toxocara* seroprevalence rate of 13.9%.[16] In general, prevalence rates are greater in children because of potential for geophagia and otherwise poor hygienic practices. *B. procyonis*–associated neural larva migrans can be severe as the larvae grow and migrate through the tissues of the body, reaching sizes up to 1500 to 2000 µm. Because of this large size, as few as one to three larvae in the brain can be fatal. The severity of clinical disease depends on the number of eggs ingested, the number of larvae entering the brain, and the location and extent of migration damage. Because no effective treatment exists for larva migrans, prevention of these infections is paramount.

Prognosis

The prognosis for ascarid infections in dogs and cats is generally excellent.

Cestodes

The most common tapeworms infecting the SI of dogs or cats are *Dipylidium caninum*, *Taenia* spp., *Echinococcus multilocularis*, and *Echinococcus granulosa*. Cats or dogs are infected with *D. caninum* by ingesting infected *Ctenocephalides felis*. Dogs or cats are infected with *Taenia* spp. or *Echinococcus* spp. by ingesting other infected vertebrate hosts. The adult tapeworms live within the SI but usually are not associated with clinical signs of disease. Proglottids of *Taenia* spp. or *D. caninum* are often noted around the perineal area of infected animals. Eggs (*Taenia* spp. or *Echinococcus* spp.) or egg packets (*D. caninum*) can be detected on microscopic examination of feces after flotation procedures. Praziquantel (all three genera), epiquantel (*Taenia* spp. and *D. caninum*), and fenbendazole (*Taenia* spp.) are commonly prescribed drugs (see Chapter 37). Infections are prevented by controlling fleas (*D. caninum*) and preventing dogs or cats from hunting or scavenging (*Taenia* spp. and *Echinococcus*). *Echinococcus* spp. (ingestion of eggs) and *D. caninum* (ingestion of infected fleas) are zoonotic to people. The prognosis for these tapeworm infections in dogs and cats is generally excellent.

Protozoans

Cryptosporidium Spp.

Etiology

Cryptosporidium spp. are coccidians that reside in the SI and are occasionally associated with disease in some, but not all, infected hosts. In the past, most of the cases of mammalian cryptosporidiosis were attributed to infection with *Cryptosporidium parvum*. However, molecular studies demonstrate that cats are usually infected with the host-specific *C. felis* and dogs are usually infected with *Cryptosporidium canis*.[17-21] Infections of dogs and cats can be quite common with prevalence rates of 2% to 5% of animals with or without diarrhea, depending on the method of diagnostic testing.[12,13,21-25] In one study of samples collected from centers around the United States,

Cryptosporidium spp. DNA was amplified from feces of 29.4% of cats and 16.1% of dogs with diarrhea.[22]

Pathophysiology

C. felis and *C. canis* are transmitted among cats and dogs and by the ingestion of oocysts in feces from mutual grooming, shared litter-boxes, ingestion of contaminated food or water, and ingestion of infected prey species. Approximately 20% of the oocysts produced in the intestine are "thin-walled" oocysts that fail to form an oocyst wall. These oocysts rupture within the intestines and when the sporozoites are released, autoinfection occurs, which allows for rapid amplification of infection. In one study of cats inoculated with *C. parvum*, *C. parvum* DNA was detected by day 2 after inoculation, but oocysts weren't detected until day 7.[26] Thick-walled oocysts are passed in the feces, are environmentally resistant, are infective when passed, and are the likely source of new infections.

Although infection of dogs and cats with these agents is common, most infected animals do have clinical signs. Diarrhea is generally more common in young animals.[27-41] Coinfection with other protozoans like *Giardia* spp. (dogs and cats) or *Tritrichomonas foetus* (cats) may be associated with more significant illness than with single infections.[42,43] The presence of immunosuppressive disorders like lymphoma, feline leukemia virus infection, and canine distemper virus can potentiate the development of clinical signs of disease. When it occurs, *Cryptosporidium* spp. diarrhea is associated with impaired intestinal absorption and enhanced secretion. Histopathologically, infected animals show loss of intestinal microvilli, degeneration of host epithelial cells, villus atrophy, and lymphocytic-plasmacytic infiltration.[37,44] It is possible that susceptibility to cryptosporidiosis in animals could have a genetic component as suggested for humans.[45,46]

Clinical Examination

Most dogs or cats with *Cryptosporidium* spp. infection are clinically normal. When diarrhea occurs, it is usually watery, without mucous, blood, melena, or straining, and therefore is classified as small bowel-type diarrhea. On abdominal palpation, the SI may feel slightly thickened. Some of the infected dogs or cats with *Cryptosporidium* spp. infection and diarrhea have had underlying diseases like IBD, lymphoma, *T. foetus*, canine distemper virus, and/or feline leukemia virus, and so may have physical examination findings consistent with these conditions. Clinical signs of disease appear to be more likely in cats infected with *C. felis* than dogs infected with *C. canis*.

Diagnosis

Infectious causes of small diarrhea are common in dogs and cats and so the combination of wet mount examination and fecal flotation are usually performed as part of the initial diagnostic workup.[47] However, *Cryptosporidium* spp. oocysts are frequently missed because of the small size (approximately 4×6 μm) and low numbers in infected dog or cat feces (often <500 oocysts/g feces). Modified acid-fast staining of a thin fecal smear can be performed to aid in the diagnosis of cryptosporidiosis. *Cryptosporidium* spp. are generally the only enteric organism of the appropriate size that stains pink to red with acid-fast stain. However, acid-fast staining only detects approximately 70% of *Cryptosporidium* spp.–infected animals when a single sample is tested.[48] Fecal antigen tests for *Cryptosporidium* spp. are available for use with human feces, but results of these assays have been variable when applied to feces from infected animals.[48-50] Fecal antigen assays are based on antibodies against *C. parvum* and high false-negative rates may reflect antigenic differences between *C. parvum*, *C. felis*, and *C. canis*. Fluorescein-labeled monoclonal antibodies react with *Cryptosporidium* spp. oocysts and *Giardia* spp. cysts (Merifluor IFA, Meridian Biosciences, Cincinnati, OH). In limited studies, this assay appears to detect both *Giardia* spp. and *Cryptosporidium* spp. isolates from dogs and cats.[22,26,48] PCR is currently available to detect *Cryptosporidium* spp. DNA in canine or feline feces and is more sensitive than immunofluorescence assay (IFA) in feline studies.[22,26,51] PCR products can be evaluated by genetic sequencing to further determine what *Cryptosporidium* spp. is associated with the infection (Veterinary Diagnostic Laboratory, Colorado State University, Ft. Collins; http://dlab.colostate.edu/). *Cryptosporidium* spp. oocysts or DNA can be detected in normal dogs and cats, consequently positive test results do not prove a disease association.

Treatment

Highly digestible diets used for small bowel diarrhea might resolve some of the clinical signs. More than 100 compounds have been used in attempts to treat *Cryptosporidium* spp. infections in mammals and no compound is consistently effective.[52-54] There have been essentially no controlled treatment studies in dogs or cats and all protocols should be considered empirical. *Cryptosporidium* spp.–associated diarrhea in pets sometimes resolves after administration of tylosin (10 to 15 mg/kg PO q12h), azithromycin (10 mg/kg PO daily), paromomycin (150 mg/kg PO q12-24h), or nitazoxanide (25 mg/kg PO q12-24h). It is unlikely that tylosin has anti-*Cryptosporidium* effects and so cases with apparent responses may relate to the antibiotic or antiinflammatory effects of the drug. Tylosin and nitazoxanide are GI irritants. Paromomycin can be nephrotoxic in cats if absorbed and has had variable results in humans with cryptosporidiosis.[55-57] If the cat or dog shows clinical improvement within the first 7 days of therapy and toxicity has not been noted, treatment should be continued for 1 week past clinical resolution of diarrhea. Some cats with *Cryptosporidium* spp. infection, with or without *Giardia* coinfection, have required several weeks of treatment prior to resolution of diarrhea. The role of fiber, silymarin, or probiotics in addition to antimicrobial therapy is unknown at this time. Some cats and dogs with resistant cryptosporidiosis have underlying diseases (e.g., IBD, *T. foetus*, and immunodeficiency syndromes) and the diagnostic workup should be continued if therapeutic failures occur. No drug treatment has been shown to consistently eliminate *Cryptosporidium* spp. infections. Thus the primary goal for the treatment of dogs or cats with cryptosporidiosis is to eliminate diarrhea. As infection is unlikely to be eliminated, following results of *Cryptosporidium* spp. diagnostic tests in normal animals seems to have little clinical utility.

Prevention

Cryptosporidium oocysts are environmentally resistant but can be ruptured by steam cleaning. Avoidance of contaminated food and water or potential paratenic hosts is the primary means of prevention.

Public Health Considerations

DNA of *C. felis* or *C. canis* have been amplified from the feces of some immunosuppressed people suggesting that zoonotic transfer of these agents can occur.[19] However, the number of proven cross-infections is small and it appears unlikely that healthy or immunocompromised people acquire *Cryptosporidium* spp. infection from healthy cats or dogs.[58] Thus healthy pets are not considered significant human health risks for HIV-infected people by the Centers for Disease Control and Prevention (www.cdc.gov/hiv/pubs/brochure/oi_pets.htm).

Prognosis

Cryptosporidium spp. diarrhea can be difficult to treat in dogs or cats with concurrent diseases. However, in normal animals, diarrhea generally resolves with or without treatment.

Giardia Spp.

Etiology

The genus *Giardia* contains multiple species of flagellated protozoans that are indistinguishable morphologically. Host specificity was thought to be minimal for *Giardia* spp., but not all small animal isolates cause disease in human beings. There have been varying results concerning cross-infection potential of *Giardia* spp. Recent genetic analysis has revealed two major genotype assemblages in people.[18-20] Assemblage A (*Giardia duodenalis*) has been found in infected humans and many other mammals including dogs and cats. Assemblage B (*Giardia enterica*) has been found in infected humans and dogs, but not cats. There are specific genotypes of *Giardia* that commonly infect dogs (*Giardia canis*; Assemblages C and D) and cats (*Giardia felis*; Assemblage F) but are uncommonly identified in people. Prevalence rates for *Giardia* infection vary depending on the area studied, the diagnostic method used, and the health status of the animal, however, prevalence rates are commonly 5% to 10% in healthy or clinically ill dogs or cats.[3,12,13,15,24,25,59]

Pathophysiology

Giardia spp. are found on the surface of enterocytes, with the highest concentrations of the organisms being found in the duodenum of dogs and the ileum in cats. As the organisms are on the surface, pathogenesis is unlikely to be secondary to direct cell damage. Some of the pathogenic mechanisms proposed for *Giardia* spp. infections include production of toxins, disruption of normal flora, induction of IBD, inhibition of normal enterocyte enzymatic function, blunting of microvilli, and dysmotility.[60] There are many subclinically infected dogs and cats, and so *Giardia* is not always an effective primary pathogen. It has proven difficult to induce clinical signs of diseases in otherwise normal experimentally infected animals. For example, in one study, administration of 10^5 cysts induced infection in only 17 of 26 kittens of which diarrhea was only detected in 1 kitten for 1 day.[61] There may be strains than vary in their pathogenicity or other host factors may play an important role in determining whether disease will develop. The presence of immunosuppressive diseases or coinfections may potentiate the development of clinical signs of disease as discussed for cryptosporidiosis.[43,62]

Clinical Findings

Many dogs and cats have subclinical infection. When clinical disease occurs, the diarrhea is soft to watery and frequently has adherent mucus. Chronic malabsorption occurs in some animals and weight loss may be readily detected. On physical examination the SI may be slightly thickened and the animal can appear unthrifty. There may also be physical examination findings of coexisting syndromes that may potentiate giardiasis.

Diagnosis

The primary diagnostic tests for *Giardia* spp. infections are examination of direct fecal smear, direct saline preparation, passive fecal flotation, centrifugal fecal flotation (zinc sulfate and sugar are used most frequently), fecal IFA, fecal antigen ELISA, and fecal PCR assay. These tests can be used alone or in combination.

The direct smear and direct saline preparations can be used in the clinic for the presence of trophozoites of *Giardia* spp. (small bowel diarrhea), *T. foetus* (large bowel diarrhea), and *Pentatrichomonas hominis* (large bowel diarrhea). For the direct saline preparation, a 2-mm × 2-mm × 2-mm quantity of fresh feces is mixed thoroughly with 1 drop of body temperature 0.9% NaCl or water. The surface of the feces or mucus coating the feces should be used as the trophozoites are most common in these areas. After application of a coverslip, the smear is evaluated for motile organisms by examining it under ×100 magnification. Culture (*T. foetus*), antigen testing (*Giardia*), or PCR (*T. foetus* or *Giardia*) can be used to distinguish between specific organisms if the morphology is unclear.

Fecal flotation with the zinc sulfate or the sugar centrifugation technique (specific gravity 1.18 to 1.20) is optimal for the demonstration of *Giardia* spp. cysts and is more sensitive for detection of *Giardia* spp. cysts than passive flotation (www.capcvet.org).[7,63] Although sensitivity is less than 100% when a single sample is evaluated, fecal flotation remains the primary *Giardia* diagnostic test because of the ability of these assays to identify many other potential coinfections. Cysts are shed intermittently and their presence does not correlate very well with clinical signs of disease. Combination of fecal flotation with wet mount examination in cases with diarrhea or with a fecal antigen assay will increase sensitivity. In addition, sensitivity of fecal flotation increases to greater than 90% if at least three stool specimens are examined within 5 days.

Multiple ELISAs for detection of *Giardia* antigens in feces are available. In experiments performed in my laboratory, one assay labeled for veterinary use (SNAP Giardia, IDEXX Laboratories, Portland, ME) detected *G. canis* and *G. felis*.[64] False-positive and false-negative rates are estimated to be approximately 2% to 5%. Although it is unknown why false-positive reactions occur, it is likely that other fecal antigens are nonspecifically binding to the reagents. False-negative results likely relate to the sensitivity cutoffs of the individual assays. In one study, combination of fecal flotation with one commercially available *Giardia* spp. antigen assay had a combined sensitivity of 97.8%.[50]

Fluorescein-labeled monoclonal antibodies that react with *Cryptosporidium* spp. oocysts and *Giardia* spp. cysts (Merifluor IFA, Meridian Biosciences, Cincinnati, OH) are available in most veterinary diagnostic laboratories. In limited studies, this assay appears to detect both *Giardia* spp. and *Cryptosporidium* spp. isolates from dogs and cats.[65-67] Compared to *Giardia* antigen assays, this assay has the advantage of detecting a common coinfection and as the feces are examined microscopically, false-positive reactions are uncommon as the organism morphology can be assessed. The primary disadvantages include the need for a fluorescence microscope and additional technician time when compared with *Giardia* antigen assays.

A number of genes have been assessed for the amplification of *Giardia* DNA by PCR.[68] Results for assemblage determination can vary based on the gene chosen and it is possible that some dog or cat isolates could be genotyped as "potentially zoonotic" by one gene but as "host specific with another."[30] In experiments in our laboratory, *Giardia* PCR fails to amplify DNA from approximately 20% of samples that are positive for *Giardia* cysts or antigens. At this time, PCR testing is only recommended for assessment of the *G. duodenalis* assemblage in cats and dogs, and the use of multilocus genotyping is recommended.[69] This service is available at the Veterinary Diagnostic Laboratory at Colorado State University (http://dlab.colostate.edu/).

Treatment

Use of many drugs for the treatment of canine or feline giardiasis was extrapolated from use in humans.[70] Because dog and cat *Giardia* spp. have been difficult to grow in culture, there are minimal data

Table 57-6 Drugs Used for the Treatment of *Giardia* Spp. Infections

Drug	Species	Dose
Metronidazole	B	15 to 25 mg/kg PO q12-24h for 5 to 7 days
Ronidazole	F	20 mg/kg, PO q12h for 14 days (primarily used for *T. foetus*; neurotoxicity common)
Tinidazole	C	44 mg/kg PO q24h for 3 days
Ipronidazole	C	126 mg/L of water PO ad libitum for 7 days
Fenbendazole	B	50 mg/kg PO daily for 3 to 5 days
	B	15 mg/kg PO q12h for 2 days (less commonly used because of bone marrow toxicity)
Pyrantel, praziquantel, febantel	C	Label dose for 3 days
	F	Feline dose: 56 mg/kg (based on the febantel component) PO daily for 5 days
Quinacrine	C	9 mg/kg PO q24h for 6 days
	F	11 mg/kg PO q24h for 12 days
Furazolidone	F	4 mg/kg PO q12h for 7 to 10 days

B, Canine and feline; C, canine; F, feline.

on antimicrobial sensitivities. It is likely that sensitivities vary amongst different isolates and it is currently impossible to predict which anti-*Giardia* drug will be effective in an individual case. Although there have been multiple drugs used for the treatment of giardiasis in dogs and cats, there are few studies that utilized dose titrations and evaluation of drugs in experimentally infected animals. In most studies, fecal samples were only assessed for short periods of time after treatment and neither was immune suppression induced nor necropsy performed to evaluate whether infection was eliminated or merely suppressed. Infection with *Giardia* does not appear to cause permanent immunity and so reinfection can occur, a finding that also hampers assessment of treatment studies.

The primary goal of *Giardia* treatment is to stop diarrhea. Because healthy pets are not considered significant health risks to immunocompetent people, elimination of infection (which is difficult) is a secondary goal. Treatment options currently available or used historically include metronidazole, tinidazole, ipronidazole, ronidazole, fenbendazole, albendazole, pyrantel/praziquantel/febantel, quinacrine, furazolidone, and nitazoxanide (Table 57-6).[70-83]

Care should be taken when using metronidazole or ronidazole as central nervous system (CNS) toxicity can occur.[84-86] Because albendazole is associated with bone marrow suppression, many clinicians use fenbendazole or febantel when that class of drugs is chosen.[87]

If clinical findings suggest concurrent *C. perfringens* overgrowth, use of metronidazole may be indicated as this drug is an antibiotic with activity against *Clostridium* spp. If there are clinical findings that suggest concurrent infection with a nematode, fenbendazole or febantel are indicated. Many clinicians currently use fenbendazole once daily for 3 to 5 days as initial therapy. Some clinicians currently recommend the combination of metronidazole and fenbendazole (www.capcvet.org). Others only resort to combination therapy if there is evidence of a persistent infection that is not cleared by monotherapy. If the first drug fails to control diarrhea and the organism is still detected in feces, a second drug from an alternate class is indicated. The addition of fiber to the diet may help control clinical signs of giardiasis in some animals by helping to suppress bacterial overgrowth or by inhibiting organismal attachment to intestinal microvilli. Immunotherapy with the *Giardia* vaccine has aided in eliminating cyst shedding and diarrhea in some infected dogs.[88] However, in a controlled study in 16 experimentally infected cats, vaccination as immunotherapy was ineffective with one strain of *Giardia*.[89] In addition, both commercial products have been discontinued. Probiotic administration has been promoted as potentially beneficial in the control of giardiasis. In one study, dogs treated with silymarin and metronidazole had superior clinical responses to dogs treated with metronidazole alone.[90] However, in another study, administration of a commercially available probiotic (FortaFlora, Nestle Purina PetCare, St. Louis, MO) did not affect the outcome of *Giardia* infection.[91] In one study, bathing the dog on the last day of treatment was a beneficial adjunct therapy.[77] In dogs and cats with persistent diarrhea and *Giardia* spp. infection, a more extensive workup to attempt to diagnose other underlying diseases is indicated if several therapeutic trials fail. Common underlying disorders include cryptosporidiosis, *T. foetus* in cats, IBD, bacterial overgrowth, exocrine pancreatic insufficiency, and immunodeficiencies.

Public Health Considerations

Healthy pets are not considered significant human health risks by the Centers for Disease Control (www.cdc.gov/hiv/pubs/brochure/oi_pets.htm) and there is no current recommendation to test healthy dogs or cats for *Giardia* spp. infection. However, some dogs and cats are infected with the zoonotic assemblages and the same assemblage has been detected in dogs and people in the same family.[92-95] All healthy dogs and cats should be screened for hookworm and roundworm infection once or twice yearly as previously discussed. Thus healthy dogs and cats that are harboring *Giardia* cysts will be detected. As some *Giardia* spp. may be zoonotic, treatment of healthy infected animals should be considered with each owner. Treatment of healthy animals is controversial because all of the drugs can potentially cause side effects, animals with normal stools are not considered human health risks, treatment is unlikely to eliminate infection, and reinfection can occur within days. For example, in a study of naturally infected dogs, approximately 15% of treated dogs were still *Giardia* infected when rechecked 9 or 16 days after treatment.[76] In another study, 50% of the healthy, *Giardia*-positive dogs had adverse reactions to fenbendazole or nitazoxanide and 62.5% of those that successfully completed therapy were positive for *Giardia* cyst or antigen on day 34.[64] It is unknown whether these infections were not eliminated or if the dogs were reinfected. If treatment is deemed appropriate by the clinician and pet owner, many clinicians currently recommend administration of a 5-day course of fenbendazole in apparently healthy dogs and cats that test positive for *Giardia*. The American Association of Feline Practitioners (AAFP) Advisory Panel on Zoonoses recommends attempting to remove the source of infection during the treatment period and performing a fecal centrifugal flotation after *Giardia* treatment one

time, within 2 to 4 weeks after the end of the treatment period (www.aafponline.org). If the animal is healthy and negative for cysts, retesting is not indicated again until the next scheduled fecal flotation. Currently it is not recommended that the IFA or fecal PCR assays be used as a recheck test for any of the *Giardia* antigen assays. It is currently unknown how long *Giardia* antigens will persist in feces after successful treatment.

Occasionally, animals will be *Giardia* cyst-negative but *Giardia* antigen-positive. These animals either have a low-grade infection or a low percentage of animals (approximately 2% to 5%) have false-positive antigen test results. To further evaluate for cyst shedding, the veterinarian can perform an IFA test or two additional fecal flotations (three negative centrifugal flotation assays run within 5 days is considered adequate to ruleout a *Giardia* infection in both animals and humans); if these other test results are negative, the antigen test was likely falsely positive.

Prevention

Prevention of giardiasis involves boiling or filtering of water collected from the environment prior to drinking and disinfection of premises contaminated with infected feces with steam cleaning or quaternary ammonium compounds (1 minute contact time). Paratenic hosts should be controlled and treatment and bathing of all animals in the environment should be considered. Feces from infected animals should be removed from the environment promptly. The previously licensed *Giardia* spp. vaccines for dogs and cats were classified by American Animal Hospital Association (AAHA) and AAFP as generally not recommended as preventatives. Both products have been discontinued by their manufacturers.

Prognosis

Most dogs and cats with clinical giardiasis ultimately will have clinical signs of disease resolve with treatment and so the prognosis in otherwise healthy animals is good.

Isospora Spp.

Etiology

Dogs are the definitive hosts for *Isospora canis*, *Isospora ohioensis*, *Isospora neorivolta, and Isospora burrowsi* and cats are the definitive hosts for *Isospora felis* and *Isospora rivolta*.[96] These protozoans are host specific, have worldwide distribution, and infections are very common, particularly in young animals. In one Austrian study, 8.7% of dogs younger than 2 years of age were infected; 78% of the positive samples were in puppies younger than 4 months of age.[97] In the United States, CAPC reports prevalence rates for *Isospora* spp. infection from 3% to greater than 30% (www.capcvet.org).

Pathophysiology

Infection by *Isospora* spp. in dogs or cats is initiated by ingestion of sporulated oocysts in the environment or by ingesting tissues of other infected vertebrate intermediate hosts.[96-98] Infection may also occur if dogs or cats ingests sporulated oocysts carried by paratenic hosts like flies, cockroaches, or dung beetles.[99] The enteroepithelial phase occurs in the SI of infected animals which culminates in the passage of unsporulated oocysts in feces. The prepatent and patent periods vary slightly by species. In one study of dogs experimentally infected with *I. canis*, the mean prepatent period was 9.8 days (range: 9 to 11 days, n = 22 dogs), the patent period was 8.9 days (range: 7 to 18 days, n = 20 dogs), and all of the puppies developed diarrhea, suggesting the organism can be a primary pathogen.[98] In contrast, the prepatent period for *I. ohioensis* in one study was 6 to 7 days and diarrhea was variable.[97] Numbers of oocysts shed in infected animals can vary dramatically.[97,98] Depending on the environmental conditions, sporulation can occur in as little as 12 hours. Clinical disease is most common in young, debilitated, and immunocompromised animals. All of the *Isospora* spp. replicate in the SI but the regions with the heaviest infection varies by the species. Microscopic lesions observed in some infected animals includes villus atrophy, dilation of lacteals, and hyperplasia of lymph nodes in Peyer patches.

Clinical Findings

Isospora spp. infections are generally only associated with disease in puppies and kittens. Clinically ill puppies and kittens can exhibit vomiting, abdominal discomfort, inappetence, and watery diarrhea that sometime contains blood. Depending on the age of the animal and the parasite burden, severe dehydration and death can occur. Puppies and kittens with subclinical infection can repeat shedding and clinical signs of disease during stressful periods.

Diagnosis

Isospora spp. oocysts are large, occur in large numbers, and are generally easy to identify on microscopic examination of feces after fecal flotation. However, normal animals also pass *Isospora* spp. oocysts and so positive test results do not always prove a disease association. False-negative fecal flotation results are uncommon in clinically infected animals but occasionally clinical signs precede oocyst shedding and a second fecal flotation may be needed to prove infection in some cases.

Treatment

Coccidiosis is generally self-limited and most healthy puppies and kittens will resolve clinically without therapy. However, administration of treatment can speed resolution of disease and may lessen environmental contamination and the potential for infecting other in contact animals. The only approved treatment for coccidiosis in the United States is sulfadimethoxine administered at a dose of 50 to 60 mg/kg daily for 5 to 20 days (dogs and cats). Other drug regimens have been used with some success, including trimethoprim-sulfa (30 to 60 mg/kg of trimethoprim daily for 6 days in animals weighing more than 4 kg or 15 to 30 mg/kg trimethoprim daily for 6 days in animals weighing less than 4 kg) and a variety of protocols using amprolium alone or in combination with sulfadimethoxine. However, ponazuril and toltrazuril are coccidioidal and therefore are superior for the treatment for coccidiosis.[100,101] Ponazuril has been used most frequently in the United States. The drug can be administered off label at 20 mg/kg PO twice, 1 to 7 days apart or at 50 mg/kg PO once. Many compounding pharmacies in the United States will appropriately formulate the drug by prescription.

Prognosis

Most *Isospora* spp.–infected puppies and kittens will survive infection making the prognosis good to excellent.

Prevention and Public Health Considerations

Isospora spp. oocysts are very resistant to environmental conditions and disinfectants. The key to control is to provide good sanitation including prompt removal of feces prior to oocyst sporulation. Steam cleaning can be used to destroy oocysts that contaminate surfaces. Treatment of dams and queens with anticoccidial agents prior to parturition can lessen the occurrence of coccidiosis in young animals. In environments with heavy infections, treatment of all in contact animals, particularly puppies and kittens, could be

considered. *Isospora* spp. of dogs and cats do not infect people. Ponazuril administered to all at-risk puppies and kittens on intake to shelters may aid in the control of coccidiosis.[101]

Other Protozoans

While *Sarcocystis* spp., *Besnoitia* spp., *Hammondia* spp., *Toxoplasma gondii*, and *Neospora caninum* complete the sexual phase of the life cycle in the intestinal tract of dogs or cats, this phase of replication is rarely linked to GI clinical signs of disease. Clinical illness associated with *T. gondii*, *N. caninum*, and *Sarcocystis neurona* generally results from the tissue phase of the infections. However, IBD was linked to *T. gondii* infection in two cats.[102]

Fungal, Oomycetes, and Algae Infection

The fungal, oomycetes, and algae infections may diffusely involve the whole GI tract, and are discussed in detail in "Infection of the Large Intestine" in Chapter 58.

Bacteria

A number of bacteria are associated with GI signs of disease and may colonize or infect the SI. *Campylobacter* spp., *Clostridium* spp., *E. coli*, and *Salmonella* spp. are discussed in this chapter. *Yersinia* spp., and other mixed enterocolitic infections are discussed in Chapter 58 The syndrome of small intestinal bacterial overgrowth (or dysbiosis) is discussed in another section of this chapter.

Campylobacter Spp.

Etiology

C. jejuni, *Campylobacter coli*, *C. upsaliensis*, and *Campylobacter helveticus* are commensal organisms found in the GI tract of healthy dogs and cats throughout the world.[103-105] The high prevalence of these organisms in healthy nondiarrheic dogs (*C. jejuni*, 49%; *C. coli*, 5%; *C. upsaliensis*, 19%) and cats (*C. jejuni*, 46%; *C. coli*, 1%; *C. upsaliensis*, 5%; *C. helveticus*, 22%) complicates diagnosis.[106-109] Under certain conditions, however, *Campylobacter* can induce significant GI tract pathology. Young age, immunoincompetence, concurrent GI infections, prior therapeutic interventions (e.g., antibiotics), and poor hygienic conditions appear to be the greatest risk factors for the development of infection.[110]

Pathophysiology

At some point, *Campylobacter* organisms become enteroinvasive and induce the host inflammatory response. *C. jejuni* localizes in mucus-filled crypts of the intestine and colon where it induces a superficial erosive enterocolitis.[110,111] Colonic epithelial glands undergo hyperplasia and thickening with exfoliation of the brush-border and goblet cells. The colonic epithelium becomes cuboidal, crypt height is reduced, and crypt abscess are present. Shallow crypts and blunt irregular villi are features of the ileum response to infection.

Clinical Examination

Clinical signs are watery diarrhea, often containing mucous and blood pigments, tenesmus, anorexia, fever, and vomiting.[111,112] Concurrent infections with *Salmonella*, *Giardia*, or parvovirus cause more severe disease.

Diagnosis

Direct examination of a fresh fecal sample is the method of diagnosis in many instances. Large numbers of curved, highly motile bacteria along with increased numbers of leukocytes is presumptive evidence of *Campylobacter* infection. With Gram staining, large numbers of faintly staining Gram-negative, slender, curved (gull-wing shaped) rods are evident. Fecal cultures or PCR are the most conclusive ways to determine the presence of *Campylobacter*.[106-108] *C. jejuni* is best cultured microaerophilically at 42°C (107.6°F) for 48 hours on special *Campylobacter* blood agar plates.

Treatment

Erythromycin is the treatment of choice, although tetracyclines, aminoglycosides, clindamycin, and quinolones are also effective. Posttreatment cultures should be performed to confirm eradication. Pet owners should be advised about the importance of proper hygiene.

Prognosis

The prognosis for recovery and cure are generally excellent unless an underlying immunosuppressive condition has increased the susceptibility to infection.

Clostridium Perfringens

Etiology

C. perfringens is a Gram-positive, spore-forming, obligate anaerobic rod-shaped bacterium that contributes to the microbial ecology and nutrition of the colon in healthy dogs and cats.[113] Under certain conditions, proliferation and sporulation of *C. perfringens* permits enterotoxin A (or CPE) production, which may then induce mucosal damage, fluid secretion, and large bowel-type diarrhea. Evidence for and against a role for *C. perfringens* in the pathogenesis of large bowel diarrhea has been put forward. Enterotoxigenic *C. perfringens* is associated with canine nosocomial diarrhea,[114] hemorrhagic enteritis,[103] and acute and chronic large bowel diarrhea.[115,116] On the other hand, many dogs harbor *C. perfringens* and CPE in the GI tract without developing clinical signs.[104,105,110] Until more definitive evidence is obtained, including the fulfillment of the Koch postulates, *C. perfringens* should probably be considered as a suspected pathogen in large bowel diarrhea.

Pathophysiology

The presumed pathogenicity of *C. perfringens* requires an anaerobic environment, sporulation, and enterotoxin production. There are problems with this hypothesis however; enterotoxin may be demonstrated in the feces without sporulation, and enterotoxin may be found in the feces of healthy dogs. *C. perfringens* isolates are classified as one of five toxigenic types (A to E) based on the production of one or more of four major (α, β, ε, ι) and seven minor (δ, θ, κ, λ, μ, ν, and sialidase) toxins.[117] Although all five types of *C. perfringens* are capable of producing CPE, the majority is produced by type A strains. As with enterotoxigenic *E. coli* (ETEC) strains, CPE is believed to induce crypt epithelial cell secretion.

Clinical Examination

C. perfringens–associated colitis is believed to be a major cause of acute, nosocomial, as well as chronic, large bowel diarrhea. Acute nosocomial diarrhea often begins within 1 to 5 days of boarding or kenneling. Affected dogs develop diarrhea, often with blood pigments, mucous, and tenesmus. These diarrheas are usually self-limiting and may resolve with supportive care alone. Chronic large bowel diarrheas associated with *C. perfringens* are similar to other large bowel-type diarrheas, that is, chronic, intermittent, and recurring signs of colitis.

Diagnosis

There is no gold standard for the diagnosis of *C. perfringens*–associated diarrhea. Ideally, the diagnosis would be made on the basis of positive test results with Gram staining, fecal culture, ELISA enterotoxin (CPE) assay, PCR enterotoxin (*cpe*) genotyping, and ruleout of other colonic diseases on colonoscopy and biopsy.[118-121] Compared to normal dogs (without diarrhea), diarrheic dogs are more often CPE ELISA- and *cpe* PCR-positive, but many normal dogs are positive on both assays.

Treatment

Recent in vitro antimicrobial susceptibility testing suggests that *C. perfringens* should be susceptible to ampicillin, erythromycin, metronidazole, and tylosin.[122] These antibiotics have also been used in vivo with good success. It should be emphasized that many of the same patients respond to supportive care, including intravenous fluids, intestinal protectants, and bland or fiber-supplemented diets.

Prognosis

Affected animals usually respond to appropriate therapy within a matter of days. The prognosis for recovery is excellent.

Clostridium Difficile

C. difficile is believed to share many ecological factors with *C. perfringens*,[123,124] but the role of this organism as a pathogen in dogs and cats has not been firmly established. Compared with normal dogs (without diarrhea), diarrheic dogs are more often toxin A ELISA-positive even though they may be *toxin A* PCR-negative.[121] As with *C. perfringens*, many healthy dogs and cats carry *C. difficile* without developing clinical signs. In one recent study it was difficult to experimentally infect dogs with this organism, and those that were infected did not develop clinical signs.[125] Antibiotic-associated diarrheas develop in dogs and cats but they may have a pathogenesis other than *C. difficile*.

Escherichia Coli

Etiology

Most strains of *E. coli* are true commensal organisms that are not associated with clinical signs. Strains of *E. coli* that cause diarrhea in animals can be grouped into five main categories: ETEC, enteroinvasive (EIEC), enteropathogenic (EPEC), enterohemorrhagic (EHEC), and enteroadherent (EAEC) organisms.[126] Identification of pathogenic strains requires modern molecular technology such as bioassays, DNA hybridization, and PCR amplification.

Pathophysiology

Infection may result in enteritis, colitis, or both.[127] ETEC strains adhere to the surface of epithelial cells and produce heat-labile and/or heat-stable toxins that induce crypt epithelial cell secretion. EIEC strains invade, replicate in, and destroy epithelial cells. EPEC strains are neither enterotoxigenic nor enteroinvasive, but they do attach to and efface the brush-border of the enterocytes. EHEC strains produce verocytotoxins that induce hemorrhagic ileitis and colitis. EAEC strains also induce enterocyte pathology, but their mechanism of action is poorly understood. ETEC, EPEC, and EHEC have all been isolated from dogs and cats with diarrhea. *E. coli* endotoxin colonic absorption of water and sodium and contributes to the diarrhea seen during and after episodes of sepsis.[128]

Clinical Examination

Affected animals typically have diarrhea and hematochezia with clinical signs relevant to the SI, colon, or both.

Diagnosis

E. coli can be grown from the feces of healthy dogs and cats, so a positive culture does not necessarily reveal the identity of an underlying pathogen. In addition to positive culture, diagnosis may require enterotoxin assays, and DNA hybridization and PCR amplification.[129-133]

Treatment

Antibiotics should be used only in those cases in which there is firm evidence of bacterial infection. Fluoroquinolones appear to be a very effective classification for the treatment of enteric *E. coli* infections.

Prognosis

The prognosis is generally good for recovery and cure if infection is recognized early in the clinical course.

Salmonella

Etiology

Salmonella spp. are predominantly motile, Gram-negative facultative anaerobic rod-shaped bacteria found in the feces of normal and diarrheic animals.[104,105] As with many other commensal organisms of the GI tract, the high prevalence of these organisms complicates diagnosis. From 1% to 30% of the fecal samples or rectal swabs taken from healthy domestic pet dogs, 16.7% of dogs boarded in kennels, and 21.5% of hospitalized dogs were found to be positive on bacteriologic culture for *Salmonella*. From 1% to 18% of healthy cats and 10.6% of random source research colony cats were also culture-positive for *Salmonella* (summarized in reference 122). Despite these findings, several species of *Salmonella* have been impugned in the pathogenesis of acute enterocolitis in dogs and cats. *Salmonella typhimurium* is the species most commonly isolated from diarrheic feces of dogs and cats, although other species have been identified.[134-136]

Pathophysiology

Those most at risk for *Salmonella* infection are young and immunoincompetent animals, those with concurrent GI infections (e.g., parvoviral or parasitic infections), and those animals who have had prior therapeutic interventions (e.g., antibiotics or glucocorticoids).[110] *Salmonella* is an enteroinvasive organism that induces an acute inflammatory response resulting in enterocolitis, mucosal sloughing, and secretory diarrhea. Most *Salmonella* infections are resolved via the local immune response, but bacterial translocation and septicemia may evolve into systemic inflammatory response and multiple organ dysfunction syndromes in some patients. Early recognition is important in preventing this sequela.

Clinical Examination

The main clinical signs of *Salmonella* enterocolitis are anorexia, lethargy, fever, vomiting, diarrhea with mucous and blood pigments, dehydration, abdominal pain, and tenesmus. With bacterial translocation and septicemia, affected animals may have evidence of pale mucous membranes, weakness, tachycardia, tachypnea, and vascular collapse.

Diagnosis

Culture, serotyping, and PCR are the best methods of diagnosing *Salmonella* infections.[134]

Treatment

Treatment varies according to the severity of the clinical signs. Mild, self-limiting forms of enterocolitis may in fact resolve with little more

than supportive therapy. Antibiotic therapy in such cases may prolong fecal shedding and encourage development of the carrier state. In animals with severe hemorrhagic diarrhea, history of immunosuppression, suspected or documented septicemia, and/or evidence of systemic inflammatory response syndrome, parenteral antibiotics should definitely be used. If culture results are unavailable, therapy should include enrofloxacin, amoxicillin, or trimethoprim-sulfa, all of which are effective against *Salmonella*. Posttreatment cultures should be performed to confirm eradication, and pet owners should be advised of the public health importance of the disease.

Prognosis

The prognosis for recovery in nonsepticemic patients is generally good, although some animals may remain chronic carriers with recrudescence during periods of stress or unrelated disease. The prognosis for the septicemic patient is more guarded.

Rickettsia

Neorickettsia Helminthoeca

Etiology

Neorickettsia helminthoeca is a gram-negative organism in the family Anaplasmataceae that induces a clinical syndrome called *salmon poisoning disease* in dogs.[137] The syndrome is currently recognized in the Pacific Northwest of the United States, British Columbia in Canada, and an area in southern Brazil.[137-140] A similar clinical syndrome in dogs was called *Elokomin fluke fever* in Washington but now appears likely to have been caused by a strain of *N. helminthoeca*.

Pathophysiology

Nanophyetus salmincola is the trematode vector of *N. helminthoeca* and requires three hosts for the completion of its lifecycle.[137] A river snail, *Oxytrema silicula*, is the first intermediate host and is infected by rediae and cercariae of *N. salmincola*. The snail releases free-living cercariae that penetrate the skin of salmon, lose their tails, and become metacercariae that develop in a number of tissues of the salmon with heavy concentrations in the kidneys, liver, heart, and tail. The life cycle is completed when the adult trematode develops in the intestine of mammals or birds that eat fish. The syndrome has also been induced in dogs that have been fed infected snails. *N. helminthoeca* survives through all stages of the trematode. The adult flukes develop deep within the intestinal tissues causing local edema and inflammation in 5 to 6 days. The fluke releases *N. helminthoeca*, which infects intestinal histiocytes and disseminates in blood and lymph to lymphoid tissues. Mesenteric lymph nodes enlarge greatly from edema and an influx of inflammatory cells. Diarrhea results from the inflammation of intestinal lymphoid tissues and can be hemorrhagic. The typical incubation period is 5 to 7 days.

Clinical Examination

Clinical signs of disease in dogs starts with fever, anorexia, and vomiting. Affected dogs can also develop periocular swelling, ocular discharge and nasal discharge which have been confused with canine distemper virus infection. Local and generalized lymphadenopathy can be detected in most cases when clinical signs are first recognized. Diarrhea is generally small bowel-type in character, but can become bloody and be confused with canine parvovirus infection. Rapid, marked weight loss, and extreme polydipsia have been reported in some dogs and death is common.

Diagnosis

History, clinical signs, detection of *N. salmincola* eggs after microscopic examination of feces after fecal sedimentation, and response to therapy can be used to make a presumptive diagnosis. Clinical pathology abnormalities can include thrombocytopenia, lymphopenia, eosinophilia, increased alkaline phosphatase activity, and marked hypoalbuminemia.[137] Cytologic examination of enlarged lymph nodes after staining with Giemsa can reveal intracytoplasmic neorickettsial bodies within reticuloendothelial cells and lead to a definitive diagnosis. Current infection can be documented by demonstrating rising antibody titers, culture, immunohistochemical staining of tissues, or PCR assay.[137]

Treatment

Supportive care for dehydration is key to the management of dogs with salmon poisoning disease. *N. helminthoeca* is susceptible to tetracycline, doxycycline, and oxytetracycline. Parenteral treatment is indicated in dogs with concurrent vomiting. *N. salmincola* is susceptible to praziquantel.[141]

Prognosis

Without treatment, up to 90% of clinically affected dogs die within 6 to 10 days of developing clinical signs. Permanent immunity occurs in dogs that survive infection.

Prevention and Public Health Considerations

Dogs should not be allowed to feed on raw, uncooked, or smoked salmon in endemic areas. Freezing fish at −20°C (−4°F) for at least 24 hours or thoroughly cooking the tissues kills both the fluke and *N. helminthoeca*. *N. salmincola* infection can result in GI disease in people,[142] but it is unclear whether *N. helminthoeca* is pathogenic in people.[137]

Viral

Canine Enteric Coronavirus

Etiology

Canine enteric coronavirus (CCV) is a single-stranded enveloped RNA virus that replicates in the cytoplasm of small intestinal epithelial cells.[143] There are several genetic variants that occur in different parts of the world and prevalence varies by genotype and country.[144-148] CCV RNA has been amplified from the feces of more than 40% of dogs with gastroenteritis in some countries,[145] but CCV RNA can also be amplified from the feces of normal dogs. Canine respiratory coronavirus is genetically distinct from canine enteric coronavirus.[149]

Pathophysiology

CCV is transmitted by fecal–oral route via a contaminated environment and is highly contagious especially in neonatal puppies. Older dogs can be infected but seem to be less likely to develop clinical signs of disease. The inoculation period is approximately 1 to 4 days. CCV replicates intracellularly in the intestinal microvilli which become short and blunted. Necrosis and hemorrhage are rare in contrast to canine parvovirus infections. There are CCV variants that are more pathogenic than others and disease appears to be unusual in puppies greater than 6 weeks of age in the United States.[150,151] Co-infection with other infectious agents like canine parvovirus was thought to potentiate CCV-associated illness in some studies.[152]

Clinical Examination

Susceptibility to CCV associated gastroenteritis does appear to be overrepresented in any individual breed or sex. The primary clinical sign is small bowel–type diarrhea that may be preceded by vomiting. Secondary findings include fever, lethargy, anorexia, dehydration, and death in some affected puppies.

Diagnosis

Amplification of CCV RNA from feces by RT-PCR assay is currently the most frequently used diagnostic procedure in the United States. However, as normal dogs can be positive for CCV RNA, the positive predictive value of these assays is less than 100%.[148] Depending on the timing of tested, assay results can be falsely negative.

Treatment

Fluid therapy and other supportive care is used for the treatment of CCV-associated GI disease in puppies.

Prognosis

With appropriate supportive care, the prognosis for puppies with CCV infection is generally good.

Prevention and Public Health Considerations

CCV is rapidly inactivated by many detergents and disinfectants. Multiple CCV-containing vaccines are available in the United States. However, as clinical illness is usually only detected in very young dogs in this country, the AAHA Vaccine Panel does not generally recommend this vaccine antigen.[153] There are no proven human health risks with CCV.

Feline Coronaviruses

Etiology

Feline enteric coronavirus (FECV) and feline infectious peritonitis virus (FIPV) infections can cause GI disease in some cats.[154,155] Although enteric infection generally results in mild GI signs, systemic infection can induce a clinical syndrome with diverse manifestations commonly referred to as FIP.[155] There are multiple field strains of FECV and FIPV with varying degrees of virulence. FIPV capable of inducing FIP develop in the GI tract of some infected cats as mutations or recombinant strains of endemic FECV. FECV are commonly shed in feces, rarely in saliva, and are very contagious but minimally pathogenic.[156]

Pathophysiology

Coronaviruses can be detected in feces by use of RT-PCR as early as 3 days postinfection.[156] In studies of FECV-infected, closed cat colonies, almost every cat becomes infected, with some cats shedding continuously. Viral RNA has been detected in the ileum, colon, and rectum of cats with persistent shedding. FIPV-infected monocytes can disseminate throughout the body, potentially resulting in FIP, which has diverse manifestations related to the development of vasculitis or pyogranulomatous disease of multiple organs.[155] GI disease associated with FIP can result from focal obstruction.[157]

Clinical Examination

Enteric replication of feline coronaviruses commonly results in fever, vomiting, and mucoid diarrhea. GI disease from FECV is most common in kittens and is generally self-limiting or responsive to supportive care within days. Fever and weight loss are common with both the effusive and noneffusive forms of FIP, and small bowel diarrhea can occur chronically in some cats. A solitary ileocecocolic or colonic mass resulting in obstruction with vomiting and diarrhea occurs in some cats.[157] The other polysystemic manifestations of FIP are reviewed elsewhere.[154,155]

Diagnosis

There are no specific clinical or routine laboratory findings leading to a definitive diagnosis of FECV- or FIPV-associated GI tract disease. Because virus isolation and electron microscopy are not practical clinically, RT-PCR is used most frequently to amplify coronavirus RNA in feces. However, positive test results do not prove that diarrhea is caused by a coronavirus as normal cats can also be positive. Definitive diagnosis of FIP-associated GI obstruction is based on detection of characteristic histopathologic findings, virus isolation, demonstration of the virus in tissue by use of immunocytochemical or immunohistochemical staining, or by RT-PCR demonstration of viral RNA in tissues.

Therapy

FECV-associated GI signs of disease are treated with supportive care and are generally self-limiting. GI obstruction from focal FIP is generally treated surgically.

Prognosis

Most kittens with FECV-associated GI disease respond rapidly to therapy. Cats with focal GI obstruction from FIP may progress to systemic disease, which has a grave prognosis.

Prevention and Public Health Considerations

Prevention of coronavirus infection is best accomplished by avoiding viral exposure. Although viral particles of FECV and FIPV can survive in dried secretions for up to 7 weeks, routine disinfectants inactivate the virus. An intranasally administered, mutant strain of coronavirus that induces mucosal immune response but minimal systemic immune response is available (Primucell FIP, Pfizer Animal Health, Exton, PA). Whether the vaccine protects against FECV or all field strains, mutations, or recombinants of FIPV is unknown. It is unlikely the vaccine is effective in cats that have previously been infected by a coronavirus and is considered generally not recommended by the AAFP.[158] There is no known zoonotic transfer of FIP coronavirus or enteric coronavirus to humans.

Canine Distemper Virus

Etiology

Canine distemper virus (CDV) induces disease predominantly in terrestrial carnivores, but many other species, including seals, ferrets, skunks, badgers, porpoises, and exotic Felidae, have been infected by either CDV or related viruses.[154,159]

Pathophysiology

CDV replicates in lymphoid, nervous, and epithelial tissues and is shed in respiratory exudates, feces, saliva, urine, and conjunctival exudates for up to 90 days after natural infection. Replication in small intestinal epithelial cells results in the GI signs seen in acute CDV infection. Clinical signs of disease generally develop approximately 8 to 9 days after infection, with the severity of illness dependent on the strain of CDV and the immune status of the host when primary infection occurs.[154,155] If poor immune response exists, massive replication of the virus in the epithelial cells of the respiratory tract, GI system, and genitourinary system usually results in death from polysystemic disease. Dogs with moderate immune responses by days 9 to 14 postinfection, usually only have mild

respiratory or GI clinical signs related to replication in epithelial tissues. Dogs with good cell-mediated responses and virus-neutralizing antibody titers by day 14 postinfection clear the virus from most tissues and may not be clinically affected. Most infected dogs develop CNS infection, but clinical signs of CNS disease occur only in dogs with low or no antibody response.

Clinical Examination

Many clinically affected dogs are unvaccinated, inappropriately vaccinated, failed to receive colostrum from an immune bitch, or are otherwise immunosuppressed. Dogs with vomiting or small bowel–type diarrhea from CDV infection generally also have evidence of depression, malaise, oculonasal discharge, or cough. CNS signs may or may not be present. Tonsillar enlargement, fever, and mucopurulent ocular discharge are common physical examination findings. Increased bronchial sounds, crackles, and wheezes are usually auscultated in dogs with bronchopneumonia. When CNS disease occurs, it is usually characterized by hyperesthesia, seizures, cerebellar or vestibular disease, paresis, and chorea myoclonus that generally develop within 21 days of recovery from systemic disease. Ocular abnormalities associated with CDV infection include anterior uveitis, optic neuritis with resultant blindness and dilated pupils, keratoconjunctivitis sicca, and retinochoroiditis (medallion lesions).

Diagnosis

Lymphopenia and mild thrombocytopenia are consistent hematologic abnormalities in dogs with GI signs of CDV infection. Interstitial and alveolar pulmonary infiltrates are common radiographic findings in dogs with concurrent respiratory disease. Documentation of a fourfold increase in the CDV serum IgG titer over a 2- to 3-week period or detection of IgM antibodies in serum is consistent with recent infection or recent vaccination, but does not prove clinical disease. Definitive diagnosis of CDV infection requires demonstration of viral inclusions by cytologic examination, direct fluorescent antibody staining of cytologic or histopathologic specimens, histopathologic evaluation, virus isolation, or RT-PCR documentation of CDV RNA in peripheral blood, cerebrospinal fluid, urine, or conjunctival scrapings.[154,159-163] Viral inclusions can rarely be found in erythrocytes, leukocytes, and leukocyte precursors of infected dogs. Inclusions are generally present for only 2 to 9 days following infection and therefore often are not present when clinical signs occur. Recent administration of modified live CDV-containing vaccines can lead to positive results in direct fluorescent antibody assays and RT-PCR assays, making the positive predictive value of these tests less than 100% in recently vaccinated puppies. False-positive results have been detected occasionally in direct fluorescent antibody assays performed on conjunctival cells from specific pathogen-free puppies and results of these tests should be interpreted cautiously.[162]

Treatment

Therapy for the GI signs of CDV infection is nonspecific and supportive. Secondary bacterial infections of the GI tract are common and, if indicated, should be treated appropriately.

Prognosis

The prognosis for dogs with GI signs of CDV infection is generally good. However, in dogs with poor immune responses during primary infection, signs of CNS disease may develop several weeks after resolution of the GI tract signs. The prognosis for dogs with CNS disease resulting from CDV infection is poor.

Prevention and Public Health Considerations

CDV survives in exudates only for hours at room temperature and is susceptible to most routine hospital disinfectants. Dogs with GI or respiratory signs of disease should be housed in isolation so as to avoid aerosolization to susceptible populations and care should be taken to avoid transmission by contaminated fomites. Multiple effective CDV vaccines are available and when administered appropriately to immunocompetent puppies, can result in a sterilizing immunity that persists for years.[153,164] There is no proven public health risk associated with CDV.

Canine Parvoviruses

Etiology

Canine parvoviruses (CPVs) are nonenveloped DNA viruses that replicate in rapidly dividing cells.[143] These viruses emerged in the late 1970s, arose from the feline panleukopenia virus, and now have worldwide distribution. Currently, CPV-2b and CPV-2c are the predominant genotypes in most countries studied, including the United States.[165-168]

Pathophysiology

After a susceptible dog has oronasal exposure to secretions containing a CPV-2 virus, the organism infects lymphoid tissue and induces viremia for 1 to 5 days. CPV-2 preferentially infects rapidly dividing cells of multiple tissues, including the crypt epithelial cells of the intestine. Villus blunting, decreased absorption, inflammation, and necrosis are responsible for the classic signs of vomiting and diarrhea, the latter of which frequently contains blood. The severe inflammation and necrosis allow translocation of enteric flora that is commonly associated with sepsis. CPV-2 are shed for approximately 3 to 14 days after infection and shedding can begin prior to clinical signs. CPV-2 are environmentally resistant.

Clinical Examination

Dogs with partial or sterilizing immunity to CPV-2 frequently develop subclinical infection. Clinical signs are most likely to develop in puppies younger than 12 weeks of age that have no prior immunity. Inappetence is often the first clinical manifestation and most clinically affected puppies develop foul-smelling bloody diarrhea. Concurrent problems frequently include vomiting, leukopenia, fever, and secondary bacteremia, sepsis, and disseminated intravascular coagulation. Other clinical findings associated with CNS or cardiac inflammation may occur in some puppies.

Diagnosis

Presence of characteristic clinical and laboratory findings frequently lead to a presumptive diagnosis of CPV-2–associated disease. Infection can be documented by demonstrating the viruses in feces by electron microscopy, virus isolation, fecal antigen tests, or PCR assay of feces or blood.[143,169,170] Fecal antigen assays and PCR assays are used most frequently in clinical practice. Recent administration of modified live vaccines containing CPV-2 can lead to transient positive results in both types of assays.[169] Severe necrosis can lead to false-negative results in fecal antigen tests. Whether this occurs with PCR assay results has not been proven. It was recently shown that one currently available fecal antigen ELISA detects both CPV-2b and CPV-2c.[170]

Treatment

Clinical disease for CPV-2 infection is primarily supportive with administration of replacement fluids and electrolytes being paramount. Antiemetics are often indicated and antibiotics with a

Gram-negative and anaerobic spectrum are usually administered to puppies with clinical evidence of bacteremia or sepsis. Other therapies, like interferons, passive immunotherapy, colony-stimulating factors, and oseltamivir, are administered by some clinicians and in some small studies with inconclusive results.[171,172] Other GI supportive therapies, like bland diets and probiotics, are often prescribed during the recovery period.

Prognosis

The prognosis with CPV-2–associated GI disease can be poor. However, with rapid and appropriate supportive care many puppies will survive.

Prevention and Public Health Considerations

Avoiding exposure to CPV-2 is the best form of prevention until puppies have been fully vaccinated. However, the organisms are ubiquitous in areas frequented by dogs and exposure is common. Inactivated and attenuated live CPV-2 containing vaccines are available and appropriate vaccination results in sterilizing immunity in normal dogs and may be persistent for life. The AAHA supports the use of attenuated live, high-antigen mass vaccines in most situations.[153] There has been concern that the CPV-2b–containing vaccines do not cross protect against the more newly emergent CPV-2c.[173] However, recent studies show that cross protection induced by CPV-2b–containing vaccines is likely.[174,175] To date, there is no evidence of zoonotic transmission of CPVs to humans.

Feline Panleukopenia Virus

Etiology

Feline panleukopenia virus (FPV) is a nonenveloped DNA virus with worldwide distribution that potentially induces severe clinical signs of GI disease in susceptible cats.[176] Recently, it was shown that cats also can be infected with CPV-2b and CPV-2c.[177,178] Although many veterinarians in developed countries rarely diagnose FPV infection in client-owned cats, infection is still widespread in feral cats. In one study 33% of feral cats that presumably had not been vaccinated had FPV antibody titers.[179]

Pathophysiology

Previously exposed or vaccinated cats generally limit FPV replication and remain clinically normal. After a susceptible cat has oronasal exposure to secretions containing FPV, viremia occurs with an incubation period of approximately 2 to 7 days prior to development of clinical signs of disease. As for CPV in dogs, FPV invades and destroys actively dividing cells including those of the bone marrow, lymphoid tissues, intestinal epithelium, cerebellum of young animals, retina, embryonic, and fetal cells. In the GI tract, the resultant cellular destruction results in dilated intestinal crypts, degeneration of villi, edema, and necrosis, which are responsible for the clinical signs of disease. High numbers of viral particles are shed during the acute phase of infection and may be detected in feces for weeks following clinical recovery. FPV can survive for longer than a year in a suitable external environment.

Clinical Examination

The primary clinical signs of FPV infection include fever, depression, anorexia, vomiting, diarrhea, and acute death. Some cats with FPV have vomiting without diarrhea. On physical examination, dehydration, abdominal discomfort, thickened SI, and enlarged mesenteric lymph nodes may be detected. Less information is available concerning clinical signs in cats infected with CPVs, but these infections seem to be less severe than FPV infections.

Diagnosis

Presence of appropriate clinical signs and the presence of panleukopenia in a kitten that is FeLV antigen-negative strongly suggests FPV infection. As with dogs, feline parvovirus infections can be documented by demonstrating the agents in feces by electron microscopy, virus isolation, fecal antigen tests, or PCR assay of feces or blood.[176,180-182] Antigen assays developed for CPV-2 also detect FPV.[180,181] Recent administration of modified live vaccines containing FPV can give transient positive results in both canine antigen assays and parvovirus PCR assays so vaccination history should be considered in the interpretation of parvovirus test results in cats.[181,182]

Treatment

Clinical illness from parvovirus infections in cats is primarily supportive with administration of replacement fluids and electrolytes. Antiemetics are often used for persistent vomiting and antibiotic therapy for secondary bacteremia or sepsis may be indicated. Other therapies, like interferons, passive immunotherapy, and antiviral drugs, have been attempted by some but controlled data supporting use of these treatments is not available. GI supportive therapies like bland diets and probiotics are often prescribed during the recovery period.

Prognosis

Mortality rates for FPV infection in susceptible kittens can be very high even with administration of appropriate supportive care.[176] Clinical illness associated with CPV-2 infections in cats appears to be less severe and may have a better prognosis.

Prevention and Public Health Considerations

Immunization with FPV-containing inactivated or attenuated live vaccinations provides long-lasting sterilizing immunity. It is possible that some FPV-containing vaccines induce protection against canine parvovirus strains that may result in clinical illness.[183] The AAFP recommends use of attenuated live vaccines in high-risk kittens in an attempt to rapidly induce primary immune responses in the presence of potential maternal immunity.[158] There are no proven public health risk associated with parvovirus infections of cats.

Other Viruses

There are other viral infections of dogs and cats that may occasionally result in GI signs of disease in dogs or cats. For example, rotaviruses (dogs and cats), reoviruses (cats), and astroviruses (dogs and cats) have been detected in the feces of some animals with diarrhea.[143,184] FeLV infection is associated with a panleukopenia-like syndrome.[185] Both FeLV and feline immunodeficiency virus infections are associated with intestinal lymphoma and both organisms can induce immune deficiency during the late stages of infection, which can promote GI disease induced by opportunistic infections. Lastly, feline immunodeficiency virus infection can induce a distinct enteropathy that is associated with diarrhea.[154]

BACTERIAL OVERGROWTH (INTESTINAL DYSBIOSIS)

Alexander J. German

Bacterial Flora

The normal small intestinal flora is a diverse mixture of aerobic, anaerobic, and facultative anaerobic bacteria, full details of which

are covered in Chapter 2. The size of the bacterial microflora increases from the duodenum to the colon, and is regulated by various factors, including intestinal motility, substrate availability, cidal/bacteriostatic secretions (e.g., gastric, biliary, and pancreatic), and the presence of a functional ileocolic sphincter. Disruption of any of these factors may lead to qualitative or quantitative bacterial flora abnormalities.

There is much debate about what constitutes a normal bacterial population in dogs and cats. When luminal contents are sampled and conventional bacterial culture techniques are used, common species include *Staphylococcus* sp., *Streptococcus* sp., Enterobacteriaceae, *E. coli*, *Clostridium* sp., and *Bacteroides* sp., with a greater proportion of obligate anaerobic bacteria being reported in cats than in dogs. However, greater diversity can be seen when mucosal populations are assessed in addition to luminal contents.[1] Recent studies employing newer techniques (e.g., sequencing of the 16S rRNA gene, fluorescence in-situ hybridization), demonstrate that conventional techniques underestimate the true complexity of the bacterial flora because a significant number of bacterial species do not grow.[2,3] By conventional techniques, the total upper small intestinal bacterial counts of healthy cats range from 10^2 to 10^8 colony-forming units (CFU)/mL, and are higher than those reported in humans ($<10^{3-5}$ CFU/mL).[4] However, there is no clear consensus as to what constitutes a "normal" SI population in healthy dogs, and some studies suggest that healthy dogs can harbor up to 10^9 CFU/mL bacteria in the proximal SI.[5,6] Therefore, when using conventional culture techniques, the "cutoff" for normal flora in dogs and cats cannot be extrapolated from humans. Furthermore, clinicians must realize that numbers are likely to be greater, when taking into account the species that cannot be cultured by conventional means. The SI flora is relatively resistant to dietary changes; studies using different diets, or the addition of fructooligosaccharides to the diet have failed to demonstrate significant effects on the number or type of bacteria in the proximal SI of dogs and cat,[7,8] although some effects have been demonstrated on the colonic flora in cats.[9]

The resident bacterial flora is an integral part of the healthy SI; organisms are broadly divided into those with health positive effects, those that are health neutral, and, finally, those species that may have health-negative effects (Table 57-7; Figure 57-19). Beneficial effects include inhibition of the growth of bacterial pathogens (by producing antimicrobial factors, occupying receptor sites, and competing for nutrients), facilitating digestion and absorption of various nutrients, synthesizing vitamins, and stimulating immune function.[10] Health-negative effects include intestinal putrefaction, production of carcinogens, hepatic damage, and clinical signs such as diarrhea and constipation. In addition, studies implicate the intestinal flora in the development of obesity in humans.[11] Finally, loss of immunologic tolerance to the normal bacterial flora has been implicated in the development of chronic intestinal inflammation, abnormal intestinal function, and perhaps even neoplasia. An inability to tolerate a normal bacterial flora may explain the antibiotic-responsive enteropathy in German Shepherd dogs.[12]

Table 57-7 Comparison of Enteric Flora and Effects on Health in Various Species

	Humans	Dogs	Cats
Health positive	Bifidobacteria Lactobacilli	Bifidobacteria Lactobacilli	Lactobacilli
Health neutral	Enterococci *E. coli* Streptococci Bacteroides	Enterococci Eubacteria Streptococci Fusobacteria Bacteroides	Corynebacteria Enterobacteria Streptococci Clostridia Lc –ve Bacteroides
Health negative	*Pseudomonas aeruginosa* *Proteus* sp. Staphylococci Clostridia *Veillonella*	Clostridia	Clostridia Lc +ve

LC +ve: expresses the zinc-dependent proteolytic light chain (LC) portion of the clostridial enterotoxin. LC -ve: does not express the zinc-dependent proteolytic light chain (LC) portion of the clostridial enterotoxin.
From Rastall RA: Bacteria in the gut: friends and foes and how to alter the balance. *J Nutr* 134(8 Suppl):2022S, 2004.

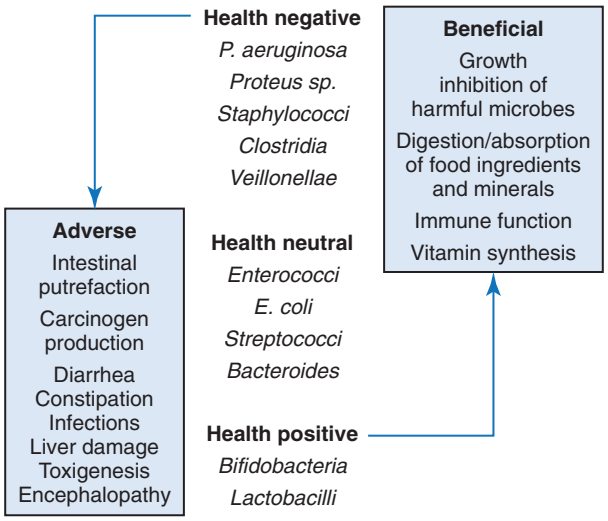

Figure 57-19 Comparison of enteric flora and effects on health in various species. (Redrawn from Rastall RA: Bacteria in the gut: friends and foes and how to alter the balance. *J Nutr* 134:2022S, 2004.)

Clinical Syndromes

Small Intestinal Bacterial Overgrowth (Or Intestinal Dysbiosis)

Genuine bacterial overgrowth is defined by an increase in the absolute number of bacteria in the upper SI during the fasting state (i.e., the number of "colony-forming units" cultured per milliliter of duodenal juice [CFU/mL]). In humans, SIBO arises secondary to a number of underlying disorders that interfere with the control mechanisms (as described previously). Although the existence of this condition in humans is not disputed, its existence in canine patients has been a subject of much controversy. By conventional methods of microbial culture in humans, SIBO is diagnosed when upper small intestinal bacterial numbers exceed 10^5 or 10^4 CFU/mL of intestinal juice for total bacteria and obligate anaerobes, respectively. Although these values were initially adopted for dogs, a number of studies suggest a larger microbial population (e.g., 10^7 CFU/mL or greater) in asymptomatic dogs.[6] Small intestinal bacterial numbers are also greater in cats. Therefore the current diagnostic criteria for SIBO in companion animals are inappropriate, and may lead to misdiagnosis in many cases. Nonetheless, a genuine bacterial overgrowth may exist in conditions equivalent to those in humans, and it is appropriate to use the term SIBO in such circumstances.

Box 57-5 Diseases Causing Secondary Small Intestinal Bacterial Overgrowth (Intestinal Dysbiosis)

Decreased gastric acid production (achlorhydria)
- Spontaneous (e.g., atrophic gastritis)
- Iatrogenic (e.g., acid-blocking drugs, surgical resection)

Increased small intestinal substrates
- Exocrine pancreatic insufficiency
- Malabsorptive disorders?

Partial obstructive disorders
- Chronic intussusceptions
- Stricture
- Neoplasia

Anatomic disorders
- Surgical resection of ileocolic valve
- Blind loop ("self-filling type")

Motility disorders
- Primary/idiopathic
- Secondary

Hypothyroidism
Electrolyte disorders
Intestinal surgery
Sepsis
Peritonitis

Potential associations have been reported for SIBO (Box 57-5). In all such conditions it is logical to assume that a genuine increase in bacterial numbers occurs, although few studies have documented its magnitude or whether the overgrowth is actually responsible for the clinical signs. Furthermore, although diagnostic investigations may identify the presence of secondary SIBO, in practice it is better to concentrate the diagnostic effort on identifying the underlying process. As in humans, therefore, canine SIBO is best viewed as a clinical sign or pathogenetic mechanism rather than a diagnosis in its own right. The consequences of a secondary SIBO include interference with absorption of nutrients (including cobalamin and possibly taurine) and fluid, because of microvillar enzyme dysfunction, altered mucosal permeability, deconjugation of bile acids, and stimulation of colonocyte secretion.[13,14]

Idiopathic Antibiotic-Responsive Diarrhea

Historically, the term *idiopathic SIBO* was used to describe an antibiotic-responsive condition of large-breed (especially German Shepherd) dogs,[13] in which no underlying cause could be recognized. In fact the most consistent sign, as suggested by the name, is a predictable response to and remission with antibacterial therapy. Given that recent studies question whether a genuine increase in bacterial numbers occurs, these cases have been renamed idiopathic antibiotic-responsive diarrhea (ARD).[12] Although cats might feasibly suffer from secondary SIBO, an idiopathic antibiotic-responsive condition similar to that in German Shepherd dogs has not been documented in this species.[15]

Most cases of idiopathic ARD have been seen in young German Shepherd dogs, although other breeds may be affected. There may also be similarities with the recently reported "tylosin-responsive diarrhea" (see later).[16] Recent hypotheses on pathogenesis suggest that host–bacterial interactions may be important. In this respect, ARD may develop secondary to defects in the mucosal barrier, aberrant mucosal immune responses, qualitative changes in the enteric bacterial flora, or a triangulation of these mechanisms. Defects in the mucosal barrier are supported by studies documenting abnormal permeability and the presence of brush-border enzyme defects.[13,14] A further extension of the hypothesis of defective mucosal barrier is the suggested association with IgA deficiency or dysregulation.[17] Some, but not all, reports suggest that German Shepherd dogs with intestinal disease may have defective small intestinal IgA production, although mucosal IgA^+ plasma cell numbers in affected dogs are either normal or increased.[18] However, IgA deficiency has not consistently been identified in German Shepherd dogs,[19,20] and the pathogenesis may be more complex. Recent studies suggest differences in relative expression of allelic variants of the IgA heavy gene in various dog breeds including German Shepherd dogs.[21,22] However, there is no clear association between the different allelic variants and the manifestation of GI disease.[23]

A further suggestion is that ARD arises secondary to a loss of tolerance toward endogenous bacterial antigen. Indirect evidence for this hypothesis comes from the findings that dogs with ARD have increased lamina propria $CD4^+$ T cells and increased expression of certain cytokines.[18,24] Such a hypothesis is supported by the fact that antibacterial agents lead to resolution of clinical signs, and decreased cytokine expression, but not a decline in bacterial numbers.[24] That the most effective antibacterials are those with immune-modulating properties (e.g., oxytetracycline, metronidazole, tylosin) may support this hypothesis. A final possibility is that the condition arises from defective acquired immune responses to an occult infectious agent (e.g., enteropathogenic *E. coli* or *Clostridium* species). Therefore the predisposition of German Shepherd dogs to this syndrome could be explained by genetic susceptibility to infection as a result of major histocompatibility complex class II antigen expression. In this respect, there could be similarities in pathogenesis with histiocytic ulcerative colitis in Boxer dogs.[25]

At the current time, there are many suggestions as to the pathogenesis of idiopathic ARD. Unfortunately, there is currently no direct evidence to support any particular hypothesis and further work is required.

Tylosin-Responsive Diarrhea

A condition has been described in dogs from Finland that has many similarities with idiopathic ARD.[16] Detailed investigations suggest that no underlying cause for signs could be determined; furthermore, bacterial numbers were normal, there were no characteristic changes on folate or cobalamin assay, and serum unconjugated bile acid concentrations were unhelpful. In addition, there was complete resolution of signs while on tylosin and, in many cases, relapse occurred upon discontinuation of therapy. The main difference from the classical description of idiopathic ARD was that a range of ages of dog was represented, and a mixed-pattern diarrhea noted. However, its true idiopathic nature was not demonstrated, as detailed diagnostics were lacking in many cases. Despite this limitation, the similarities with idiopathic ARD are striking; although the authors of the paper favored the term *tylosin-responsive diarrhea*, the likelihood is that this is a form of idiopathic ARD.

Clinical Findings

The most common signs for secondary SIBO and idiopathic ARD are chronic small intestinal diarrhea and weight loss or failure to thrive. Other signs include vomiting, appetite alterations (anorexia, polyphagia, scavenging, and coprophagia), excessive borborygmi, and abdominal discomfort. In addition, signs of large bowel diarrhea are sometimes noted. Signs are similar for tylosin-responsive diarrhea aside from the fact that a mixed-pattern diarrhea is seen.[16]

A thorough history is important, as this may demonstrate an underlying cause (e.g., previous GI surgery) in cases of secondary SIBO. If a partial obstruction is the cause of a secondary SIBO, the history often involves relapsing small intestinal diarrhea, weight loss, and a favorable response to antibacterial therapy; the intermittent clinical signs in such cases are thought to be the result of the recurrent diarrhea temporarily flushing out the overgrowth. For cases of idiopathic ARD, deterioration on glucocorticoid therapy may sometimes be noted in the history. Abdominal palpation may demonstrate a structural cause of secondary SIBO, for example, partial intestinal obstruction, although it is unremarkable in cases of idiopathic ARD.

Diagnosis

Secondary SIBO can be detected by a number of tests, but it is essential to detect the underlying cause. A complete investigation is recommended, for example, routine hematology, serum biochemical analysis, urinalysis, fecal bacteriology and parasitology, diagnostic imaging, and gastroduodenoscopy. EPI can be diagnosed by measuring serum TLI concentration, partial obstructions can be detected with diagnostic imaging, and an enteric pathogen might be detected on fecal analysis. However, findings are usually unremarkable or nonspecific in cases with idiopathic ARD. At this stage, a treatment trial with antibacterial agents (see Chapter 39) should be contemplated, because *response to empirical therapy* is currently the best means of diagnosing idiopathic ARD. True idiopathic ARD can be diagnosed if the following criteria are established:

- No other etiologic cause is identified with detailed preliminary testing and/or histopathologic assessment of small intestinal biopsies.
- There is a positive response to an antibiotic trial (e.g., resolution of clinical signs including weight gain).
- Relapse of clinical signs occurs upon withdrawal of treatment, and remission is achieved when antibiotic therapy is recommenced.

However, although response to antibacterials is critical for the diagnosis, a thorough diagnostic evaluation should ideally be performed to make certain that other reasons for a response to antibacterials (especially the causes of SIBO) have first been eliminated. Given current concerns over the development of antibiotic resistance by various bacterial flora, indiscriminate use of antibiotics in dogs and cats with diarrhea or gastroenteritis is ill-advised. Although the consequences of inappropriate antibiotic therapy are often mild and self-limiting, postantibiotic salmonellosis has had fatal consequences in cats.[26]

Diagnostic Tests for Small Intestinal Bacterial Overgrowth

Both direct and indirect tests are available, but none have been properly validated for companion animals, and widely accepted reference ranges have not been properly established. Therefore the results of these tests must be interpreted with caution. The main direct test is quantitative bacterial culture of duodenal juice. Indirect tests include hydrogen breath tests and serum biochemical analyses.

The current diagnostic gold standard for SIBO is *duodenal juice culture*, and the most commonly quoted figure for the upper limit for small intestinal bacterial numbers is 10^5 CFU/mL. However, the validity of this cutoff is questionable because quantitatively larger numbers (approximately 10^7 CFU/mL in some studies) have been documented in healthy dogs, while numbers as high as 10^9 CFU/mL have been found occasionally in cats and asymptomatic dogs.[4,5,8,9] Some of the discrepancies may reflect difficulties and differences in the methodology, as numbers vary widely when individual animals are repeatedly sampled.[1]

Use of an inappropriately low cutoff value will lead to the overdiagnosis of SIBO, probably explaining why it has been reported to be present in 50% of dogs with chronic intestinal disease.[27] In reality true secondary SIBO is rare, with the exception of SIBO secondary to EPI. An increase in small intestinal bacterial numbers has been documented in experimentally induced EPI, although bacterial numbers decrease upon treatment of the EPI with enzyme replacement.[28] Therefore in many cases the SIBO itself is of no significance. However, a proportion of naturally occurring EPI cases respond suboptimally to pancreatic enzyme supplementation alone, and may require concurrent antibiotic therapy. Given that the majority of dogs affected with EPI are German Shepherd dogs, it is not clear whether this is the result of secondary SIBO, or of a concurrent idiopathic ARD. Furthermore, duodenal juice collection is technically demanding, expensive, and rarely performed routinely. Attempts at improving diagnostic accuracy have included measuring bacteria in mucosal biopsies samples, but this has not been shown to be of added benefit.[1] Finally, quantitative PCR techniques may result in improved reliability by producing a more reliable bacterial yield[2,3]; however, they have not yet been used as a means of attempting to diagnose possible SIBO.

Given the limitations of the diagnostic gold standard, indirect tests have been adapted from human methodology for use in the clinical setting. The most commonly used diagnostic tests in dogs are the measurement of *serum folate and cobalamin concentrations*. The utility of these assays is based on the theory that many bacterial species synthesize folate, while others can bind cobalamin; therefore increased numbers of small intestinal bacteria may elevate serum folate concentrations, decrease serum cobalamin concentrations, or both. However, measurements of these parameters have poor sensitivity and specificity for canine SIBO, and cannot differentiate dogs with ARD from those with other etiologies.[12] Consequently the use of folate and cobalamin measurements for the diagnosis of SIBO, and especially ARD, is questionable. However, they may still be of value in detecting vitamin malabsorption (see following discussion).

An alternative indirect means of detecting SIBO was the *measurement of hydrogen concentrations in exhaled breath*, either in a fasted state or after administration of a test meal.[29-32] However, protocols have not been universally accepted and this remains a research technique. Canine assays for *SUBA* were also recommended at one time.[33] These tests relied on the principle that conjugated bile acids that are secreted into the intestines can be deconjugated by some bacterial species (e.g., *Clostridia*, *Bacteroides*), the so-called unconjugated bile acids, which then are absorbed passively and can be measured in blood. Although early work suggested that these assays might be promising,[33] more recent work suggests that they are of limited use in the diagnosis of idiopathic ARD.[12] To my knowledge, these assays are no longer available.

In summary, none of the diagnostic tests currently available are recommended for diagnosis of either secondary SIBO or idiopathic ARD. Where secondary SIBO is suspected, it is preferable to look for the underlying cause. Given that neither quantitative bacterial culture nor indirect tests reliably identify cases that respond to antibacterials, and given that correlation between all methods is poor, their use in the diagnosis of idiopathic ARD is not recommended.

Treatment

Secondary Small Intestinal Bacterial Overgrowth

Although antibacterial therapy will improve clinical signs, appropriate treatment for the underlying condition is preferable. For EPI, pancreatic enzyme supplementation can reduce bacterial numbers because exogenous proteases have antibacterial properties. Experimental studies show that bacterial numbers in dogs with EPI decline with pancreatic enzyme supplementation alone (probably because enzymes are bactericidal and available substrate is reduced), suggesting that the problem will resolve of its own accord. However, in some clinical cases concurrent antibacterial therapy is necessary.

Idiopathic Antibiotic-Responsive Diarrhea and Tylosin-Responsive Diarrhea

For idiopathic ARD, an appropriate antibacterial should be administered for an initial period of 4 weeks. If signs relapse, a longer course may be required, and many cases require long-term (or lifelong) therapy to maintain remission of signs. The choice of antibacterial is controversial; most cases of idiopathic ARD respond well to oxytetracycline at 10 to 20 mg/kg TID PO and for long-term therapy, low doses can often maintain clinical remission (10 mg/kg SID PO). However, it should not be used before permanent tooth eruption because of staining of tooth enamel. Other suitable drugs include tylosin at 10 to 15 mg/kg BID, which, unsurprisingly, is the drug most commonly used for tylosin-responsive diarrhea in Finland. A final option is metronidazole, given at 10 mg/kg TID PO.

The mechanism of action is not currently known. Interestingly, when oxytetracycline is administered bacterial numbers do not decline significantly and resistance soon develops, despite resolution of clinical signs. Hypotheses include the possibility that these drugs are exerting a selection pressure on the intestinal microflora in the same way as a prebiotic. Alternatively, immunomodulatory effects, as reported for some of the tetracyclines, are possible.

Currently, oxytetracycline remains the first choice for idiopathic ARD in the United Kingdom, but its use for secondary SIBO is controversial and other drugs may be more appropriate, for example, tylosin or metronidazole, as their spectrum of activity is better for the organisms that are likely to be present in secondary SIBO. Furthermore, some authors question whether oxytetracycline should be used at all because it is associated with rapid development of plasmid-mediated antibiotic resistance.[34] However, given that long-term efficacy is maintained in most cases, oxytetracycline may not be acting through its antibacterial properties as it does not significantly reduce SI bacterial numbers.[24] Instead, it may either provide a selective pressure on the intestinal flora encouraging the establishment of less harmful bacteria or utilize immunomodulatory effects, which this antibiotic group possesses. Immunomodulatory activities also have been suggested for other antibacterials, namely metronidazole and tylosin, that are commonly used to treat ARD. Finally, the drug is well-tolerated and there is no evidence that adverse effects (e.g., antibacterial-associated diarrhea) are a common effect of long-term oxytetracycline use.

Whichever antibacterial is chosen, a 4- to 6-week course is appropriate initially, although the antibiotic should be changed after 2 weeks if response has been suboptimal. In some cases, premature cessation of treatment can lead to relapse and prolonged therapy is often necessary. In some animals, a delayed relapse occurs several months after cessation of antibiotics, and such cases either require repeated courses or indefinite therapy. Efficacy is often maintained despite reducing the dosage from thrice to even once daily. Dogs may also "outgrow" the problem with age, either as a result of a decrease in caloric intake, or because of developing maturity to the mucosal immune system. It also has been suggested that idiopathic ARD in German Shepherd dogs may predispose individuals to IBD in later life, but there is currently no direct evidence to support this supposition.

Adjunctive therapy may be helpful in cases of both secondary SIBO and idiopathic ARD. This involves the feeding of a highly digestible diet. The need for fat restriction is logical for secondary SIBO, given that hydroxylation of fatty acids is implicated in the disease pathogenesis. However, whether this mechanism is involved in the pathogenesis of idiopathic ARD (and tylosin-responsive diarrhea) is not currently known. In addition, restricting fat may make it difficult for a cachectic patient to gain body weight and condition. Other suggestions include adding prebiotics (e.g., fructooligosaccharides) to the diet. Although these can modulate colonic microflora,[9] the effect on small intestinal bacteria is questionable[8] and there is limited current evidence for efficacy in clinical cases. Similarly, there is no published evidence supporting the use of probiotics for either secondary SIBO or idiopathic ARD. Finally, if low cobalamin concentrations are documented, parenteral cobalamin therapy is warranted.

Prognosis

The prognosis for secondary SIBO depends upon the nature of the underlying cause, and success of therapy for the particular condition. The prognosis for idiopathic ARD is guarded; many cases relapse after therapy is discontinued, and then require prolonged or even lifelong treatment. Other cases, however, require only occasional short courses of antibacterials to maintain clinical remission. Some cases may improve spontaneously as the animal enters adulthood.

OBSTRUCTION

Nick Cave

Definition

Obstruction of the SI is a common problem in companion animal practice. Severity of intestinal obstruction is classified according to a number of parameters including clinical signs, site, and patency. If ingested nutrients are unable to pass beyond the point of obstruction, it is termed *complete obstruction*. If some nutrients pass through the point of obstruction, even if only the liquid phase, it is termed *partial obstruction*. Physical or mechanical obstructions can result from intraluminal foreign bodies, intramural masses, and extramural compression. Functional obstructions result from generalized hypomotility or spasticity of a bowel segment. Functional obstructions are discussed in the "Dysmotility" section, and the mechanical obstructions of the intestine are discussed in this section.

Foreign Bodies

Luminal foreign bodies are the most common cause of acute intestinal obstruction. In a series of 174 cases in dogs in the United Kingdom, latex nipples were the most common foreign bodies, followed by plastic or rubber balls, stones, and strings.[1] In the same study, linear foreign bodies accounted for 44% of feline cases. In a survey of working farm dogs in New Zealand, plastic ear tags and bones constituted 66% of the intestinal foreign bodies.[2] Thus the

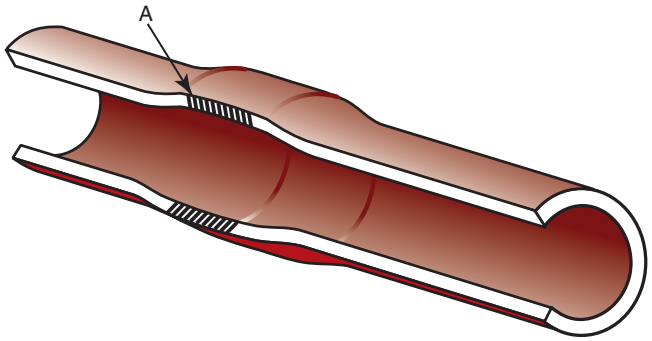

Figure 57-20 An annular bowel lesion or region of hypomotility (*shaded area*) can lead to intussusception when the adjacent contracted segment produces a kink at the border between normal and abnormal tissue (labeled A). The advancing wave of peristalsis drives the proximal segment into the lesional area creating an intussusception.

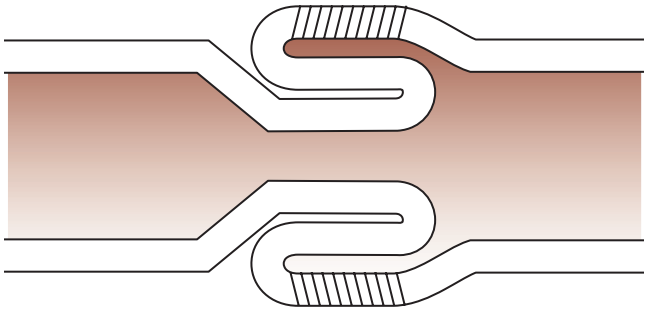

Figure 57-21 An aborad or direct intussusception is the most common form seen in dogs and cats. The internal section is termed the *intussuscipiens*, and the external (*shaded*) section is termed the *intussusceptum*.

nature of intestinal foreign bodies tends to reflect local practices and customs. In cats, trichobezoars (hairball obstructions) can cause partial or complete intestinal obstruction, often at a site of preexisting infiltrative intestinal disease.[3] Obstructive trichobezoars are rarely diagnosed in dogs and when they are seen, it is usually at a site of preexisting intestinal narrowing.[4] Foreign bodies can lodge anywhere along the small and large intestine, and there does not appear to be a predilection site, except that the jejunum, because of its length, is the most commonly affected region.[1,5] Linear foreign bodies may anchor around the base of the tongue, pylorus, or at more distal sites.[1,6] Most linear foreign bodies do not themselves obstruct the intestine, but gathering and pleating of the intestine around the foreign object causes partial to complete obstruction.

Intussusception

Intussusception represents an uncommon form of bowel obstruction, defined as the telescoping of a (usually) proximal segment of the GI tract, called the *intussusceptum*, into the lumen of the adjacent distal segment of the GI tract, called *intussuscipiens*. The most common sites in the dog are the ileocolic junction or jejunojejunum, whereas in cats, jejunojejunal is the most common type.[7-9] In general, an intussusception occurs when a migrating peristaltic wave reaches a fixed or noncontractile segment (labeled A in Figure 57-20). If the fixed or noncontractile segment is of sufficient diameter, and of sufficient length, then the proximal contracted segment will fold into the outer intussuscipiens (Figure 57-21). The majority of intussusceptions develops aborally in the direction of normal

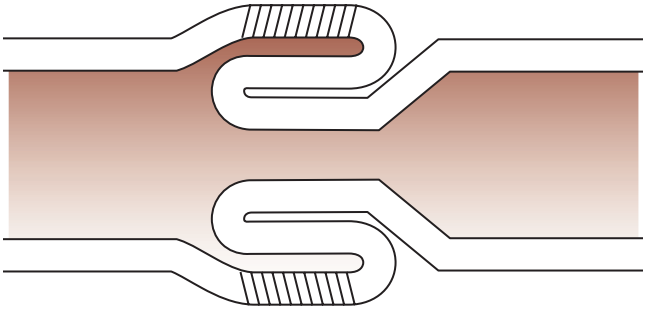

Figure 57-22 An orad or retrograde intussusception.

peristalsis, but can develop in an orad, or retrograde, direction (Figure 57-22). Alternatively, an intraluminal, or extraluminal linear fixed linkage such as a short linear foreign body, can result in formation of a kink in the wall, which progresses to a fold and then intussusception.[10]

Intussusceptions are generally more common in younger animals, many younger than 1 year of age, although the age distribution in cats appears to be bimodal.[7,8,11] Intussusception in young cats is most likely to be idiopathic, whereas in older cats it is more likely to be secondary to infiltrative disease such as lymphosarcoma or IBD. Intussusception has also been recorded in queens during the immediate postpartum period.[12] Most intussusceptions in dogs are idiopathic, although any disease that can disturb intestinal motility, such as viral enteritis, neoplasia, foreign bodies, and prior abdominal surgery, can lead to intussusception.[8,9,11,13,14] In dogs treated for severe viral enteritis (e.g., parvoviral or coronavirus), intussusception should be suspected if a sudden unexplained deterioration occurs.[13,15] Likewise, a newly diagnosed intussusception should not be assumed to be of idiopathic origin. Diagnosis always requires consideration and appropriate testing for an underlying condition.

Pathophysiology

Motility

Motility at the site of the obstruction is altered through the multiple pathogenetic effects of ischemia, inflammation, bacterial toxin absorption, and direct mechanical stimulation. In acute experimental jejunal occlusion, intestinal motor activity is almost immediately altered.[16] Initially, there is increased motor activity proximal to the obstruction, and reduced motor activity distal to it (the intestinointestinal reflex, see Chapter 1). Within 2 to 3 hours, however, hypermotility extends proximally to the duodenum, and hypomotility extends distally from the obstruction to the terminal ileum. Following occlusion of the small intestinal lumen, continued peristaltic activity proximally leads to transient increases in intraluminal pressure. Normal intraluminal pressure rarely exceeds 4 mm Hg, whereas after experimental occlusion in dogs or cats, proximal intraluminal pressure is sustained between 5 and 10 mm Hg, and peaks at 20 mm Hg during intense contractions.[17,18]

In chronic partial obstructions, there is an extensive remodeling of the muscularis layer proximal to the obstruction leading to smooth muscle hyperplasia and hypertrophy, neuronal degeneration, neoangiogenesis, and fibrosis.[19-21] (Muscularis remodeling does not occur distally despite the local mucosal atrophy that develops acutely.) The net effect of these changes is an increase in wall stiffness, loss of slow-wave activity, reduced neural responses, and reduced contractile capacity. In chronic partial obstruction, wall stress and strain rise significantly proximal to the obstruction as a

bolus is advanced by peristalsis. Mechanoreceptor stimulation triggers further increases in pressure to force the chyme through the obstruction. This may lead to localized luminal bulging. Most of this remodeling and degeneration is reversible over time once the obstruction has been removed, although neuronal degeneration may be irreversible and hypomotility may persist in some patients, particularly in more chronic cases.[22]

Mucosa

The mucosa proximal to the occlusion is stimulated to secrete water and electrolytes into the intestinal lumen. Distal to the obstruction, villus atrophy of the mucosa and reduced brush-border enzyme expression develop rapidly.[18] Although physical disruption to local vascular supply occurs, increased vascular pressure is not the mechanism for fluid hypersecretion. When the jejunum is experimentally occluded surgically in gnotobiotic dogs, proximal segment hypersecretion does not take place,[23] illustrating the role of the enteric microflora in the pathogenesis of the continued fluid secretion proximal to the obstruction. Vomiting of this hypersecreted fluid contributes to the dehydration, acid–base, and electrolyte disturbances of the disorder. Although there is a relative hypersecretion, the actual volume of fluid that accumulates proximal to the acute obstruction is surprisingly small and of low protein content.[24]

Intussusceptions commonly lead to more significant vascular compromise, and both lymphatic and venous vessels are occluded resulting in edema and hemorrhage, both intramurally, and into the intestinal lumen. Intramural and serosal hemorrhage can lead to fibrinous adhesions that prevent manual reduction of the intussusception.

Bacteria

Experimental occlusion of the SI leads to rapid death in conventional raised dogs. However, gnotobiotic dogs can survive for prolonged periods despite complete intestinal obstruction.[25,26] When a mixed intestinal microflora is reintroduced into an occluded intestine, it too leads to rapid death. However, common intestinal bacteria vary greatly in their pathogenicity after intestinal obstruction. *C. perfringens* mono-inoculation results in rapid death, *Bacteroides fragilis* mono-inoculation results in death after several days, whereas *E. coli* mono-inoculation inconsistently results in death. This emphasizes the importance of treating cases of intestinal obstruction with anaerobicidal antimicrobial agents.

The clearing function of the peristaltic waves is perhaps the most important factor that limits microbial numbers in the SI. It has long been known that a reduction in MMC activity leads to an increase in intraluminal bacteria, and a qualitative shift in the population distribution toward Gram-negative and anaerobic bacterial species.[27] In the segment proximal to an acute intestinal obstruction, there is a marked proliferation of both aerobic and anaerobic enteric microflora, but most markedly anaerobic and Gram-negative facultative aerobes.[28,29] Overgrowth of bacteria is required for induction of proximal enteritis and disturbance in mucosal secretory function. At the same time, bacterial translocation into the systemic and portal circulation is dramatically increased and leads to colonization of the hepatic parenchyma.[28] In experimental jejunal obstruction in rats, technetium-labeled *E. coli* readily translocate within 4 hours of the obstructing event.[30] Bacteria migrate from the strangulated segment into the peritoneal cavity, and are then disseminated systemically. Significant translocation of bacteria is observed in the heart, liver, and kidney. Higher numbers of bacteria migrate from the strangulated section, consistent with the importance of vascular integrity for maintaining normal barrier function.

Pain

Intestinal obstruction is a painful condition, although some affected animals do not demonstrate much discomfort. Several factors contribute to pain generation, including intestinal dilation, mechanical trauma, ischemia, and bacterial toxin absorption. Sensory nerve fibers innervating the mucosa, submucosa, muscle, myenteric plexus, and serosa, respond to mechanical distortion of the gut wall, particularly distention, but also contraction of smooth muscle, and changes in the chemical environment of the intestinal lumen.[31] Distention triggers release of substance P, which stimulates the secretomotor neurones via neurokinin $(NK)_1$ and NK_3 receptors, resulting in chloride and water secretion.[32] Through mediators such as substance P, nitric oxide, and neurokinin A, motor activity can be stimulated or inhibited, and alterations in electrolyte, mucus and fluid secretion, arteriolar dilation, vascular permeability, mast cell degranulation, and activation of immune cells can be induced.[31] Thus there is a bidirectional interaction in pain sensation and neurogenic inflammation during intestinal obstruction.

Intestinal Wall Integrity

As pressure at the site of obstruction progressively increases, lymphatic and then venous drainage is impaired while arterial perfusion is maintained, resulting in intestinal wall edema. Local endothelial barrier leakage and arteriovenous shunting causes intestinal ischemia and reperfusion injury with concomitant barrier dysfunction. Full-thickness wall necrosis may occur, leading to gross contamination of the peritoneum and septic peritonitis.

Differential Diagnoses

Patients with intestinal obstruction can present with acute clinical signs, as is often the case with complete obstruction, or with chronic clinical signs, which is more consistent with a partial obstruction. The differentials for patients with an acute onset of signs are those common to any patient with acute-onset vomiting, although acute intestinal obstruction is usually distinguished from self-limiting causes on the basis of the severity, history, and physical exam findings. The key differential diagnoses for acute onset of vomiting are discussed more fully in Chapter 23. Key differentials for abdominal pain are discussed in Chapter 6. Chronic partial intestinal obstruction should be considered for any patient with chronic vomiting, small intestinal-type diarrhea (Chapter 11), weight loss (Chapter 24), and evidence of PLE.

Evaluation of the Patient

History

Although any dog or cat of any age or breed can present with an intestinal foreign-body obstruction, young dogs and cats, especially large-breed dog conformations, are overrepresented in most case series.[1,33] Intussusceptions are more common in young dogs and cats, although they may be secondary to underlying disease (e.g., lymphoma) in older animals. The clinical signs of intestinal obstruction vary with the site and completeness of obstruction, degree of distention, presence of peritonitis, and whether there is concurrent systemic sepsis. The most obvious clinical signs are anorexia, abdominal pain, depression, and vomiting. In experimental intestinal obstruction, these signs are followed by profound dehydration, shivering and ataxia, and eventually collapse, coma, and death.[34] Chronic partial foreign-body obstructions and chronic patent intussusceptions are generally less severe in their clinical signs, for example,

vomiting and abdominal pain, and consequently nonspecific lethargy, inappetence, intermittent vomiting, and weight loss may be the only presenting clinical complaints. In acute cases, owners will frequently be aware of the possibility of foreign-body ingestion, and they should be questioned closely to ascertain the possibility.

In experimental complete occlusion of the duodenum, vomiting occurs within hours, and in almost all cases.[34] In surgically induced distal jejunal occlusion in dogs, only four of 38 dogs vomited during a 4-day postoperation period, and the volume of vomitus was small.[24] Thus the frequency and severity of vomiting may more importantly reflect the site of occlusion and factors other than simple mechanical occlusion. Nonetheless, vomiting is the most common presenting sign in both dogs and cats. When absorptive capacity is preserved oral to the site of the obstruction, fluid losses in vomitus may not be as severe. In general, it appears that more distal obstructions (e.g., jejunal) are associated with a lower frequency of vomiting than are seen with proximal obstructions (e.g., duodenal).[24] Proximal obstructions generally result in the loss of large amounts of ingested and secreted intestinal fluid. The duration of vomiting prior to presentation for a complete obstruction is usually 2 to 3 days, but partial obstructions can cause chronic intermittent vomiting for many weeks or months.[1,33,35] Thus intestinal foreign bodies are an important differential for patients presenting with a history of acute or chronic vomiting.

Diarrhea is less frequently reported in patients with acute complete intestinal obstruction, but it may be an important clinical sign with chronic partial obstruction. Patency of the lumen of an intussusceptum is often maintained with partial obstruction, such that intermittent vomiting and chronic diarrhea are frequently reported. Diarrhea associated with chronic partial obstruction is usually described as small bowel in character, and can be hemorrhagic in acute cases.[1] Ileocolic intussusceptions particularly are associated with hematochezia. Chronic weight loss and evidence of PLE are also seen in partial obstructions, especially intussusceptions.[36]

Physical Examination

Thorough physical examination is imperative for the differentiation of self-limiting causes of acute vomiting from intestinal obstruction and other life-threatening conditions. A diagnosis of intestinal foreign-body obstruction or intussusception can frequently be made on the basis of history and physical examination alone. Animals will be variably dehydrated, and in severe cases, physical parameters indicative of poor perfusion and shock may be present. Normothermia, fever, and occasionally hypothermia may be present according to disease duration, severity of necrosis and inflammation, presence of systemic sepsis, and cardiovascular status. Abdominal pain may be manifested by hunched stance, praying position, or a reluctance to stand and move.

Abdominal palpation may permit localization of pain to a specific region of intestine, or it may be more generalized, especially when peritonitis is present. Contraction of the abdominal musculature, vocalization, and aggression may indicate abdominal pain. Cats will frequently slump into lateral recumbency when abdominal pain is elicited. In many cases, a foreign body can be directly palpated.[1] Plication or bunching of the intestines may be suggestive of a linear foreign body. Gas-filled loops of bowel often are painful on palpation though minimally dilated. Intussusceptions frequently can be palpated as a firm, often painful tubular structure that is well demarcated, and cannot be indented with digital pressure, thus differentiating it from feces. The most common location for an intussusception is the cranioventral region. In some cases with severe abdominal pain, palpation may not be possible until heavy sedation or anesthesia is induced. If sedation is required for further investigation, careful palpation should be repeated.

Linear foreign bodies can have a proximal anchor point anywhere along the intestinal tract. Anchoring around the base of the tongue is sufficiently common as to make careful examination of that area imperative in a vomiting patient.[1,33]

Laboratory Evaluation

The severity of hematologic and serum biochemical changes depends upon the severity and duration of the obstruction, and presence of complicating factors such as peritonitis, systemic inflammatory response, and hypovolemia. In experimental mechanical occlusion of the jejunum, hemoconcentration, leukocytosis, mature neutrophilia, and progressive hypoglycemia are common.[34] A degenerative left shift in the white blood cell count is more likely when concurrent peritonitis is present.[37,38] Extravasation and hemorrhage may lead to hypoproteinemia, and variable degrees of azotemia may be seen consistent with reduced renal perfusion and/or blood loss.[34] Although important in the staging of disease, it is important to note that the degree of abdominal cytopathology, hematology, and serum biochemical changes does not predict survival following surgery for septic peritonitis.[37,38]

Patients with intestinal obstruction develop progressive dehydration, electrolyte imbalance, and acid–base disturbances. In a study of 138 dogs with intestinal foreign bodies, the most common electrolyte and acid–base abnormalities were hypochloremia (51.2%), metabolic alkalosis (45.2%), hyperlactatemia (40.5%), hypokalemia (25%), and hyponatremia (20.5%).[33]

It has been previously suggested that obstructions of the proximal SI are more likely to result in the loss of gastric chloride in excess of sodium. This would lead to an increased strong ion difference and a metabolic alkalosis, whereas more distal small intestinal obstructions would more likely result in metabolic acidosis.[39] Evidence-based data studies by Boag et al. have instead shown that there is no association between the site of obstruction (proximal vs. distal) and biochemical abnormalities including venous pH, serum lactate, potassium, and chloride.[33] Hypochloremic, hypokalemic metabolic alkalosis was reported in 12% and 13% of dogs with proximal and distal obstructions, respectively.

Chronic intussusception in dogs is commonly associated with hypoproteinemia, and varying degrees of hyponatremia, hypokalemia, and hypochloremia.[36] Because of the strong association between preexisting enteric disease and the development of intussusception, it is likely that biochemical abnormalities are influenced by the underlying disease, rather than the effect of the intussusception.

Diagnostic Imaging

History and physical examination findings, including direct palpation of a foreign body or intussusception, are often sufficient to justify preparation for exploratory laparotomy, but direct imaging should be performed to confirm the diagnosis prior to laparotomy. Chapter 26 discusses diagnostic imaging of the intestinal tract more fully.

Plain Radiography

Radiopaque foreign bodies are easily identifiable on plain radiography (Figure 57-23), but even when present, it is imperative to determine whether there is evidence of obstruction that would warrant immediate surgical intervention, or if it is reasonable to delay surgery to determine whether the object will pass from the GI tract. In other cases where there is intussusception or a radiolucent

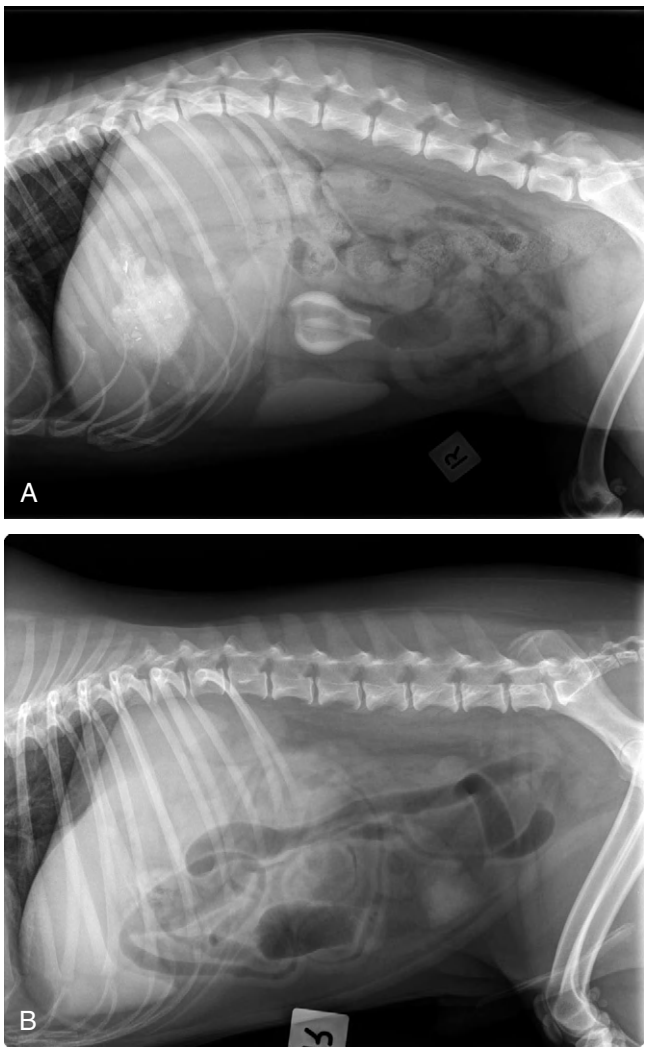

Figure 57-23 **A,** Lateral abdominal radiograph of a dog with a radiopaque foreign body. Notice the fluid-distended loop of small intestine cranial to the object. Radiopaque sand-like material can be seen in the stomach. **B,** Ventrodorsal radiograph of the same dog. In the left caudal abdomen there is a focal region of increased soft tissue/mild mineral opacity within the intestinal lumen associated with fluid distention on one side, and gas distention (with fluid bubbles) on the other side.

foreign body, the radiographic evaluation is focused on the detection of dilated intestinal loops, "gravel" appearance of intestinal contents, free abdominal gas and loss of abdominal detail, and intestinal mass effect.

Dilated Intestinal Loops. Intestinal obstruction leads to the accumulation of variable amounts of gas and/or fluid in the proximal segment. Several different parameters for assessing intestinal width have been suggested, but the best validated parameter is serosal-to-serosal width exceeding 1.6 times the height of the fifth lumbar vertebral body at its narrowest point.[40] Other suggested parameters include serosal-to-serosal width less than 1.2 cm in the cat, and less than twice the width of the twelfth rib.[41] With changes in patient positioning, gas and fluid will redistribute along the normal intestine, thus orthogonal views are important to increase sensitivity and specificity. Complete obstruction will usually lead to dilation of more than one loop proximally, and chronic obstruction can lead to extensive dilation. As the bowel becomes progressively distended, affected loops may lie closely adjacent to one another, creating a "stacked" appearance effect. In contrast, partial or very acute obstructions may not be associated with significant dilation at all. Thus the absence of intestinal dilation should not be used to exclude the possibility of intestinal obstruction.

Linear foreign bodies characteristically produce a bunched or pleated appearance on plain or contrast radiography.[41] In addition to intestinal pleating, tapering, enteric gas bubbles, intestinal needles, and evidence of bowel obstruction are common.[6] Linear foreign bodies are more likely to be associated with peritonitis from perforation of affected loops, which can produce a "ground-glass" appearance and loss of serosal detail, as well as potentially leading to the accumulation of free abdominal gas.

"Graveling" of Intestinal Contents Proximally. Chronic partial obstructions cause sedimentation and accumulation of insoluble, granular, slightly opaque material proximal to the site of obstruction. The appearance of this material has been described as "graveling" and "fecal-like," and its presence in the SI, rather than colon, is indicative of obstruction.

Free Abdominal Gas and Loss of Serosal Detail. The presence of free abdominal gas and loss of serosal detail on plain radiography is strongly associated with GI perforation and peritonitis, and is an indicator for rapid surgical intervention. Peritoneal gas frequently accumulates dorsally on the lateral radiograph and can be seen delineating the diaphragm dorsally and cranially to the liver margin. On the ventrodorsal image, gas may again be seen between the diaphragm and liver margins.

Intestinal Mass Effect. The differentiation between radiolucent foreign body and intussusception on plain radiography is often difficult, and a simple characterization of ileus with suspicion of obstruction may be the limit of confidence. In some cases, an intussusception may create a soft-tissue density or mass effect. Ileocolic intussusceptions are characteristically apparent in the ventrodorsal view caudal to the stomach, causing displacement of the unaffected SI caudally and to the right.

Contrast Radiography

Barium-contrast radiography is indicated if the history and physical examination is equivocal, plain radiography is nondiagnostic, and ultrasonography is not available. The recommended dose is 10 to 15 mL/kg of a 30% wet weight suspension of barium sulfate. Films should be taken at 0, 15, 30, and 60 minutes following barium administration and hourly thereafter until a diagnosis is made or the barium has been transported to the colon. In health, the barium should arrive in the ileum within 60 minutes and the ileocecal sphincter after 2 hours. Filling defects and transit time are the key radiographic features for obstruction. The pattern of barium at the site of obstruction varies greatly. Contrast may accumulate proximal to the obstruction, precisely delineating the shape of the foreign body, or revealing luminal filling defects. In the case of intussusception, patency of the lumen of the intussuscepted segment determines if barium will pass, which can be seen as a thin stream of barium within the narrowed lumen. In some cases, barium will flow into the surrounding enveloping intussuscipiens producing a tube-within-a-tube effect.

Contrast radiography can also be performed utilizing BIPSs. BIPSs are a convenient method to detect partial intestinal obstructions.[42] The principal advantage of BIPS over liquid barium is the ease of interpretation, especially in cases where a partial obstruction

can be excluded by unimpeded transit into the colon. BIPSs are administered as capsules or mixed with food, thus avoiding the difficulties of administration of liquid barium. Unlike liquid barium, BIPS transit more closely approximates the transit of food in the GI tract. In cats and dogs that present for chronic vomiting or diarrhea, one protocol is to (a) administer the BIPS with food, (b) take radiographs 2 hours later to rule out gastric dumping, and (c) take radiographs at 8 hours to detect delayed gastric emptying. If the radiographs taken at 8 hours do not reveal some large spheres in the colon, a third set of radiographs later that same day or early the next morning should be taken to rule out partial bowel obstructions. Persistent bunching of the spheres in the SI is highly suggestive of physical obstruction of the small bowel, particularly if the markers have bunched in a dilated loop of SI or if "graveling" is apparent. If the small bowel loop in which the bunching occurs is not dilated or graveling is not apparent, a repeat radiograph should be taken 1 or 2 hours later to ensure persistence of the bunching.

Fasting and enema administration improve the diagnostic accuracy of liquid contrast techniques, and a full study may require 12 to 24 hours to definitively establish transit into the colon. In acute presentations, and especially when the patient is compromised or septic, these require a delay in intervention that may not be optimal. For these reasons, and for reasons of diagnostic accuracy, contrast radiography has largely been supplanted by ultrasonography as a means of detecting mechanical intestinal obstruction.

Ultrasonography

Intestinal dilation caused by mechanical obstruction is readily detected with ultrasonography. In addition, intestinal motility can be subjectively assessed in the proximal and distal segments. It has been reported that in chronic obstruction, generalized decreased intestinal motility is seen, whereas increased motility is more commonly associated with acute obstruction.[43] Such a description is consistent with changes reported with experimental obstruction.[16]

The ultrasonographic appearance of intussusception is best characterized by a transverse view of the lesion, depicting the wall layers as a multilayered series of concentric rings, or a target-like lesion (Figure 57-24).[9,14,44] The rings have a hyperechoic or anechoic center surrounded by multiple hyperechoic and hypoechoic concentric rings. When viewed in a longitudinal direction, the intestinal layers appear as multiple hyperechoic and hypoechoic parallel lines. Other possible findings include invagination with mesenteric fat, concurrent inflammatory pseudocysts, mesenteric lymphadenopathy, and mass-like, or even a kidney-like appearing soft tissue.[9,14,44]

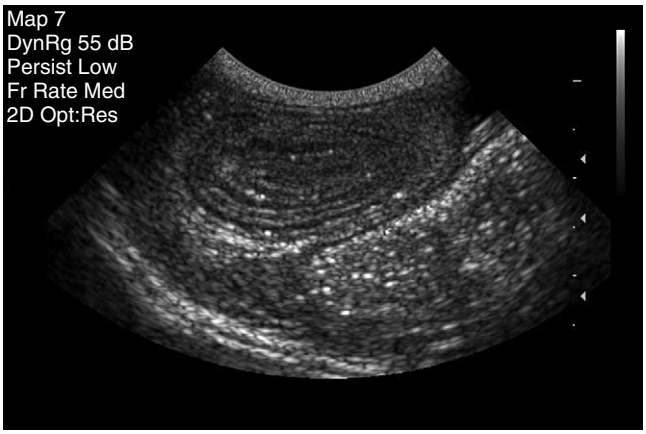

Figure 57-24 Ultrasonogram of an intussusception in transverse section showing the multilayered appearance.

Ultrasonographic evaluation has the added benefit of enabling guided fine-needle aspiration of abnormal bowel at the site of obstruction or intussusception. This would be indicated when an underlying intestinal mass, or diffuse loss of layering consistent with lymphosarcoma is suspected. A cytologic diagnosis prior to laparotomy may be invaluable for treatment planning, or even in a decision not to treat.

Treatment and Management

General Principles

Some intestinal foreign bodies will successfully pass into the colon despite clinical signs consistent with complete obstruction. In a patient with mild acute clinical signs, repeated imaging with careful monitoring is appropriate and necessary. Failure of movement of a foreign body within 8 hours, or failure of the object to pass into the colon within 36 hours, are indications for surgery.[45] It should also be noted that spontaneous resolution of an intussusception has been reported in the dog.[46] Therefore any delay between diagnosis and intervention should be followed by palpation and/or repeated imaging to confirm the persistence of the obstruction immediately prior to laparotomy.

Medical Preoperative Management

The primary therapeutic aim is to surgically relieve the intestinal obstruction. Rapid intervention improves the prognosis, although many patients do require preoperative stabilization. Establishment of adequate tissue perfusion by correcting dehydration is essential and of paramount concern. Volume resuscitation should continue until there is evidence of normal tissue perfusion, stabilization of central venous and arterial blood pressure, and urine production. In most cases, this can be adequately achieved using routine crystalloid replacement principles and therapy. Normal saline (0.9%) is reserved for cases of known hypochloridemic alkalemia because of its acidifying effects when administered in large volumes. The value of colloid solutions is still unsettled. In an experimental model of acute intestinal obstruction in dogs, the administration of synthetic colloid reduced loss of fluid into the intestinal lumen when compared with crystalloids.[47] This effect was consistent with a transient increase in plasma oncotic pressure. Nonetheless, evidence of improved outcome has not yet been provided in clinical patients, and the choice of crystalloids or colloids should be individualized according to evidence of low oncotic pressure and cost. A suggested approach is to start with crystalloid therapy, and administer a colloid solution if adequate perfusion and normotension cannot be achieved or maintained. In the face of severe hypotension (e.g., <60 mm Hg) or hypoalbuminemia, crystalloids, colloids, and plasma, may have to be administered concurrently.

Electrolyte derangements should be managed according to proven severity because predictions cannot be made as to the direction or severity of electrolyte and acid–base derangements in intestinal obstruction. Hypokalemia is especially problematic because of its deleterious effect on intestinal motility and systemic arterial pressure.[48,49] Thus a full preoperative evaluation would include a minimum database of packed cell volume, total plasma solids, serum electrolytes, and arterial or otherwise venous pH. If this information is not available, a conservative and sensible empirical fluid choice for rehydration and support is a high, strong ion gap electrolyte solution such as lactated Ringer solution, with potassium added to approximately 24 mmol/L.[39] Care should be taken not to exceed a

potassium infusion rate of 0.5 mmol/kg body weight/h during initial resuscitation.

Antibiotic therapy is essential because of the likelihood of systemic sepsis, and the risk of contamination during surgery. Antibiotic therapy should be commenced preoperatively, and the duration of antibiosis should be determined following surgical correction. The vast spectrum of potential pathogens dictates broad-spectrum antibiotic coverage for Gram-negative and Gram-positive aerobes and anaerobes. Gram-positive efficacy can be achieved with a β-lactam such as amoxicillin with or without a β-lactamase inhibitor, or a first-generation cephalosporin. Efficacy against Gram-negative bacteria can be achieved with an aminoglycoside, providing renal perfusion is adequate, or a fluoroquinolone, if azotemia is present. Anaerobic coverage may be adequate with the β-lactam alone, but the addition of metronidazole or clindamycin is warranted. Administration should be parenteral during the perioperative period. It is not known whether changing to oral administration postoperatively yields any added benefit. The disturbance in the microflora that ensues could contribute to delayed recovery. In the absence of evidence, continued parenteral administration is recommended as long as is practical.

Surgical Management

Although endoscopic retrieval may be successful in some cases of gastric foreign bodies, it is impossible to ascertain foreign material in the more distal GI tract. Small intestinal obstructions are best removed via laparotomy and enterotomy. Following careful inspection for integrity and adequate perfusion, intussusception should be reduced with or without resection. Chronic or nonreducible intussusceptions should be resected. The involved segment should always be carefully inspected for the possibility of local underlying disease such as neoplasia, and intestinal histopathology is indicated if any suspicious lesions or irregularities on palpation are detected. In all cases of intestinal obstruction, devitalized intestine should be resected, and appropriate decontamination of the peritoneal cavity through copious warmed sterile lavage.

Postoperative Care

Intravenous fluid therapy should be continued as required, and electrolyte and acid–base status should be monitored as needed. Empirical analgesia is indicated, regardless of the appearance of pain preoperatively. Reduced intestinal motility or complete paralytic ileus can complicate and prolong recovery. Neuronal pathology, enteritis, surgical manipulation, and persistent electrolyte derangements may all contribute to postoperative intestinal dysmotility. Insufficient evidence is available for firm recommendations in dogs and cats, but human experience suggests analgesia is important.[50]

Experimental studies show that early postoperative enteral feeding after intestinal anastomosis reduces intestinal inflammation, and increases the strength of the anastomotic site when compared with oral fasting for 48 hours.[51] Furthermore, the wound strength of the abdominal incision is increased when complex diets are fed enterally, compared with oral dextrose solution for 72 hours.[52] In a randomized trial of human patients treated surgically for intestinal perforation, early enteric feeding accelerates the recovery of normal intestinal motility, improves nitrogen balance, reduces weight loss, and reduces the risk of sepsis.[53,54] Interestingly, the risk of dehiscence is not necessarily reduced with the early introduction of enteral nutrition in clinical cases either in humans or in dogs.[54,55] The optimal nutritional formulas following enterotomy have not yet been established.

Regardless of the etiology, there is decreased motility with delayed gastric emptying and reduced segmental contractions in almost all cases.[56,57] Feeding decreases the development and duration of ileus in most intestinal pathologies. A recent metaanalysis on the recovery of human patients following a wide spectrum of abdominal surgical procedures demonstrated that early introduction of feeding resulted in shorter time to the presence of bowel sound and a trend toward shorter hospital stays.[58] At worst, continuing oral feeding will have no detrimental effect on motility, and at best it will promote normal motility and prevent ileus.

Multiple factors, including luminal nutrients, pancreaticobiliary secretions, and humoral agents are implicated in controlling the intestinal adaptive response after intestinal injury. Despite the multifactorial regulation of intestinal adaptation, luminal nutrients are fundamental to the adaptive response such that recovery is minimized or prevented in the absence of luminal nutrients. This conclusion is largely based on studies that show significant adaptive intestinal regrowth in rats and dogs fed orally compared with those fed parenterally following an intestinal resection. Indeed even in the absence of intestinal injury, total parenteral nutrition causes dramatic intestinal atrophy in dogs, cats, rats, and humans.[59-61] This fasting-induced atrophy is accompanied by inflammatory cell infiltrates in the lamina propria, increased intestinal permeability, and increased bacterial translocation.

Consequently, the early implementation of enteral nutrition with a complex diet is recommended in all patients following enterotomy or anastomosis unless there are specific contraindications. However, it is unlikely that attempting to feed the daily maintenance energy requirements is a sensible approach in the short-term postoperative period, and certainly not in cases of continued vomiting. Therefore it is recommended that only 25% of the animals resting energy requirements be fed as a highly digestible, low-fat diet, whereby intestinal recovery may be optimized, and exacerbation of diarrhea and vomiting is minimized. This can be offered orally, syringe fed, or administered as a liquid enteral diet via nasoesophageal tube or other feeding tube.

Relief of an intestinal obstruction does not result in immediate normalization of intestinal motility, and the persistence of hypomotility or ileus is more likely the longer the obstruction is present.[22] It is unknown if prokinetic drug therapy following relief of acute or chronic obstructions is helpful in dogs or cats. However, treatment with metoclopramide is effective in reducing the postoperative ileus in dogs that is experimentally induced by abrasion of the intestinal serosa.[62]

The prognosis for survival following enterotomy is generally very good, with reported survival rates of between 83% and 99%.[15,33] Studies to date have not specifically evaluated different preoperative, surgical, or postoperative protocols to establish best practice standards; however the prognosis for recovery from acute obstruction is improved with prompt treatment, which emphasizes the need for rapid diagnosis. The presence of intestinal perforation or leakage and septic peritonitis is proposed to be a negative prognostic indicator, but that has not been conclusively proved. Dehiscence of enterotomy sites is a major postoperative complication, and is more common following foreign-body removal than other reasons for enterotomy.[55] Reported dehiscence rates following foreign-body surgery range from 2.9% to 27.7%.[5,33,55,63] The risk of dehiscence following enterotomy is significantly increased if there is preoperative peritonitis, more than 15% loss of body weight prior to surgery, hypoalbuminemia, and leukocyte left shift.[55,63]

It is unknown whether the biomechanical remodeling that occurs proximal to a chronic partial obstruction could influence

tissue healing and risk of dehiscence following enterotomy. Future research is likely to elucidate if surgical margins that are extend beyond the simple points of adequate blood supply to regions devoid of architectural change, might improve the prognosis.[64-80]

DYSMOTILITY

Robert J. Washabau

Intestinal Motility Patterns

Contractions in the SI serve three general functions: mixing of the ingesta with digestive enzymes and other secretions, circulation of the intestinal contents to facilitate contact with the intestinal mucosa, and net propulsion of the intestinal contents in an aborad direction. Intestinal contractions are governed by four motility patterns: segmentation, peristalsis, intestinointestinal inhibition, and the migrating motility complex (see Chapter 1).[1]

Segmentation

If a contraction is not coordinated with activity above and below, intestinal contents are displaced both proximally and distally during the contraction and may, in fact, propagate orad during the period of relaxation. Such contractions appear to divide the bowel into segments, which accounts for the term *segmentation* given to the process. Segmentation serves to mix and locally circulate the intestinal contents. Segmentation primarily involves circular smooth muscle contraction (Figure 57-25).

Peristalsis

The SI is capable of eliciting a highly coordinated contractile response that is propulsive in nature. When the bowel is distended by a bolus of food the bowel responds with contraction orad and relaxation aborad to the point of distention. The neurotransmitters involved in the orad contraction are acetylcholine and substance P, and the neurotransmitters involved in the caudad relaxation are vasoactive intestinal peptide and nitric oxide. These events tend to move the material in an aborad direction. Short-segment peristalsis of the bowel is the norm in dogs and cats (see Figure 57-27). If short-segment peristalses occur sequentially they can propel a bolus the entire length of the gut in a short period of time. This peristaltic response, first characterized by Bayliss and Starling, is referred to as the "Law of the Intestine," and is less frequent than short-segment peristalses.

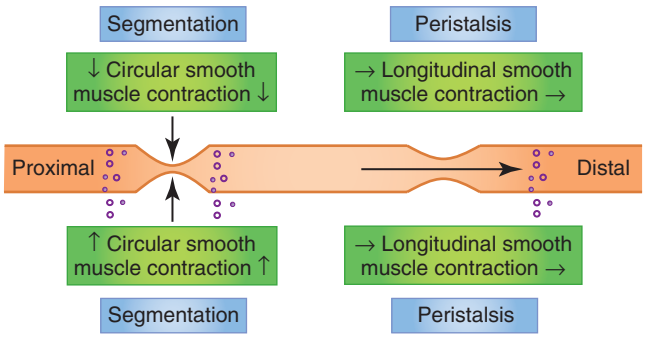

Figure 57-25 Segmentation- and peristaltic-type contractions in the small intestine.

Intestinointestinal Inhibition

If an area of the bowel is grossly distended, contractile activity in the rest of the bowel is inhibited. This reflex prevents the movement of ingesta into more distal segments of intestine that have been severely distended or obstructed. This reflex is mediated by the extrinsic (autonomic) nervous system.[2]

Migrating Motility Complex

The migrating motor complex propagates indigestible materials, mucus, and secretions from the stomach to the colon during the fasting state. The enteric nervous system regulates the periodicity and migration of the migrating motility complex, but the GI hormone motilin reinforces the migrating motility complex activity. Cats do not have migrating motility complexes, and instead have a migrating spike complex that is less vigorous than the canine migrating motility complex.[2,3]

Breed Differences in Gastrointestinal Transit Time

Significant differences in physiology and pharmacology have been found in dog breeds. There are more than 400 breeds of dogs recognized worldwide and 156 breeds recognized by the American Kennel Club. Among these various dog breeds, several important differences in metabolism have been noted, for example, P-glycoprotein–mediated metabolism, copper storage, and growth rates.[4,5] Differences in GI transit characteristics have also been noted. The GI tract of large-breed dogs (e.g., those weighing 60 kg) comprises 2.8% of their total body weight. In contrast, it comprises 7% of the total body weight of small-breed dogs (e.g., those weighing 5 kg). Breed-related differences in fecal water content could reflect differences in GI transit time, intestinal fermentation, diet, metabolism, and drug absorption. Using radiopaque markers (1.5-mm diameter administered in food), 12-week-old large-breed puppies (e.g., Great Danes) exhibited a significantly longer orocecal transit time (3.4 hours) as compared with small-breed puppies (e.g., Miniature Poodle, 2.5 hours). The longer transit time appears to reflect both a longer gastric emptying time and a longer small intestinal transit time among breeds. There also appear to be differences in intestinal permeability between dog breeds. The lactulose/rhamnose ratio reflects the relative absorption across the intestinal tight junction (transcellular absorption) versus the intestinal surface area (paracellular absorption, which occurs across the cell membrane of the enterocyte). The lactulose/rhamnose ratio is substantially greater in the Greyhound breed than in the Golden Retriever breed. Breed and age characteristics must be taken into account when differentiating normal and abnormal transit times. Chapter 26 outlines transit study techniques and times in more detail.

Definition of Ileus

Ileus has been defined as the functional inhibition of propulsive bowel activity, irrespective of pathogenetic mechanism.[6,7] There are several underlying causes of ileus, including dysautonomia, postoperative ileus, opioid-induced bowel dysfunction, muscular dystrophy,

visceral myopathy, viral enteritis, radiation enteritis, idiopathic pseudoobstruction, and hypothyroidism. Some ileus disorders are more readily treated than others.

Dysautonomia

Etiology

Dysautonomia is a generalized autonomic neuropathy that was originally reported in cats in the United Kingdom, but that has now been documented in dogs and cats throughout Western Europe and the United States.[8-16] The clinical signs reflect a generalized autonomic dysfunction but megaesophagus, esophageal hypomotility, gastric and small bowel distention and hypomotility, and urinary bladder distention are fairly consistent findings.[8,10,16] Aspiration pneumonia and megacolon are seen less frequently.

Pathophysiology

Degenerative lesions are found in autonomic ganglia, intermediate gray columns of the spinal cord, and some sympathetic axons.[10,12,13] Despite an intensive search for genetic, toxic, nutritional, and infectious etiologic agents, no definitive etiology has ever been established.

Clinical Signs

Vomiting, diarrhea, anorexia, lethargy, weight loss, dysuria, and inspiratory dyspnea are the most frequent clinical signs reported in dogs. In cats, dilated pupils, esophageal dysfunction, dry nose, reduced lacrimal secretions, prolapse of the third eyelid, regurgitation, and constipation are the most frequent clinical signs.[12]

Diagnosis

A clinical diagnosis is made in most cases based on historical and physical examination findings. Additional findings consistent with the diagnosis include (a) esophageal dilation and hypomotility on survey or barium contrast radiographs; (b) delayed gastric emptying on barium-contrast radiographs; (c) reduced tear production in Schirmer tear tests; (d) atropine-insensitive bradycardia; and (e) bladder and colonic distention on survey radiographs. There are few differential diagnoses to consider in a dog or cat presenting with the myriad manifestations of the syndrome. Early in the course of the illness, however, other differential diagnoses to consider are colonic or intestinal obstruction, other causes of megaesophagus, and lower urinary tract disease.

Treatment

Supportive care (e.g., artificial tears, elevated feedings, expressing the urinary bladder, antibiotics, etc.) is still the basis of therapy in this disorder, although some dogs and cats are reported to show mild improvement with parasympathomimetic drugs (e.g., bethanechol or metoclopramide). Gastrostomy tube feedings or total parenteral nutrition may sustain some animals until they regain neurologic function.

Prognosis

In general, dysautonomia carries a guarded to poor prognosis for long-term survival in both the dog and the cat. Twenty percent to 40% of affected cats are likely to recover, although cats may take 2 to 12 months to do so.[12-16] Recovery rates are lower still in the dog.[10,12] Complete recovery is uncommon and many cats and dogs are left with residual impairment, for example, intermittent regurgitation, dilated pupils, and fecal or urinary incontinence.

Postoperative Ileus

Etiology

Postoperative ileus has been defined as "ileus that develops following abdominal surgery, resolving spontaneously with 2 to 3 days."[17] It may be exacerbated by opioid administration during and following surgery. Multiple mechanisms have been proposed for the etiopathogenesis of postoperative ileus.[17]

Postoperative ileus is a significant problem in human medicine and constitutes the most important reason for delayed discharge from the hospital after abdominal surgery. The economic impact of postoperative ileus has been estimated to be $750 million to $1 billion in the United States. Similar data are not yet available in veterinary medicine.

Pathophysiology

Laparotomy and manipulation of the viscera are the main mechanisms underlying postoperative ileus, but other factors such as anesthetic agents and postoperative pain medication contribute to the delay in recovery of normal transit. The effect of general anesthetic agents is short lasting and therefore of only minor importance. The use of opioids to control postoperative pain has a much greater impact on postoperative motility. Postoperative opioids have significantly improved patient comfort in the early postoperative phase, but these drugs potently inhibit GI transit. Efforts to reduce the dose of opioids or to antagonize their effects with peripherally acting opioid μ-antagonists such as methylnaltrexone or alvimopan are important to minimize the detrimental effect of opioids on GI motility.

The main cause of postoperative ileus relates to the surgical procedure itself.[17,18] The first (or neurogenic) phase is neurally mediated and involves neural reflexes activated during and immediately following surgery. The second (or inflammatory) phase is triggered by the influx of leukocytes in manipulated intestinal segments and is responsible for the sustained inhibition of GI motility (Figure 57-26).[17]

Figure 57-26 Schematic of the two phases involved in postoperative ileus. The first phase starts during abdominal surgery and ends soon after it. The second inflammatory phase starts approximately 3 to 4 hours after surgery, lasts much longer, and is therefore clinically more relevant. (Reproduced with permission from Boeckxstaens GE, de Jonge WJ: Neuroimmune mechanisms in postoperative ileus. *Gut* 58:1300, 2009.)

Box 57-6 Causes of Intestinal Dysmotility in Dogs and Cats

- Dysautonomia
- Postoperative ileus
- Opioid-induced bowel dysfunction
- Muscular dystrophy
- Visceral myopathy
- Viral enteritis
- Radiation enteritis
- Idiopathic pseudoobstruction
- Hypothyroidism

Clinical Examination

Nausea, vomiting, intestinal distention, and abdominal pain are the most important clinical signs of postoperative ileus in dogs and cats. Fever and leukocytosis also may be found depending upon the type and severity of abdominal surgery.

Diagnosis

The diagnosis of postoperative ileus is usually straightforward, and an exclusion of other known causes of ileus (see Box 57-6). Laboratory testing (complete blood count, serum chemistry, urinalysis) are sometimes performed to rule out metabolic disorders such as liver disease and renal failure. Abdominal imaging (e.g., survey radiography and ultrasonography) should be performed to exclude other causes of ileus and their complications, for example, mechanical obstruction, peritoneal free air or fluid accumulation, and pancreatitis.

Treatment

Orogastric Intubation

Intermittent orogastric or nasogastric intubation may be of benefit particularly in those patients with gaseous GI distention.

Early Postoperative Feeding

Early postoperative feeding has been recommended as a means of decreasing the duration of postoperative ileus. Feeding may stimulate a reflex that coordinates propulsive activity and elicits the secretion of GI hormones, causing an overall positive effect on bowel motility.

Laparoscopic Procedures

Laparoscopic procedures offer the theoretical advantage of decreased tissue trauma compared with open abdominal procedures. This decrease in tissue trauma may lead to faster recovery of postoperative bowel function. Animal studies have found significant decreases in the duration of postoperative ileus after laparoscopic versus open abdominal procedures.[18]

Prokinetic Agents

GI prokinetic agents have a clear place in the management of postoperative ileus. Chapter 52 discusses these drugs and their clinical usage in greater detail.

Cyclooxygenase-2 Inhibitors

Mechanical stretch in intestinal obstruction induces marked expression of cyclooxygenase (COX)-2 in intestinal smooth muscle cells, and stretch-induced COX-2 plays a critical role in the suppression of smooth muscle contractility in bowel obstruction.[19] Therefore COX-2 inhibitors may have therapeutic potential in stretch-related disorders of the gut.

Opioid μ-Antagonists

Opioid μ-antagonists like alvimopan and methylnaltrexone may be useful in antagonizing the effects of morphine-like opioid agonists if that is part of the underlying pathogenesis of postoperative ileus.[20,21]

Electrical Stimulation

Although not yet clinically applicable, GI pacing is achievable in the canine stomach and SI (but not the colon).[22-26] The maximal entrainable frequency of the gastric and small intestinal slow waves is approximately 20% higher than the intrinsic frequency. In the future, stimulation parameters may be identified that will entrain slow waves, thereby normalizing gastric and intestinal dysrhythmias.[22-26]

Prognosis

The prognosis for short-term postoperative ileus is generally good to excellent. In animals with complicated, refractory postoperative ileus, the prognosis is less clear. More aggressive therapies may be needed in this patient population. In such cases, intestinal failure may result culminating in intestinal transplantation as a last resort.[27-29]

Opioid-Induced Bowel Dysfunction

Etiology

Opioid-induced bowel dysfunction may be part of a postoperative ileus syndrome, or it may relate solely to the use of opioid μ,δ-agonists as part of an analgesic therapeutic regimen. Opioids are a mainstay in the treatment of acute and chronic pain. Although opioids are very effective for pain relief from cancer and other nonmalignant diseases, their use is often limited by side effects. The most common adverse side effects are constipation and vomiting, but they also alter small bowel function causing opioid-induced bowel dysfunction. Opioid-induced bowel dysfunction can occur immediately after the first dose and persist for the duration of therapy. The peripherally acting μ-receptor antagonists methylnaltrexone and alvimopan are a new class of agents designed to reverse opioid-induced side effects on the GI tract without compromising pain relief.[30-36]

Pathophysiology

Endogenous opioids include endorphins, enkephalins, and dynorphins. They act selectively at opioid receptors composed of the μ, δ, and κ subtypes. Opioid μ receptors are present in the central and peripheral nervous system, as well as the GI tract. There are many species and site differences, but μ receptors have been reported on the interstitial cells of Cajal, smooth muscle, and epithelial cells. The predominant opioid effect appears to be at the local level and includes stimulation of absorption (villus epithelial cells), inhibition of secretion (crypt epithelial cells), increased segmentation (circular smooth muscle), and reduced peristalsis (longitudinal smooth muscle; reviewed in Chapter 1 in greater detail). Exogenously administered opioids have the same overall effect of opioid inhibition of peristalsis and secretion leading to the syndrome of opioid-induced bowel dysfunction.[31,32]

Clinical Examination

Constipation and vomiting are the primary clinical signs of opioid-induced bowel dysfunction. Left untreated, constipation can progress to fecal impaction and mechanical obstruction.

Diagnosis

The patient usually has a well-documented history of opioid μ-agonist therapy, for example, morphine, in the management of a pain syndrome. Still, it would be important to rule out other causes

of ileus, metabolic disorders, and mechanical obstruction. Therefore the minimum database should include laboratory data (complete blood count, serum chemistry, urinalysis) and imaging (survey abdominal radiography or ultrasonography).

Treatment

In most instances, discontinuation of the opioid μ-agonist is sufficient to ameliorate clinical signs. With persistence of clinical signs after drug withdrawal, laxative (reviewed in Chapter 50) and other therapies may be used to treat constipation, although it should be emphasized that a definitive role in the treatment of opioid-induced bowel dysfunction has not yet been proven. Any of the laxative agents (bulk, lubricant, osmotic, stimulant, emollient; see Chapter 50) could be used to attenuate the constipating effect of the opioid μ-agonist. Misoprostol, a synthetic prostaglandin E analogue also could be used to improve intestinal and colonic transit times.[36]

If the central analgesic effect of the opioid μ-agonist is paramount, the patient could be treated concurrently with an opioid μ-antagonist, methylnaltrexone or alvimopan, both of which will improve GI transit without inhibiting the central analgesic effect of the opioid μ-agonist. In dogs, methylnaltrexone at a dose range of 1 to 5 mg/kg subcutaneously abolishes the effect of morphine on GI transit without interfering with the central analgesic effect.[32] Safe and effective doses of alvimopan have not yet been reported in the dog.

If morphine must be used preoperatively, the epidural route (vs. continuous low-dose infusion) facilitates the time of appearance of the first gastric interdigestive migrating complex (the migrating motility complex) in dogs with paralytic ileus after open abdominal surgery.[37]

Prognosis

The prognosis for acute opioid-induced bowel dysfunction is generally good to excellent. Because chronic opioid-induced bowel dysfunction may persist it has a more guarded prognosis.

Muscular Dystrophy

Etiology

Duchenne-type muscular dystrophy in the Golden Retriever dog is an X-linked genetic disorder that is characterized primarily by progressive muscular weakness. Involvement of the GI tract is frequent and may occur at any level from stomach to intestine and colon.[38] The disorder is caused by mutations in the dystrophin gene responsible for production of the dystrophin membrane protein.[39] The absence of dystrophin is accompanied by alteration of the dystrophin–glycoprotein complex and results in progressive degeneration of the heart, skeletal, and smooth muscle with subsequent replacement by fibrosis and fatty infiltration.

Pathophysiology

The gastroenterologic clinical signs have been attributed to motility disorders caused by smooth muscle damage, but histologic evidence of alterations has not been a consistent finding. In a more recent report, Golden Retriever dogs affected with Duchenne-type muscular dystrophy had marked degenerative lesions in the smooth musculature of the GI tract, urinary, and reproductive systems. GI smooth muscle lesions were associated with the clinical findings of gastroparesis, gastric dilation, and intestinal pseudoobstruction.[38]

Clinical Signs

Dysphagia, regurgitation, gastroparesis, abdominal pain, and intestinal distention have been reported in affected animals. Gastroenterologic clinical signs may be the first sign of dystrophic disease and may precede the appendicular musculoskeletal features. The impairment of GI function may be gradual and undetected by the pet owner, breeder, or veterinarian.[38]

Diagnosis

Definitive diagnosis may be confirmed on the basis of history and physical examination findings, serum creatine kinase activity, genomic DNA analysis, muscle electrophysiology, gross morphology, and histologic features.[39] Ileus may be difficult to detect in the whole animal and may require the use of endoscopy, ultrasonography, and scintigraphy.

Treatment

Despite major advances in our understanding of the pathophysiology of the disease, therapy is still largely supportive and symptomatic. Gene replacement therapy has not yet succeeded in restoring muscle function or in prolonging life.

Prognosis

At the present time, the prognosis for cure is poor. With supportive and symptomatic therapy, some affected animals have survived for as long as 51 months.[38]

Visceral Myopathy

One case of visceral myopathy in a 6-month-old domestic short-hair cat has been reported in the veterinary literature.[40] The kitten had a 6-day history of anorexia, intermittent vomiting, and diarrhea, and severely dilated loops of hypomotile intestine were found on survey abdominal radiography and ultrasonography. Intestinal dilation was confirmed at the time of surgery, and a 20-cm section of jejunum was resected. In the proximal jejunum, there was marked atrophy of the longitudinal muscle of the muscularis externa layer and diffuse severe degenerative vacuolar change within the myocytes and endomysial cells. The circular muscle layer was of normal thickness and morphology. Villus stunting and fusion were evident in the mucosa. In the distal jejunum, the mucosa and submucosa were normal, but the longitudinal muscle layer was markedly atrophic with focal degeneration, calcification, loss of myocytes, and replacement by proliferating fibroblasts. Based upon descriptions of human visceral myopathy, the findings were thought to be consistent with a diagnosis of visceral myopathy causing chronic intestinal pseudoobstruction.[40] The cat was alive and doing well 20 months after surgery.

Parvoviral Enteritis

Ileus is a frequent finding in puppies affected with parvoviral enteritis.[41] The ultrasonographic appearance of the GI tract was characterized in 40 puppies with confirmed canine parvoviral enteritis.[41] Sonographic findings included fluid-filled SIs in 92.5% of the cases (Figure 57-27), and of the stomach and colon in 80% and 62.5% of the cases, respectively. Generalized atony was present in 75% of the cases, and weak peristaltic contractions indicative of functional ileus were observed in the remaining 25% of cases. The duodenal and jejunal mucosal layer thicknesses were significantly reduced when compared with normal puppies with mean duodenal mucosal layer measuring 1.7 mm and jejunal mucosal layer 1.0 mm. A mucosal layer with diffuse hyperechoic speckles was seen in the duodenum (15%) and the jejunum (50%). The luminal surface of the duodenal mucosa was irregular in 22.5% and the jejunal mucosa in 42.5%.

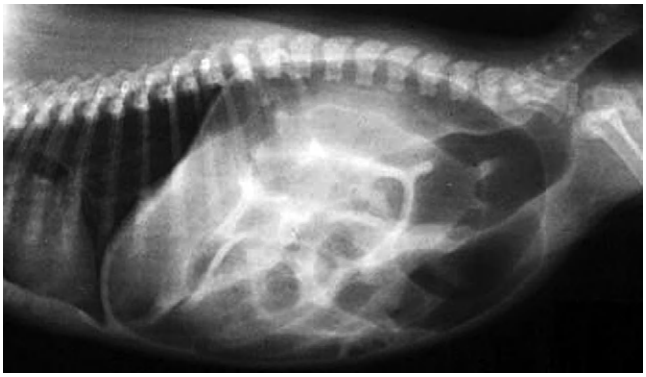

Figure 57-27 Survey lateral radiograph of a 4-month-old mixed-breed puppy with severe intestinal distention and chronic intestinal pseudoobstruction.

Changes were accompanied by generalized indistinct wall layering in all animals. A mortality rate of 30% was found in this patient population.[41]

Radiation Enteritis

Radiation produces a variety of changes in GI tract motility and ileus is a common clinical finding.[42] Most of the changes observed with radiation enteritis occur in other pathologic states. These include delayed gastric emptying, retrograde giant contractions and vomiting, giant migrating contractions, and abdominal cramping and diarrhea.[43] The threshold for these contractile events to occur and their control mechanisms are incompletely understood. Many studies suggest that treatment (i.e., 5-HT_3 antagonists) prior to exposure may be the best method to prevent the contractions from occurring. The role of dose rate is unclear. Within hours of a significant exposure to radiation, these contractions begin to occur and contribute significantly to the early stages of radiation illness.

Idiopathic Intestinal Pseudoobstruction

Etiology

Chronic intestinal pseudoobstruction is defined by the presence of chronic intestinal dilation and dysmotility in the absence of mechanical obstruction.[44] In humans, chronic intestinal pseudoobstruction has many causes that have been simplified into abnormalities of enteric smooth muscle (myopathies) and the enteric nervous system (neuropathies).[40] Such visceral myopathies and neuropathies are primary causes of chronic intestinal pseudoobstruction, and myopathies are either familial, or sporadic and idiopathic. Pseudoobstruction can also arise secondary to other underlying disorders, such as progressive systemic sclerosis, amyloidosis, muscular dystrophy, generalized neuromuscular diseases, endocrinopathies, infectious disease, and drug toxicity.[40]

Pathophysiology

Only 11 cases of chronic intestinal pseudoobstruction have been reported in companion animals (nine dogs and two cats).[44-49] Four dogs had atrophy, fibrosis, and mononuclear cell infiltration of the muscularis externa similar to what is observed in progressive systemic sclerosis in humans. Two dogs had atrophy of the muscularis externa but not fibrosis, either with or without mononuclear cell infiltration, whereas one dog had hyperplasia of the circular muscle without atrophy, fibrosis, or inflammation. In only two reported dogs with pseudoobstruction was the pathology described as primarily affecting the circular or longitudinal smooth muscle. Only two reports mention myocyte vacuolar degeneration, but it was not a prominent feature and marked myenteric plexus vacuolar degeneration was present, suggesting an underlying primary neuropathy. One of the cats reported with pseudoobstruction actually had diffuse intestinal lymphosarcoma with no additional histopathologic details.

Clinical Signs

As with visceral myopathy, the primary clinical signs seen with chronic intestinal pseudoobstruction are anorexia, intermittent vomiting, and diarrhea. Signs may be referable to one segment of the gut, but the disease is usually diffuse.

Diagnosis

Abdominal imaging showing intestinal dilation with no evidence of mechanical obstruction is the hallmark of the pseudoobstruction. Full-thickness intestinal histology is required to identify underlying causes of chronic intestinal pseudoobstruction.

Treatment

Because of the diffuse nature of the disease, surgical resection of diseased intestine is not generally recommended. Resection only benefits selected patients with localized disease. Medical therapy should otherwise be aimed at correcting electrolyte and acid–base disturbances, treating infection or sepsis, supporting nutritional needs, suppressing the inflammatory or immune response, and instituting prokinetic therapy (see Chapter 52).[44-49]

Prognosis

Aside from the apparent recovery reported in one cat with visceral myopathy, most of the cases of chronic intestinal pseudoobstruction had a poor outcome.

Hypothyroidism

Untreated or poorly regulated hypothyroidism is associated with important changes in GI motility. Compared with euthyroid dogs, thyroidectomized dogs have decreased frequency of electrical control activity of the stomach and jejunum, decreased occurrence of electrical response activity (spike potentials) following stimulation, and decreased mechanical response to feeding.[50]

NEOPLASIA

Philip J. Bergman

Incidence and Risk Factors

The first publication of a canine intestinal tumor was by Schlotthauer and Grindlay in 1951.[1] Since then a variety of investigations have increased our understanding of the biology of intestinal tumors. In most studies the incidence of intestinal tumors is reported to be less than 10% of all tumors,[2-7] and intestinal tumors represent approximately one-fifth (dogs) to one-third (cats) of all alimentary tumors.[8] The most common intestinal tumor in most studies is lymphoma, comprising one-third of all feline tumors compared with approximately 6% in dogs.[2,4]

Small intestinal neoplasia occurs typically in older dogs (mean age: 6 to 10 years) and cats (mean age: 10 to 13 years).[2,9-17] The mean age for feline alimentary lymphoma was younger when FeLV was more prevalent.[18-20] Although not significant, there is a slight male predisposition for canine intestinal tumors,[13,15] but this is less clear in cats.[9,21-23] Approximately 90% of dogs with GI lymphoma and 80% with leiomyoma/leiomyosarcoma are male.[16,24,25]

Large breeds of dogs (e.g., German Shepherds, Collies) appear to be most at risk for small intestinal neoplasia, specifically adenocarcinoma,[14,26] but leiomyosarcomas were reported to be rare in working military German Shepherd and Belgian Malinois dogs.[27] Siamese cats are consistently reported to be predisposed to intestinal lymphoma and adenocarcinoma, with one study suggesting an eightfold increased risk.[2,9,21,28]

There are no known chemical agents or microorganisms that are reliably associated with increased risk for intestinal neoplasia in dogs. The same is true for cats except for the clear associations with FeLV and feline immunodeficiency virus.[29-32] Most cats with intestinal lymphoma are older and FeLV-negative by serology, but a significant portion of these cats are positive for FeLV by immunohistochemistry or PCR studies of the tumor tissue.[33] Of further note is the change in presentation of feline lymphoma that occurred in recent decades. When the prevalence of FeLV was high, the most common presentation of feline lymphoma was of cranial mediastinal and multicentric disease in young, FeLV-positive cats, whereas now the most common presentation is of an older, serologically FeLV-negative cat with alimentary lymphoma.[18,34]

The risk of gastric cancer is greatly increased in people with *Helicobacter pylori* infection,[35,36] but this association has not been confirmed in dogs or cats to date. One domestic cat and a cougar were found to have concurrent *Helicobacter* infection and intestinal neoplasia (lymphoma in the domestic cat and intestinal adenocarcinoma in the cougar), but these studies do not allow for delineation of causation.[37,38] Based on the lack of a large number of reported concurrent cases of *Helicobacter* and intestinal neoplasia in cats, in addition to the fact that some cats normally shed *Helicobacter* sp., this agent at present appears to play minimal to no role in the induction of feline intestinal neoplasia and may be part of the normal feline GI flora.[39,40]

Pathology and Biologic Behavior

A large number of different types of neoplasia can be found in the intestine, including epithelial (e.g., carcinoma or adenocarcinoma), neuroendocrine, mesenchymal (e.g., sarcoma) or discrete/round cell neoplasia.[17] Most small intestinal neoplasia in dogs and cats is malignant, whereas more distal areas of the GI tract tend to have more benign disease. Lymphoma is the most common intestinal tumor with a variety of reported subtypes including lymphoblastic, epitheliotropic, lymphocytic, and large granular lymphocytic (also called granulated cell tumor or globule leukocyte lymphoma).[14,20,23,24,41-49] The predominant immunophenotype in feline intestinal lymphoma has historically been considered to be tumors of B-cell origin arising from germinal centers and Peyer patches; however, more recent literature suggests that B-cell predominance is no longer the case.[23,50,51] The presence of FeLV in the tumor is not now associated with immunophenotype, contrary to previous reports of younger, serologically positive cats with primarily T-cell immunophenotypes.[18,50] Approximately 80% of cats and 25% of dogs will have distant spread of alimentary lymphoma at presentation or surgery.[21,24] Although lymphoma is often thought to be a systemic disease in dogs, additional study is necessary to better delineate the metastatic propensity of solitary canine GI lymphoma, and therefore the potential need for chemotherapy in addition to local treatment options.

Most cats with epitheliotropic or large granular lymphocytic intestinal lymphoma are serologically FeLV-negative. Large granular lymphocytic intestinal lymphomas are generally very aggressive tumors, typically have heterochromatic granules, and are perforin-positive on immunohistochemistry.[46,52-54]

The second most common intestinal tumors are those of epithelial origin including adenocarcinoma (glandular), solid or undifferentiated carcinoma (no glandular formation), mucinous carcinoma (>50% mucinous), and signet ring carcinoma (>50% of the cells producing copious mucin which thereby gives a signet ring cytologic phenotype).[2,9,14] The most common sites of metastasis of an intestinal carcinoma are the lymph node, liver, lung, omentum, mesentery, spleen, bone, kidney, peritoneum (e.g., carcinomatosis), skin, and testes.[12,55-58]

The third most commonly reported intestinal neoplasm in dogs is of smooth muscle lineage (leiomyoma and leiomyosarcoma).[15-17,59-61] A more recently reported variant of leiomyosarcoma and occasionally leiomyoma in dogs is the GI stromal tumor (GIST).[25,62,63] GISTs are generally more commonly noted in the large intestine, but are reported arising in the SI and stomach. On immunohistochemistry, GISTs are typically vimentin-positive, cytokeratin-negative, and CD117 (c-kit, a transmembrane tyrosine kinase)-positive, and have minimal expression of smooth muscle actin. CD117-positive tumors (e.g., GISTs) may have a lower metastatic rate than CD117-negative leiomyosarcomas.[25,64]

Less common tumors of the canine SI are carcinoid, mast cell tumor (the third most common intestinal tumor in the cat), extraskeletal osteosarcoma, ganglioneuroma, hemangiosarcoma, and extramedullary plasmacytoma. Carcinoids are of neuroendocrine origin and contain secretory granules comprising a variety of substances including gastrin, secretin, serotonin, and somatostatin.[10,17,65] Primary intestinal carcinoids are locally aggressive and commonly metastasize to the liver.[10,66] Primary intestinal mast cell tumors are relatively common in cats, but rare in dogs.[67-71]

History and Clinical Signs

Clinical signs in dogs and cats with SI neoplasia include diarrhea, vomiting, weight loss, anorexia, melena, and possibly signs associated with nephrogenic diabetes insipidus (associated with smooth muscle tumors) or anemia. Clinical signs associated with obstruction, perforation, and/or peritonitis also are possible in severe cases. Clinical signs associated with paraneoplastic syndromes from small intestinal neoplasia include cutaneous, hyperviscosity, biochemical, and hematologic syndromes.[72-74] GI leiomyosarcoma is reported to be associated with nephrogenic diabetes insipidus.[75] The duration of clinical signs prior to presentation can be variable and range from 1 to 2 days to months, with an average of 4 to 8 weeks.[12,24,75]

Diagnosis

Physical Examination

Small intestinal neoplastic masses may be palpable in approximately 20% to 50% of dogs and 50% to 85% of cats.[9,12,13,23,24,45,55,76] Additional physical examination findings reported in dogs and cats with small intestinal neoplasia include dehydration, pain, and/or fever.[9,24,55]

Clinical Pathology

The most common finding on clinical pathology screening is anemia. This may reflect anemia of chronic disease, but is more commonly due to blood loss into the GI tract, which may then cause melena and possibly elevation in blood urea nitrogen.[12,13,15,16,23,45,55] Other changes include leukocytosis, monocytosis, and/or a left shift.[9,12,15,23,55] Serum biochemical changes include hypoproteinemia consistent with blood loss, elevations in alkaline phosphatase, and hypercalcemia (most common with lymphoma but reported across a variety of tumor types).

Diagnostic Imaging

Plain abdominal radiographs are reported to be diagnostic for an abdominal mass in approximately 40% to 50% of dogs and cats with small intestinal neoplasia.[9,12,15,24,45,55] Although difficult to offer precision across studies because of variability, a theme emerges whereby the percentage of cases with an abdominal mass on plain films is higher in dogs and cats with solid intestinal neoplasia and lower with lymphoma. This reduced ability to delineate an abdominal mass on plain films in patients with lymphoma is likely caused by numerous factors including the potential for diffuse lesions and/or the presence of peritoneal effusion and/or other organ involvement. The frequency of obstructive patterns noted on plain films in dogs and cats with intestinal neoplasia varies between studies. Because of the advent of, and widespread use of, abdominal ultrasound, use of contrast radiography has waned in the last 5 to 10 years, but this technique will find filling defects in approximately 50% to 90% of dogs or cats with intestinal neoplasia.[9,24] Three-view thoracic radiographs should be performed as part of routine staging in any case with an abdominal mass or strong suspicion of an abdominal mass. As many intestinal tumors often do not metastasize to the lungs, this is typically a low-yield procedure when staging for small intestinal neoplasia. Nevertheless it should be performed as the presence of metastasis would signal a very significant change in prognosis and therapy.

The use of abdominal ultrasound has revolutionized the diagnosis of intestinal neoplasia. Abdominal ultrasound is a much more sensitive diagnostic tool than radiography for the identification of an intestinal mass[12,13,16,26,77]; however, abdominal ultrasound alone is not diagnostic. The most frequent abdominal ultrasound changes noted in dogs and cats with intestinal neoplasia are loss of normal bowel wall layering and increased bowel wall thickness. Ninety-nine percent of dogs with intestinal neoplasia have loss of bowel wall layering, while 88% of dogs without intestinal neoplasia retain normal bowel wall layering. In addition, dogs with focal abdominal ultrasound lesions are approximately 20 times more likely to have neoplasia, and dogs with bowel thickness greater than 1 cm are at four times greater risk of neoplasia.[78] The advantages of abdominal ultrasound over plain and/or contrast radiography include (a) evaluation of other sites within the abdomen, (b) delineation of the presence or absence of carcinomatosis, (c) less time-consuming than contrast radiography, and (d) additional diagnostic utility gained through abdominal ultrasound-guided fine-needle aspirate or needle-core biopsy.[13,26,79] Other findings commonly reported with abdominal ultrasound in patients with small intestinal neoplasia include mixed echogenicity asymmetric lesions, diffusely thickened bowel loops, anechoic to hypoechoic mass lesions, and in patients with carcinomatosis, the presence of masses in the "double-sheet" region of the peritoneum where the parietal and visceral portions meet, and the presence of free fluid.[79]

Endoscopy

The use of endoscopy for the diagnosis of small intestinal neoplasia has become more commonplace over the last 10 to 20 years. Unfortunately, endoscopy has potentially significant limitations depending on the anatomic site of the tumor and the ability of the endoscope to reach the affected area. The gross appearance of neoplasia on endoscopy can range from a mass effect, to reduced dispensability of an otherwise phenotypically normal area, to a "cobblestone" and/or focal erythremic effect.[76] An additional limitation to endoscopy is the size of the biopsy sample obtained, which can lead to significant interobserver variation in histopathologic interpretation.[80] One study of feline lymphoma compared endoscopic samples with full-thickness biopsy samples collected at laparotomy. In that investigation, lymphoma was diagnosed in 10 cats from full-thickness samples, but in only three cats with endoscopic samples.[81] For those cats with gastric lymphoma, endoscopic sampling diagnosed three of four cases, whereas in cats with intestinal lymphoma none of the six cats were diagnosed by endoscopic sampling. A similar study in dogs comparing endoscopic versus full-thickness sampling had comparable outcome.[24]

Laparoscopy

The use of laparoscopy to diagnose and/or treat intestinal neoplasia has increased in the last 5 years because of increased operator proficiency and more widespread availability of the equipment.[82,83] The morbidity and surgical procedure time are greatly reduced when using laparoscopy compared to laparotomy; however, the lack of intraluminal viewing can be a significant limitation of the technique when the lesions are not producing a mass and/or full-thickness effect.

Laparotomy

Exploratory laparotomy is considered the gold standard when minimally invasive techniques are unable to provide a diagnosis of intestinal neoplasia in patients with signs of persistent and/or resistant intestinal disease. There are numerous advantages to laparotomy compared with other techniques including the ability to take full-thickness biopsies, the direct visualization of the entire abdomen, and the ability to perform therapeutic resection and anastomosis and/or placement of feeding tubes.

Treatment

Surgery

The gold standard of treatment for most intestinal neoplasia, except for lymphoma, is surgical excision. This means of gross local tumor control is possible when there is no evidence of lymph node metastasis, carcinomatosis, other distant metastasis and/or adhesions or serosal-specific abnormalities that would prevent full extirpation. In patients with lymphoma causing intestinal obstruction and/or perforation, or when diagnosis is not possible through other less-invasive means, surgery may be used for diagnosis and/or treatment.

Perioperative mortality rates are high and average 30% to 50% in patients undergoing surgery for intestinal neoplasia. The causes of such mortality include peritonitis, sepsis, and euthanasia as a consequence of the presence of gross metastasis and/or lack of resectability.[12,16]

Chemotherapy

The use of adjuvant chemotherapy after surgical resection of an intestinal epithelial tumor is relatively controversial because of the

paucity of publications. Survival greater than 1.5 years was reported in two dogs with intestinal adenocarcinoma after surgery and adjuvant chemotherapy.[13] A retrospective evaluation of adjuvant doxorubicin in cats with colonic adenocarcinoma reported a median survival time of approximately 9 months with doxorubicin versus 2 months without it.[11] It is unknown if similar results would be afforded in larger scale prospective trials of dogs or cats with small intestinal epithelial malignancies. Another study reported the use of chemotherapy in dogs with leiomyosarcoma to have variable outcome, with some dogs having long survival without chemotherapy after surgery.[16] Additional research is required to determine the usefulness of adjuvant chemotherapy in small intestinal nonlymphoid malignancies.

The use of chemotherapy in the treatment of intestinal lymphoma is less controversial; however, outcomes can be variable depending on species, anatomic site, histopathologic subtype, etc.[20,45,84,85] For example, in cats with a diagnosis of intestinal IBD or low-grade lymphocytic lymphoma (which can be difficult to distinguish histopathologically), cats treated with pulse-dose Leukeran and corticosteroid had a median survival approaching 2 years, whereas cats with intestinal lymphoblastic lymphoma treated with the same protocol had a median survival of only 3 months.[85] Few publications report outcomes of chemotherapy in dogs with intestinal lymphoma. In one case series, all eight dogs with intestinal lymphoma treated with chemotherapy were euthanized within 14 weeks.[24] Anecdotally, I believe that dogs with intestinal lymphoma often have very short survival.[14]

Radiation Therapy

Radiation therapy is rarely used in the treatment of intestinal neoplasia. There are significant toxicity concerns with the use of radiation therapy on the intestine and surrounding viscera, and it would be difficult to localize the same area of treatment for daily fractions in typical radiation therapy prescriptions because of intestinal motility.

Prognosis and Prognostic Factors

Canine Carcinoma and Adenocarcinoma

The prognosis for dogs with intestinal carcinoma or adenocarcinoma is guarded to poor. Investigators have found a 12-day survival time in dogs not treated with surgery compared with survival ranging from 4 to 10 months (40% 1-year survival) when treated surgically.[12,13,55] Unfortunately, these poor survival times are most likely a result of a high metastatic rate. In dogs with intestinal epithelial malignancies, 40% to 50% metastasize to local lymph nodes, 30% to 40% metastasize to the liver, and approximately 10% to 20% metastasize to distant sites.[10,12,55] The importance of the presence of lymph node metastasis is further highlighted by a report documenting a median survival time of dogs treated with surgery of 15 months (67% survival at 1 year) compared with only 3 months (20% survival at 1 year) when lymph node metastases were present.[12] Similarly, male dogs with intestinal epithelial malignancies were reported to have prolonged survival time compared with females.[13]

Differential expression levels of tenascin-C and vesicant are reported to occur between benign and malignant lesions in dogs, but these studies have not documented prognostic import within malignancies.[86,87] p53 is the most commonly mutated tumor-suppressor gene in human oncology and overexpression is commonly associated with immunohistochemical overexpression. Overexpression of p53 is uncommon in canine small intestinal epithelial malignancies with 15% to 23% expression noted across two studies.[88,89] In addition, p53 expression did not appear to correlate with the degree of malignancy of the tumors. COX-2 is commonly overexpressed in canine and feline small intestinal epithelial tumors and therefore the use of nonsteroidal antiinflammatory agents may represent a rational treatment approach in the primary setting with nonresectable disease or alternatively in an adjuvant setting.[90,91] To date, the only nonsteroidal antiinflammatory drug (NSAID) with a documented in vivo antitumor effect is piroxicam.[92,93] I believe that from an evidence-based medicine perspective the lead NSAID for antitumor use should continue to be piroxicam until further in vivo studies with NSAIDs of improved safety profile become available.

Canine Lymphoma

There are few publications examining outcomes for dogs with intestinal lymphoma, but as discussed previously all eight dogs with intestinal lymphoma treated with chemotherapy were euthanized within 14 weeks.[24]

Other Canine Tumors

The prognosis for dogs with leiomyosarcoma remains guarded with median survival times after surgery of 7.5 to 24 months.[15,16,64] Dogs with visceral metastasis from a leiomyosarcoma that underwent surgical removal of the primary tumor had a median survival time of almost 2 years, suggesting that metastasis may not be a strong prognostic factor.[16] When dogs with a GIST had surgical removal of the lesion, their overall median survival time was only 1 year, whereas if the large percentage of dogs with perioperative deaths were censored, the median survival time increased to approximately 3 years.[64] Maas and colleagues reported 62.6% and 52.3% 1- and 2-year survival rates, respectively, for dogs with intestinal GIST undergoing surgery.[63] Intestinal perforation was not a negative prognostic factor.[16]

Feline Carcinoma and Adenocarcinoma

The prognosis for cats with intestinal epithelial malignancies is guarded to poor. The median survival time of cats with intestinal epithelial malignancies not treated with surgery is only approximately 2 weeks,[9,55] whereas those cats taken to surgery can have high perioperative mortality rates.[56] For cats surviving the perioperative period, the median survival times are 5 to 15 months.[9,28] This prognosis is likely a result of the increased metastatic rate of epithelial malignancies in this anatomic location as approximately 50% metastasize to local lymph nodes, approximately 30% cause carcinomatosis, and approximately 20% have distant metastasis.[2,55,56] Cats with carcinomatosis may benefit from removal of the primary tumor, but this likely requires additional study because of the very small number of cats reported (n = 2).[9] The use of intracavitary chemotherapy for carcinomatosis in cats has not been examined to date; however, promising preliminary results have been noted in dogs.[94]

Feline Lymphoma

The prognosis for cats with intestinal lymphoma is variable because of a wide variety of factors. The combination of surgery and chemotherapy has no benefit over chemotherapy alone,[51] but there were only 21 cats in this study and it was not a randomized trial. I believe that for cats with a solitary intestinal lymphoma lesion, surgery should be seriously contemplated as it is one of the quickest and least-expensive mechanisms of tumor cytoreduction, especially in light of the relative chemotherapy resistance of feline lymphoma. FeLV status was highly prognostic for feline intestinal lymphoma

with FeLV-positive cats treated with chemotherapy having a median survival time of 3 months versus 17 months if the cats were FeLV-negative (but this was only true in cats with early stage lymphoma and not significant in cats with later-stage neoplasia).[19] Another study reported the primary prognostic factors to be FeLV status, substage, and response to therapy,[34] but in other studies FeLV status was not prognostic.[51,84] Immunophenotype is not of prognostic benefit in dogs or cats with intestinal lymphoma, but this may be a result of poor statistical power from small numbers of cases reported to date.[51] Labeling of argyrophilic nucleolar organizer regions is negatively correlated to clinical outcome in a variety of malignancies across species, but for feline alimentary lymphoma argyrophilic nucleolar organizer regions were not associated with duration of remission, percentage of remission, or survival time.[95] Median remission for cats with intestinal large-cell lymphoma is 5 to 7 months, but subsets that are poorly understood to date can have extended survival times.[45,84,85]

Other Feline Tumors

Cats with duodenal polyps have an excellent prognosis. One previous investigation determined that cats with surgically removed duodenal polyps were cured of their disease.[22]

Comparative Features

Small intestinal neoplasia is uncommon in humans, where there is a much higher incidence of large intestinal cancer. The reverse holds in small animal medicine where small intestinal tumors are much more common than those of the large intestine. The reasons for this difference are unknown but likely to involve differences across the species related to diet, genetics, toxin exposures, and/or physiology. Risk factors noted to date for small intestinal epithelial neoplasia in humans includes increased intake of fatty foods, red meats, high-temperature grilled meats, and salt-cured food products.[96] Risk factors noted to date for small intestinal lymphoma include celiac disease which may progress from IBD to overt lymphoma.[97]

Chronic use of COX-2 inhibitors reduces intestinal neoplasia in a variety of studies by approximately 50%.[98] Significant similarities across species are likely to exist in the potential use of COX-2 inhibitors for small intestinal epithelial tumors. Similarly, the use of tyrosine kinase inhibitors for GISTs across species is likely a result of the aforementioned commonly noted mutations in c-kit.[99]

The principles of diagnosis and treatment are similar across species. Minor differences exist in the more common use of CT scanning for the diagnosis of small intestinal neoplasia in people compared with its current use in veterinary medicine.[100] The use of tyrosine kinase inhibitors in unresectable and/or metastatic GISTs in people is commonplace, suggesting that the use of tyrosine kinase inhibitors in the same setting in dogs or cats may have potential utility.[99] There is a similar dearth of literature concerning the effectiveness of chemotherapy in the adjuvant treatment setting for people with small intestinal epithelial malignancies.[101]

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CHAPTER 58

Large Intestine

STRUCTURE AND FUNCTION

Robert J. Washabau

The large intestine of the dog and cat has evolved to serve two major functions: extraction of water and electrolytes from the fluid contents of the lumen and control of defecation. The large intestine accomplishes these functions by regulating fluid transport, bacterial fermentation, motility, immune surveillance, and blood flow. Sodium and water absorption serve to dehydrate the feces prior to defecation; mucus glycoproteins serve to trap bacterial pathogens and prevent bacterial translocation; epithelial cells, lymphocytes, plasma cells, macrophages, and dendritic cells serve to regulate the bacterial flora and the immune response to microbes; and motility serves to facilitate storage or defecation of feces. Perturbations in any of these functions may result in the problems of diarrhea, constipation, or systemic inflammatory response syndrome.

Structure

Macroscopic Anatomy

The large intestine consists of the cecum, colon, rectum, and anal canal (Figure 58-1). In dogs and cats, the ileum communicates directly with the colon, and what is referred to as the cecum in the dog and cat is actually a diverticulum of the proximal colon. The colon is further compartmentalized into ascending, transverse, and descending portions, each segment having slightly different functions and properties. The right colic or hepatic flexure separates the ascending and transverse colon, and the left colic or splenic flexure separates the transverse and descending colon. In dogs and cats, the large intestine contributes 20% to 25% of the total (small and large) intestinal length.[1,2]

The arterial blood supply to the colon is provided by the cranial and caudal mesenteric arteries, and venous return from the colon is transmitted to the main portal vein via the cranial and caudal mesenteric veins. Lymph is circulated from the colon to the right, middle, and left colic lymph nodes, and eventually into the cisterna chyli and thoracic duct. Parasympathetic innervation arises from the vagus nerve in the proximal colon, and from the pelvic nerves in the distal colon. Sympathetic innervation arises from the paravertebral ganglia and follows the lumbar splanchnic nerves and mesenteric arteries to the colonic mucosa and muscularis. Parasympathetic preganglionic fibers and sympathetic postganglionic fibers synapse on cell bodies and neurons of the enteric nervous system, respectively.

Microscopic Anatomy

As with the small intestine, the cross-sectional structure of the large intestine consists of four distinct layers, that is, mucosa, submucosa, muscularis, and serosa (Figure 58-2). The large intestine differs from the small intestine in the following important ways: villi are absent in the large intestine; the microvilli of the large intestine epithelial cells are much less abundant; goblet cells are more prominent in the large intestine; endocrine cells are less prominent in the large intestine; and crypt-to-epithelial migration is a much slower process in the large intestine.

The mucosa of the large intestine is a flat absorptive surface area differing from the small intestine in that villi are not present. However, numerous straight tubular glands (400 to 600 μm) are present in parallel cylinders and they extend from the muscularis mucosa to the mucosal surface.[3] The glands are lined by a continuous sheet of columnar epithelial cells, which are separated from the mesenchymal tissue of the lamina propria by a well-defined basement membrane. The epithelium in the lower half of the crypts is composed of proliferating undifferentiated columnar cells, mucus-secreting goblet cells, and at least three types of endocrine epithelial cells.[4] Cellular proliferation is predominantly in the lower part of the crypts in both dogs and cats. The epithelium of the upper half of the crypts consists of differentiating columnar cells, goblet cells, and a few endocrine cells. The flat absorptive surface is lined by many columnar cells as well as a moderate number of goblet cells (10 to 25 goblet cells per 100 epithelial cells),[3,5] most of which are largely depleted of their mucous granules. Intraepithelial lymphocytes are relatively sparsely distributed throughout the epithelium (one to seven lymphocytes per 100 epithelial cells),[3,5] and as in the small intestine, the predominant T cell subset is the cytotoxic-suppressor (CD8+) type.[6,7] The cellular elements of the lamina propria of the large intestine resemble closely those found in the small intestine and include lymphocytes, many plasma cells, mast cells, macrophages, eosinophils, enteric neurons, and fibroblasts.

The innermost layer of the mucosa is separated from the submucosa by the muscularis mucosae, a layer of smooth muscle cells roughly eight to 10 cells (or 70 to 80 μm) thick. The submucosa of the colon resembles the submucosa of the other tubular digestive organs. It contains many blood and lymph vessels, dense connective tissue sparsely infiltrated by cells (fibroblasts, lymphocytes, plasma cells, mast cells, macrophages, and eosinophils), and the unmyelinated nerve fibers and ganglion cells that form the submucosal plexus.

The muscularis is composed of an inner circular muscular layer forming a tight spiral circumferentially along the course of the colon and an incomplete outer longitudinal muscle layer. The ganglion cells of the myenteric plexus of Auerbach are found between the

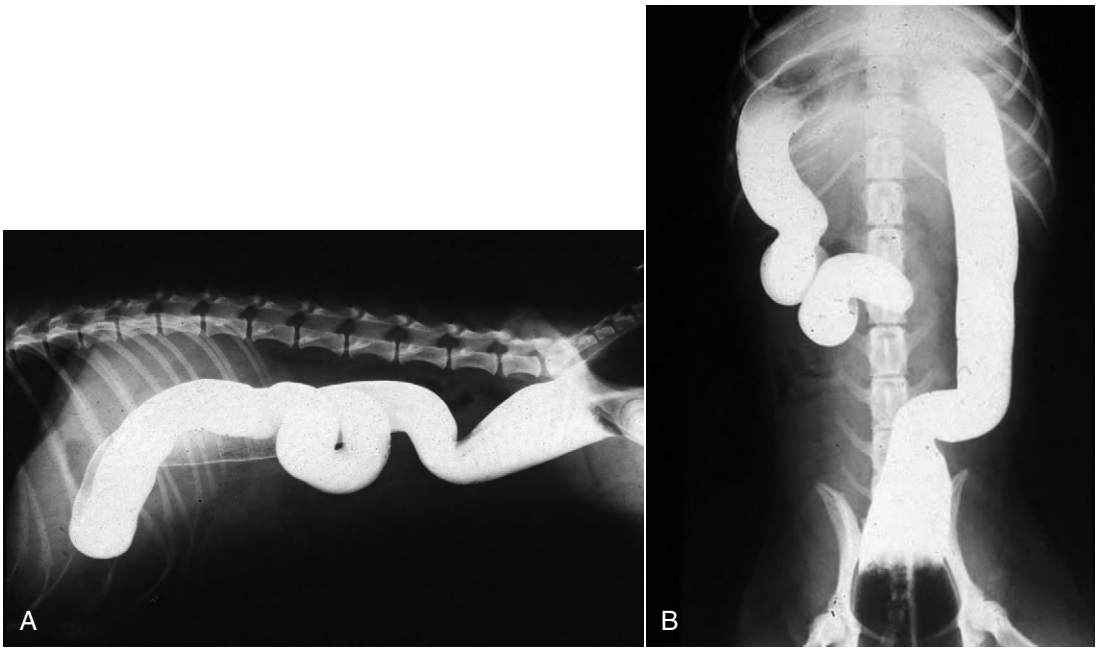

Figure 58-1 **A,** Gross anatomy of the feline colon—lateral projection, barium enema. **B,** Gross anatomy of the feline colon—ventrodorsal projection, barium enema. (Reprinted with permission from Washabau RJ: Diseases of the large intestine. In: Ettinger SJ, Feldman ED, editors: *Textbook of Veterinary Internal Medicine*, ed 6, Philadelphia, 2005, Saunders, p 1379.)

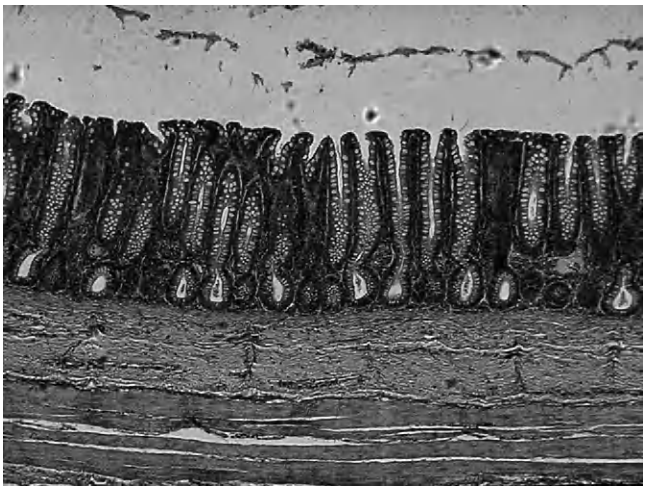

Figure 58-2 Microscopic anatomy of the canine colon. (Reprinted with permission from Washabau RJ: Diseases of the large intestine. In: Ettinger SJ, Feldman ED, editors: *Textbook of Veterinary Internal Medicine*, ed 6, Philadelphia, 2005, Saunders, p 1379.)

circular and longitudinal muscle layers. Unmyelinated postganglionic fibers are also found in the circular muscle layer and communicate with the submucosal (Meissner) plexus. The interstitial cells of Cajal, which are located on the submucosal surface of the circular smooth muscle, play a dual role as pacemaker cells and as mediators of neuromuscular transmission in the colon.[8-10]

The serosa is composed of mesothelial cells and covers only the portions of the large bowel that lay within the peritoneal cavity (cecum and colon).

Several classification systems for colonic mucosal architecture and cellularity have been proposed (see Chapter 29).[1,3,11] It should be emphasized that there are important age,[12] site,[1,3] diet,[13-16] and procedure-related[3] differences in the cellularity and architecture of the colonic mucosa, and these differences must be taken into account when interpreting colonic histology. For example, the protein and fiber content of the diet have significant effects on colonic mucosal morphology (e.g., crypt depth and cellularity).[14-16] The pathologist should always take these factors into account when interpreting colonic biopsy specimens. The method of biopsy also influences the architecture and cellularity of the mucosa. Compared to full-thickness biopsies, gland length is 25% to 30% shorter and goblet cell numbers are 70% to 75% less in endoscopic biopsies from the same animals. The shallow depth of the endoscopic biopsy apparently causes glandular collapse, and enema or cathartic preparative solutions are believed to cause discharge of mucous goblets.[3,11]

Function

Mucus Secretion

A lubricant layer of mucus forms a crucial physiologic barrier between the colonic mucosa and the luminal environment. Mucus is a constantly changing mix of secretions and exfoliated epithelial cells, the chief determinants of which are high-molecular-weight glycoproteins or mucins.[17] Gastrointestinal mucins are secreted from goblet cells as they ascend from their origin in the crypts up to the colonic epithelium. Mucin secretion is dependent upon the close integration of the cystic fibrosis transmembrane regulator (CFTR), chloride secretion, and granule exocytosis. In addition to their physiologic role as a mucosal barrier, mucins may also have a pathologic role in the metastases of epithelial tumors and enhanced susceptibility to infection.

Water Absorption

In health, approximately 2.7 L of fluid (oral intake, saliva, gastric fluid, bile, pancreatic fluid, and intestinal secretions) is presented each day to the small intestine of a 20-kg dog. Approximately 1.35 L

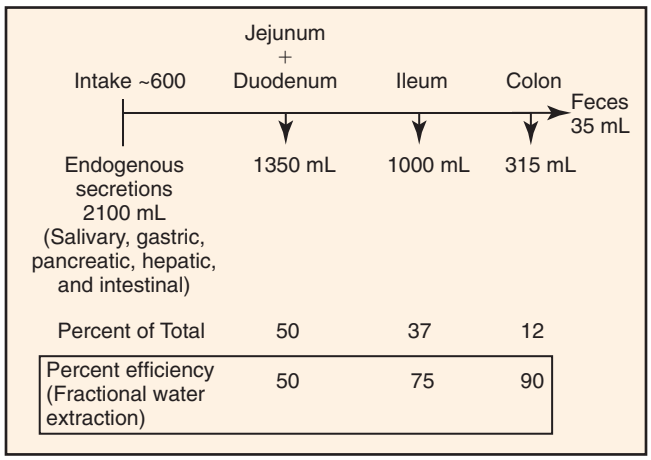

Figure 58-3 Regional daily net water turnover in the canine gastrointestinal tract. (Approximate figures: 20 kg dog, mL/24 h) (Reprinted with permission from Burrows CF: Chronic diarrhea in the dog. *Vet Clin North Am Small Anim Pract* 13:521, 1983.)

is absorbed in the jejunum, 1.0 L in the ileum, and 315 mL in the colon, leaving 35 mL in feces.[18] Thus, the jejunum absorbs 50%, the ileum 75%, and the colon 90% of fluid volume presented to it (Figure 58-3). This fluid absorptive capacity of the colon is largely determined by basal electrolyte (primarily sodium) transport and by the ability of several agonists (aldosterone and glucocorticoids) to augment electrogenic and electroneutral Na absorption. As long as ileocecal flow is less than the colonic absorptive capacity, significant alterations in small intestinal fluid movement may be present, but colonic absorption will prevent the development of diarrhea. On the other hand, when small intestinal absorption and ileocecal flow are normal, a relatively small decrease in colonic absorption (inflammatory bowel disease) will produce significant increases in fecal water output.

Electrolyte Transport

The large intestine regulates the electrolyte and water composition of the feces. There are distinct differences in the mechanisms of electrolyte transport between the ascending and descending colon,[19,20] but in general the canine and feline colon absorbs water, sodium, and chloride while secreting potassium and bicarbonate.

In many ways, the mechanisms of absorption and secretion in the large intestine are similar to those of the small intestine, but there are several important differences (Table 58-1). Active nutrient (glucose, amino acid, monoglyceride) transport is prominent in the small intestine, but there is no evidence of active glucose or amino acid absorption in the colon except during the early neonatal period. Sodium transport also differs in the colon. Glucose- and amino-acid–stimulated sodium transport is a well-established property of the small intestine, so much so that oral glucose-electrolyte solutions have been used to reduce the morbidity of cholera and other infectious diarrheal diseases of the small intestine. In contrast, glucose-coupled sodium transport does not take place in the colon and glucose-electrolyte solutions are of no benefit in diarrheal diseases of the large intestine. Sodium transport in the colon instead relies upon electrogenic transport.[20,21] The large intestine also differs in its response to mineralocorticoids. Aldosterone markedly increases sodium transport in the colon, but it has only a modest effect in the small intestine. Net sodium absorption ceases in the colon only when the luminal sodium concentration is reduced below 30 to 50 mEq/L, whereas net sodium absorption in the jejunum occurs only at luminal sodium concentrations above 130 mEq/L.[21]

Table 58-1 Special Features of Colonic Electrolyte Transport

	Small Intestine	Large Intestine
Water	Yes	Yes
Amino acid + glucose absorption	Yes	No
Lipid absorption	Yes	No
Glucose-stimulated Na absorption	Yes	No
Electrogenic Na absorption	No	Yes
Mineralocorticoid-stimulated Na absorption	Negligible	Significant

Chloride absorption in the colon has both passive and active properties. Passive chloride absorption primarily represents a potential–dependent process secondary to the electrical potential generated by electrogenic Na absorption.

Bicarbonate secretion is an important feature of colonic electrolyte function and helps to neutralize acids produced by bacterial fermentation. Chloride-bicarbonate ($Cl\text{-}HCO_3$) exchange is the primary cellular mechanism responsible for bicarbonate secretion.

The descending colon possesses both potassium absorptive and potassium secretory processes that are regulated by luminally and hormonally mediated mechanisms, and the overall net potassium movement represents the balance of these oppositely directed transport mechanisms.[20,21] The colon, therefore, has the potential to serve as an important regulatory system for the maintenance of overall potassium balance. Although renal potassium transport is critical in the overall control of potassium balance, the colon also contributes to the maintenance of potassium balance by modifying both potassium secretion and absorption, especially when kidney function is impaired.

Immune Surveillance

The colon contains a diverse array of immune cells, including T and B lymphocytes, plasma cells, macrophages, dendritic cells, antigen-presenting cells, mast cells, eosinophils, and neutrophils.[3,5-7,22-25] Immune cells are found in the epithelium, lamina propria, and submucosa of the colon. As in the small intestine, appropriate interactions between these different cell types are essential in generating either immune responsiveness or tolerance to the large array of luminal antigens.[26,27] Much less is known about colonic immunity, but some generalizations may be made. In the colon, CD8+ T cells are found primarily in the epithelium; very few CD8+ T cells are found in the lamina propria or submucosa. Most intraepithelial lymphocytes are CD3+/CD8+, a phenotype consistent with suppressor-cytotoxic functions. Lamina propria T cells on the other hand are predominantly of the CD4+ helper phenotype. Immunoglobulin (Ig) A-containing plasma cells are more prominent than IgG- or IgM-containing plasma cells in the lamina propria. Thus, in the normal colonic mucosa, a balance would appear to be maintained between helper and suppressor T-cell populations, which allows specific antigen responsiveness while avoiding hyperreactivity.[5,6,28] There are many similarities in the immune systems at both sites, but there are important differences in the immune response of the small and large intestine.

Motility

The colon has evolved to serve two important functions: extraction of water and electrolytes from the luminal contents in the ascending and transverse colon, and control of defecation in the descending colon. This specialization of function is attributed to regional differences in colonic motility patterns.[29-33] Electrical slow-wave frequency and rhythmic phasic contractions are slower in the proximal portion of the colon, thus facilitating extraction of water from the fecal mass by diffusion and active transport. Retrograde giant contractions (RGCs) and antiperistalsis further facilitate the mixing of contents in the proximal colon. In contrast to that of the proximal colon, motility of the distal colon is characterized primarily by migrating spike bursts and powerful giant migrating contractions (GMCs) that propagate the fecal mass toward the rectum.[4,33]

Colonic smooth muscle generates at least four different types of contractions to perform the complex motility functions of mixing and propulsion: (a) tone, (b) rhythmic phasic contractions (RPCs), (c) RGCs, and (d) GMCs. The time course, frequency, and force generated by each of these contractions are significantly different from each other.[30-33] The precise role of tone in circular muscle cells is not known, but the resulting decrease in the diameter of the colon may enhance the efficiency of the phasic contractions in mixing and propulsion. Tone is normally of small to moderate force and can last for prolonged periods of time (several minutes to hours). RPCs produce mixing and net slow distal propulsion of luminal contents in the postprandial and fasting state. Phasic contractions occur rhythmically at a few cycles per minute, last for approximately 3 to 5 seconds, and generate a moderate force (75 to 100 g). RGCs occur infrequently, last for approximately 20 seconds, generate a very strong force (>150 g), and are propagated from their point of origin into the ascending colon. RGCs facilitate mixing in the ascending colon. The GMCs are of a similar magnitude and frequency to the RGCs, but they generate mass movements from their point of origin to the anorectal junction. It has been suggested that different signal transduction pathways are used by smooth muscle cells to trigger different contractions.[34,35] It is remarkable that the same smooth muscle cells can generate so many different types of contractions using a limited number of second messengers.

Bacterial Fermentation

The colon contains the largest concentration of bacteria in the gastrointestinal tract, up to 10^{11} organisms per gram of feces. The colonic microflora play an important role in the nutrition of the animal primarily via the production of short-chain fatty acids (SCFAs).[36] Major fiber fermentation substrates include cellulose, hemicellulose, and pectin, substrates that typically are not digested by pancreatic or intestinal amylases. Acetate, propionate, and butyrate account for more than 85% of formed SCFAs, and they accumulate in concentrations up to 150 mmol/L in the colon of dogs.[37] SCFAs are rapidly absorbed by the colonic mucosa, are readily metabolized by colonic epithelial cells, and have various physiologic effects. Among their physiologic effects, SCFAs promote differentiation and proliferation of colonocytes,[38] stimulate absorption of water and electrolytes,[39] provide 7% to 10% of an animal's overall energy requirements,[37] and influence or modify motility of the gastrointestinal tract.[40]

The colonic flora is influenced by many factors, including host species, breed, developmental stage, dietary history, environmental conditions, geographic locale, colonic motility patterns, disease, and medication history.

In general, anaerobic bacteria (*Bacteroides* spp., *Bifidobacterium* spp., *Clostridium* spp., and *Lactobacillus* spp.) predominate in the canine colon, accounting for up to 90% of the colonic microflora. Most are facultative or aerotolerant anaerobes, not true obligate anaerobes.[41] Enterobacteria and streptococci are the predominant aerobic bacteria found in the canine colon. In the cat, approximately equal numbers of anaerobic and aerobic bacteria are found in the colonic lumen.[42]

The colonic flora changes significantly with developmental stages. The aging canine colon becomes more readily populated by *Clostridium perfringens* and other obligate anaerobes, and less populated by aerobes and aerotolerant anaerobes.[41,43] This change takes place in the ascending and descending colon, but is most significant in the descending colon where anaerobic conditions tend to predominate. Senescent changes in bacterial populations of the colon conform to the principles of successional ecology.[44] Over time, changes in pH, redox (oxidation-reduction) potential, bacterial competition, and nutrient availability facilitate the proliferation of anaerobic bacteria permitting them to eventually displace the aerotolerant forms.

The colonic flora may also be influenced by an animal's breeding and genetic background. For example, far fewer *Bifidobacterium* spp. are recovered from the feces of Beagle dogs than are recovered from other dog breeds.[43,45] This represents a problem for studies of colonic bacteriology because many of the reference studies have been generated from Beagle dogs.

Diet has a major impact on numbers and types of bacteria recovered from the colon. *Bacteroides* spp. appear to be particularly susceptible to changes in the diet.[45-47] The protein, carbohydrate, and fiber content of the diet all appear to influence the ability of bacteria to grow within the colon. Thus, dietary history should always be considered when interpreting results of fecal or colonic bacterial cultures.

Geographic locale and environmental conditions can also influence colonic bacteriology in the dog. *Bifidobacterium* spp. are readily isolated from dogs from Japan but they are inconsistently found in American dogs.[41,45] Housing conditions appear to be another confounding factor. Open housing environments[41] appear to facilitate colonization of a greater proportion of facultative anaerobic bacteria compared to closed facility conditions.[48]

Motility patterns of the colon influence the bacterial ecology of the colon. The antiperistaltic activity of the ascending and transverse colon particularly facilitates the mixing of fecal material with endogenous bacteria. Abnormalities in the motility patterns of this part of the colon lead to changes and proliferation of obligate anaerobes similar to that which is found in the descending colon.[29]

Disease and medical therapies, particularly antibiotics, alter the microbial characteristics of the colon. These changes are poorly understood in dogs and cats but they very likely contribute to clinical symptomatology (see Chapter 2).

DIAGNOSTIC EVALUATION

Robert J. Washabau

History and Physical Examination

Colitis

History

Inflammation is the most important pathophysiologic condition of the colon. Colitis is responsible for the major clinical signs of

Table 58-2 Clinical Signs Associated with Large Bowel Diarrhea

Signs	Small Bowel	Large Bowel
Weight loss	May be present	Uncommon
Vomiting	May be present	Uncommon
Flatulence	Present with malassimilation	Unusual
Defecation frequency	Normal to mild increase	Marked increased frequency
Fecal volume	Increased	Normal to mild increase
Urgency	Absent	Usually present
Tenesmus	Absent	Usually present
Mucous in feces	Usually absent	Frequently present
Hematochezia	Absent	Often present
Melena	Sometimes present	Absent
Steatorrhea	Present with malassimilation	Absent

hematochezia, mucus in the feces, dyschezia, abdominal discomfort, tenesmus, urgency, and increased frequency of defecation. The colon is an important target organ for inflammatory bowel disease (IBD) in the dog, whereas the upper gastrointestinal tract (stomach and small intestine) is more frequently involved in feline IBD. Clinical signs are useful in localizing the anatomic site of the diarrhea to the small or large bowel (Table 58-2), although some animals will have diffuse involvement of the small and large intestines.

The history should include specific questions about diet, parasite control, environment, travel history, concurrent medical disease, and drug history. Dietary sensitivity reactions[1] and parasitism are major causes of colitis in many pet populations. Dietary history should include information regarding type of diet, incidence of dietary indiscretion, supplements, snacks, and treats. Information concerning previous fecal examinations and anthelmintic usage may provide useful clues to the cause of the diarrhea. Environmental history should identify other pets in the household and the composition of their diets, and any behavioral interactions or hierarchies that might influence the development of clinical signs. The travel history may yield important information about exposure to histoplasmosis, pythiosis, and heterobilharziasis, all of which have regional distributions. Concurrent medical disease (e.g., Addison disease, IBD, pancreatitis) also helps to place the current episode of colitis in context. The drug history should include information about the use of alternative and complementary medicines that could contribute to clinical symptomatology.

Physical Examination

The physical examination may be normal in many cases of colitis. The most consistent physical examination findings are pain and irregularities of the colonic mucosa on digital rectal examination. The perineum should be examined carefully to exclude perineal diseases such as perineal hernia and perianal fistula. Physical examination may reveal other important findings, including *fever* (IBD, cecal or colonic perforation, fungal infection), *abdominal pain* (IBD, colonic neoplasia, cecal or colonic perforation), *abdominal mass* (colonic neoplasia, granulomatous colitis, intussusception), *small intestinal thickening* (concurrent small intestine IBD, small intestine lymphoma), *mesenteric lymphadenopathy* (small intestine IBD, small intestine lymphoma), *hepatosplenomegaly* (lymphoma, disseminated fungal infection), and *uveitis* (protothecosis, lymphoma). A scoring system has been developed to relate clinical signs with histologic findings in canine IBD.[2]

Constipation

History

Constipation is the second most important pathophysiologic condition of the colon. Clinical signs include reduced, absent, or painful defecation for a period of time ranging from days to weeks or months. Physical examination findings will depend on the severity and pathogenesis of constipation. Dehydration, weight loss, abdominal pain, and mild to moderate mesenteric lymphadenopathy are common findings in cats with idiopathic constipation.

Physical Examination

Physical examination might also reveal *abdominal mass* (cecal or colonic neoplasia, granulomatous colitis), *abdominal pain* (foreign bodies, colonic perforation), *autonomic neuropathy* (dysautonomia), *hind limb paresis* (lumbar spinal cord pathology), *pelvic fracture* (pelvic outflow obstruction), and *perineal hernia* (cause or complication of constipation).

For both inflammation (colitis) and constipation, the scope of the medical investigation is shaped by prior history, suspected etiology, chronicity, and signs of systemic illness (Figures 58-4 and 58-5).[3,4]

Laboratory Data

Complete blood count, serum chemistry, and urinalysis should be considered in animals with signs of colonic disease, particularly those with signs of systemic disease. These tests may provide evidence of *anemia* (chronic disease, GI blood loss), *leukocytosis* (IBD, neoplasia, cecal or colonic perforation), *eosinophilia* (parasitism, Addison disease, mast cell disease, hypereosinophilic syndrome), *thrombocytopenia* (concurrent immune thrombocytopenia), *hypoproteinemia* (protein-losing enteropathy), *hyperglobulinemia* (IBD, infection, neoplasia), *hypercalcemia* (neoplasia, fungal disease), *hypoglycemia* (leiomyosarcoma), and *hyponatremia/hyperkalemia* (Addison or pseudo-Addison disease). This minimum database is also useful to screen animals prior to anesthesia and colonoscopy. If fungal, oomycete, or algal infections are possible causes in the pet's geographic area, special serologic tests are available for the diagnosis of some of these diseases (Table 58-3). Feline leukemia virus (FeLV) and feline immunodeficiency virus (FIV) testing are warranted in cats with unexplained, chronic diarrhea.

Fecal Parasitic Evaluation

Direct fecal smears and fecal flotation studies should be performed to evaluate for helminth, protozoal, and some bacterial infections (see Table 58-3). Direct fecal smears may be useful in detecting *Giardia*, *Tritrichomonas*, and *Campylobacter* organisms. Zinc sulfate flotation is the most accurate and practical fecal flotation test available, and it may be more sensitive for the detection of *Giardia* and *Tritrichomonas* infections. Because some animals may have intermittent shedding of helminth ova and/or *Giardia* trophozoites and cysts, suspected infections should always be treated with anthelmintics or antiprotozoal agents before animals are subjected to colonoscopy.

Fecal Bacterial Culture

Fecal cultures should be considered in animals with suspected bacterial infections of the intestine and colon. Risk factors for bacterial

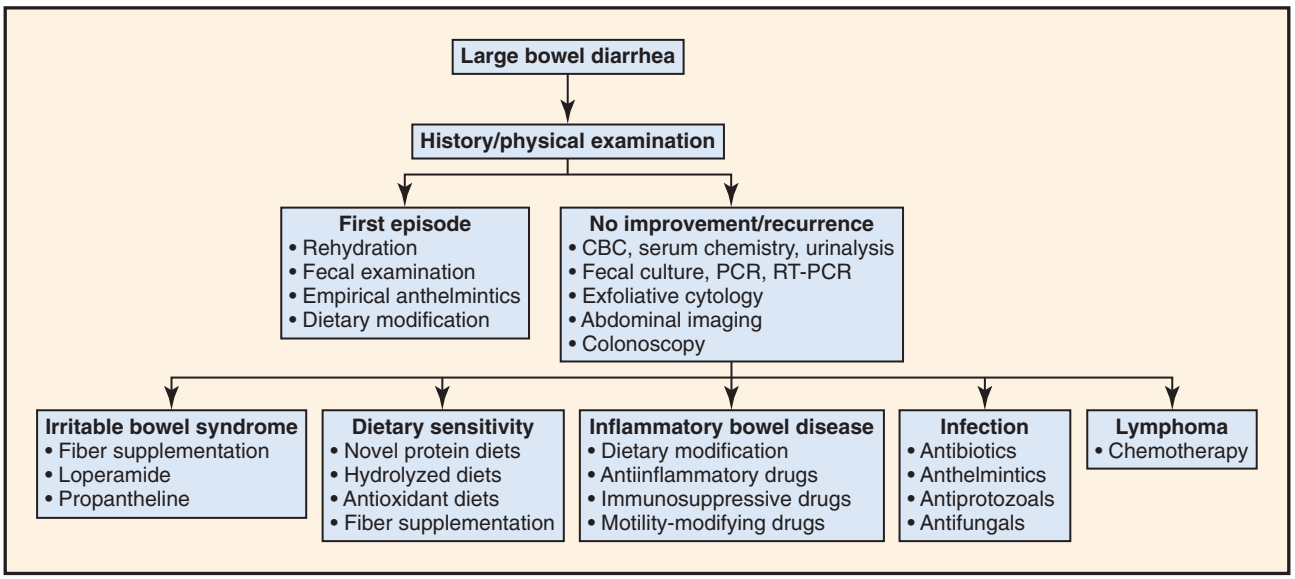

Figure 58-4 Diagnostic approach to large intestinal diarrhea. (Reprinted with permission from Washabau RJ: Diseases of the large intestine. In: Ettinger SJ, Feldman ED, editors: *Textbook of Veterinary Internal Medicine*, ed 6, Philadelphia, 2005, Saunders, p 1384.)

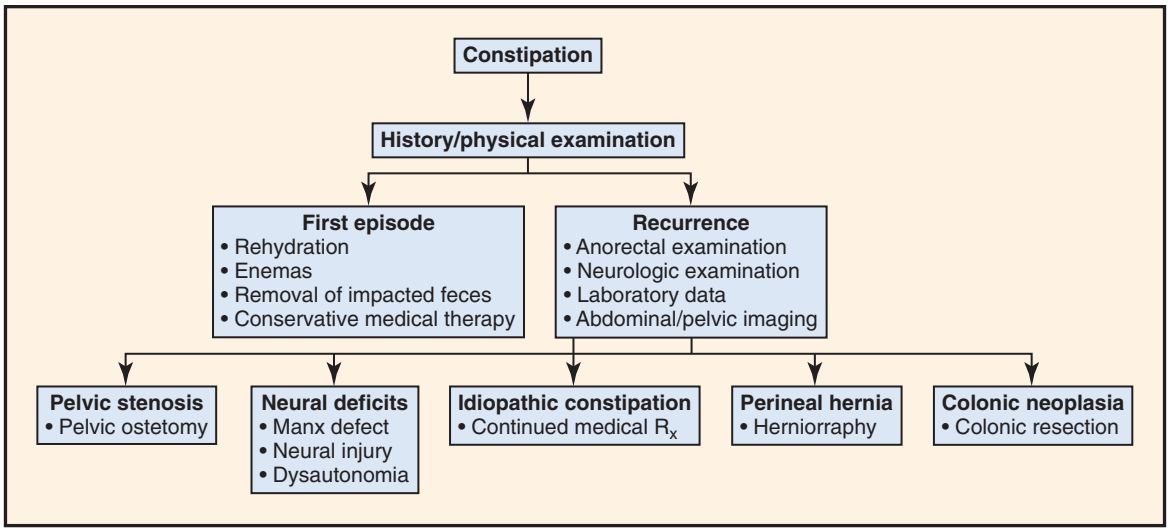

Figure 58-5 Diagnostic and therapeutic approach to constipation. (Reprinted with permission from Washabau RJ: Diseases of the large intestine. In: Ettinger SJ, Feldman ED, editors: *Textbook of Veterinary Internal Medicine*, ed 6, Philadelphia, 2005, Saunders, p 1384.)

colitis include young age, crowded or poor hygienic environmental conditions, coinfection with helminth or protozoal parasites, viral immunosuppression,[5] boarding or kenneling conditions, and multiple-pet households. Bacterial pathogens associated with colitis or enterocolitis lesions in dogs and cats have included *Brachyspira pilosicoli*, *Campylobacter* spp., *C. perfringens*, and *Clostridium difficile*, certain *Escherichia coli* (enterotoxigenic, enteroinvasive, enteropathogenic, enterohemorrhagic, enteroadherent), *Salmonella* spp., and perhaps *Yersinia enterocolitica* (see Table 58-3). The role of enteropathogenic bacteria in the pathogenesis of colitis-type diarrhea has been reviewed recently by Marks et al.[5a] Culture results should always be interpreted in light of clinical signs, other findings such as coinfections, and substantiating laboratory data such as serologies or polymerase chain reaction results. Fecal cultures should not be performed for the purpose of diagnosing small intestinal bacterial overgrowth.

Molecular Diagnosis

A number of polymerase chain reaction (PCR) and reverse transcriptase (RT)-PCR assays have been developed for gene amplification products and messenger RNAs of infectious organisms (see Table 58-3). Assays are now available for the molecular diagnosis of *Tritrichomonas foetus*, *Pythium insidiosum*, *Campylobacter jejuni*, *C. perfringens*, *C. difficile*, *E. coli*, *Salmonella* spp., and *B. pilosicoli*, and many more are likely forthcoming. Molecular detection is the standard for infectious disease diagnosis in many instances.[6]

Fecal Cytologic Examination

Exfoliative rectal or endoscopic cytology may be useful in identifying etiologic agents (e.g., fungal elements, neoplastic cells) and inflammatory cells (e.g., lymphocytes, eosinophils). Rectal smears

Table 58-3 Definitive, Suspected, and Unproved Pathogens of the Large Intestine of Dogs and Cats

Classification/Organism	Tissue Trophism	Evidence of Pathogenicity	Diagnosis
Helminths			
Trichuris vulpis–dogs	Colon	Good evidence	Fecal flotation
Trichuris serrata–cats	Colon	Weak evidence	Fecal flotation
Trichuris campanula–cats	Colon	Weak evidence	Fecal flotation
Ancylostoma caninum	Intestine, colon	Good evidence	Fecal flotation
Heterobilharzia americana	Colon	Good evidence	Fecal flotation, histology
Protozoa			
Balantidium coli	Colon	Weak evidence	Fecal flotation
Cryptosporidium parvum	Intestine, colon	Moderate to good evidence	Fecal flotation, PCR, serology
Entamoeba histolytica	Colon	Poor evidence	Fecal flotation
Giardia canis	Intestine, colon	Moderate to good evidence	Fecal flotation, PCR, serology
Isospora canis–dogs	Colon	Weak evidence	Fecal flotation
Toxoplasma gondii	Intestine, colon	Good evidence	Fecal flotation, PCR, serology
Tritrichomonas foetus–cats	Ileum, cecum, colon	Moderate to good evidence	Fecal flotation, culture, PCR
Fungi			
Histoplasma capsulatum	Intestine, colon	Good evidence	Exfoliative cytology, histology
Oomycetes			
Pythium insidiosum	Stomach, intestine, colon	Good evidence	Histology, immunohistochemistry, ELISA, PCR
Algae			
Prototheca zopfii, P. wickerhamii	Colon	Good evidence	Exfoliative cytology, histology
Bacteria			
Brachyspira pilosicoli	Ileum, colon	Weak to moderate evidence	Fecal culture, PCR, histology
Campylobacter coli, C. jejuni	Intestine, colon	Moderate evidence	Fecal culture, PCR
Clostridium perfringens	Colon	Weak to moderate evidence	Fecal culture, enterotoxin, PCR
Clostridium difficile	Colon	Weak to moderate evidence	Fecal culture, enterotoxin, PCR
Escherichia coli (EPEC, EI, EH)	Intestine, colon	Good evidence	Fecal culture, serotyping, PCR
Salmonella typhimurium	Intestine, colon	Good evidence	Fecal culture, serotyping, PCR
Salmonella krefeld	Intestine, colon	Good evidence	Fecal culture, serotyping, PCR
Yersinia enterocolitica	Colon	Poor evidence	Fecal culture

EH, Enterohemorrhagic; EI, enteroinvasive; EPEC, enteropathogenic *E. coli*. ELISA, enzyme-linked immunosorbent assay; PCR, polymerase chain reaction.

may be obtained with a cotton-tipped applicator or conjunctival spatula during anorectal examination, or with a cytology brush at the time of endoscopy. A good correlation (specificity, 97%; sensitivity, 93%) was shown between exfoliative cytology and subsequent endoscopic or surgical biopsy in one study.[7] Additional studies are still needed to verify the diagnostic value of this test.

Imaging

Survey abdominal radiographs may occasionally document colonic foreign objects, mesenteric or sublumbar lymphadenopathy, intussusception, and extraluminal compression, but survey radiographs are generally nonspecific in the diagnosis of colonic disease. Contrast studies (e.g., barium enema) are performed infrequently because of their poor sensitivity and requirement for general anesthesia. Ultrasonographic imaging has proved more useful in documenting mass lesions, lymphadenopathy, intussusceptions, and bowel thickening. Abdominal ultrasound may also be used to facilitate percutaneous aspiration of luminal masses, mucosal thickenings, and lymph nodes.[8,9] Computed tomography (CT) colonography, also known as virtual colonoscopy, has been successfully implemented in human medicine, and has been studied experimentally in the dog.[10]

Colonoscopy

Colonoscopy is indicated for the diagnosis of colitis-type diarrhea unresponsive to dietary modification and medical therapy, suspected colorectal neoplasia, chronic constipation, unexplained stricture, and evaluation of prior surgical or medical treatment.[11] Colonoscopy is performed after other noninvasive diagnostic tests (e.g., fecal parasitologic examination, fecal bacteriologic examination, exfoliative cytology, abdominal ultrasonography, survey ± barium-contrast radiography) have failed to diagnose the disease.

Rigid or flexible endoscopy may be performed, but flexible endoscopy provides better visualization and examination of the entire colon. The normal colonic mucosa is pink in color, smooth in texture, and glistening in appearance (Figure 58-6). Unlike the esophageal, gastric, and duodenal mucosa, submucosal blood vessels are readily apparent. The mucosa should not hemorrhage when abraded by the endoscope; active hemorrhage usually implies an underlying disorder such as inflammation or infection. The colonoscopic procedure should include examination of the more proximal structures—for example, ascending colon, cecum, ileocecal sphincter, and distal ileum—whenever possible. The proximal colon is an important site of inflammation, parasitism, ileocolic intussusception, cecal inversion, and neoplasia.

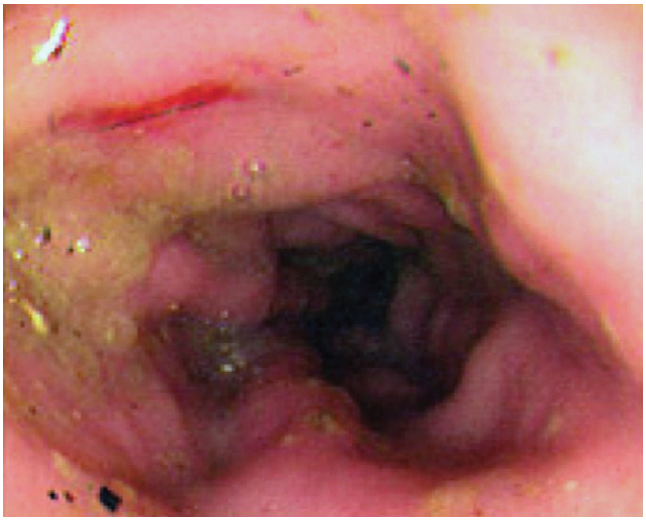

Figure 58-6 Endoscopic appearance of large intestinal inflammatory bowel disease. (Reprinted with permission from Washabau RJ: Diseases of the large intestine. In: Ettinger SJ, Feldman ED, editors: Textbook of Veterinary Internal Medicine, ed 6, Philadelphia, 2005, Saunders, p 1386.)

Box 58-1 Preparation and Patient Positioning for Colonoscopy

- Withhold food for 24 to 48 hours
- Lavage solutions → CoLyte, GoLYTELY
- 25 mL/kg, 24 and 12 hours before endoscopy
- Warm water enemas → 5 to 10 mL/kg,
- 24, 6, and 2 hours before endoscopy
- General anesthesia
- Left lateral recumbency

Fecal material must be completely evacuated before the colonic mucosa can be properly examined (Box 58-1). Incomplete bowel preparation is the major reason for an unsuccessful colonoscopic examination. Patient permitting, food should be withheld for 36 to 48 hours so that fecal material does not accumulate in the colon. The patient should also be given warm water enemas and/or gastrointestinal lavage solutions. Lavage solutions are preferable to warm water enemas,[12-14] but both may be given to facilitate successful colonoscopy. Polyethylene glycol solutions are isosmotic, are administered orally, and induce a diarrhea that rapidly removes fecal material from the bowel. Large volumes may be administered without inducing significant changes in water or electrolyte balance.[12] Electrolyte solutions should be given at a dose of 25 mL/kg at 24 and 12 hours prior to colonoscopy. Warm-water enemas should be performed gently, without irritating substances, at 24, 6, and 2 hours before colonoscopy. The combination of a 36- to 48-hour food fast, gastrointestinal lavage solution, and enemas usually results in a colon that is free of fecal fluids and solids.

Endoscopic examination of the colon has been described in detail.[11] General anesthesia is induced and the patient is placed in left lateral recumbency. The tip of the endoscope is introduced into the anorectal canal, and air is insufflated to dilate the anorectal and colonic lumen. As with upper gastrointestinal endoscopy, the tip of the endoscope should never be advanced unless the lumen is in full view. While inspecting the colonic mucosa, the endoscope is advanced through the descending colon to the splenic flexure. To facilitate passage of the endoscope through the splenic flexure, the tip of the endoscope is deflected slightly upward, and the endoscope is pushed into the transverse colon. The transverse colonic mucosa is now more visible as the endoscope enters the short, straight segment of the transverse colon. At the hepatic flexure, the tip of the endoscope is deflected caudally to enter the ascending colon. While keeping the tip of the endoscope in the center of the lumen, the endoscope is advanced the full length of the ascending colon into the cecum and ileocecal sphincter. The cecum is easily inspected, and the endoscope is then advanced through the ileocecal sphincter to evaluate the distal ileum. Endoscopic biopsies may be obtained at each sequential site or during withdrawal of the endoscope at the end of the study (see Chapter 27).

Diseased tissue, nondiseased tissue, and the transition zone between diseased and nondiseased tissue should be biopsied during colonoscopic procedures. This standard helps to verify the extent of the disease, ensures that disease in the submucosa has not been missed, and provides representative tissue samples to the pathologist to diagnose the disease.[15] In some cases of severe IBD or colonic neoplasia, advanced tissue necrosis may prevent the diagnosis of the disease process in the central part of the lesion. In the absence of gross mucosal abnormalities, three to five biopsy specimens should be obtained from each of the mid-ascending, mid-transverse, and mid-descending colonic regions (see Chapter 29).

INFLAMMATION

Frédéric P. Gaschen and Karin Allenspach

Inflammatory diseases of the colon are frequently encountered in dogs, but appear to be less common in cats. In many instances, acute nonspecific colitis may be self-limiting. However, chronic colitis is often associated with a long, sometimes waxing and waning clinical course and specific treatment is required to resolve clinical signs. Depending on patient signalment and history, dietary indiscretion, parasite infestation, and bacterial infection are common causes that need to be ruled out. The diseases discussed in this section are classically associated with noninfectious inflammation, although it appears that bacteria may play a role in multifactorial pathophysiology.

Acute Colitis

Acute colitis is characterized by a sudden onset of sometimes explosive watery diarrhea associated with the typical clinical signs of large bowel inflammation. Affected animals may also present with vomiting and lethargy. The disease often follows ingestion of toxins (e.g., spoiled food) as a component of "garbage can enterocolitis." However, intestinal parasites and bacterial infections must be ruled out systematically (or treated empirically) if deemed a likely cause based on signalment, history, and clinical signs. Acute nonspecific colitis is usually self-limiting and carries a good prognosis; most cases respond well to symptomatic treatment, which may include fluids, use of antimicrobials such as metronidazole, and a 24-hour fast followed by feeding an easily digestible, hypoallergenic diet over the following few days. Mild cases may be self-limiting. In the absence of exposure to toxins, hemorrhagic gastroenteritis should be considered as a possible differential diagnosis for dogs with bloody diarrhea of large bowel origin.

Inflammatory Bowel Disease

Definition

IBD is an idiopathic inflammatory disorder affecting the gastrointestinal (GI) tract of dogs and cats. Canine and feline IBD can be defined on the basis of clinical and histopathologic criteria. Clinically, IBD is diagnosed in animals with chronic (longer than 3 weeks' duration) GI signs such as anorexia, vomiting, diarrhea (small and/or large bowel in origin), and weight loss for which no other known cause of gastroenterocolitis can be documented. Therefore, affected animals fail to respond to symptomatic treatment, including parasiticides, antibiotics, and diet.[1] In addition, histopathologic evaluation reveals inflammatory infiltration of the colonic mucosa with predominantly round cells (lymphocytic plasmacytic colitis), eosinophils (eosinophilic colitis), neutrophils (suppurative or neutrophilic colitis), macrophages (granulomatous colitis), or a combination thereof. The inflammatory process can solely involve the colon (colitis) or affect the whole GI tract (enterocolitis).

Pathophysiology and Mechanism

Immunologic Basis of IBD

IBD is a complex disease that can affect any part of the GI tract in dogs and cats. Although the exact pathogenesis of IBD in small animals has not been elucidated, research on human and experimental IBD, as well as several studies performed recently in dogs and cats, has led to the formulation of current hypotheses.

In people, IBD encompasses two main disorders: Crohn's disease can occur anywhere in the GI tract and is characterized by a transmural inflammation, whereas ulcerative colitis is restricted to the colon and is characterized by a mucosal inflammation. IBD is clearly a multifactorial disease in which physiologic interactions of the innate and adaptive immune system with luminal microbial antigens are disrupted.[2,3] Overall, three factors are thought to be required for the development of IBD: (a) the presence of bacteria in the intestinal lumen with potential dysbiosis in the luminal microbiome; (b) defective mucosal barrier function that allows bacterial and/or food antigens to come in contact with the innate and adaptive immune cells in the lamina propria; and (c) an aberrant innate and adaptive mucosal immune response to bacterial antigens.[2,3]

In some human IBD patients, genetic alterations affecting the expression of important molecules of the innate immunity (e.g., polymorphisms in the gene encoding the nucleotide oligomerization domain 2 [NOD2]) are responsible for the abnormal recognition and response to luminal microbiota.[2] NOD2 is an intracellular pattern recognition receptor that binds to muramyl dipeptide derived from peptidoglycan common to both Gram-positive and Gram-negative bacteria.

Toll-like receptors (TLRs) are a family of transmembrane receptors with a ligand-binding extracellular domain that recognize microbe-associated molecular patterns. They are an important component of the innate immune system. In the GI tract, specific TLRs are found located on epithelial cells, macrophages, and dendritic cells. TLR2 recognizes bacterial lipopeptides, TLR4 is activated by lipopolysaccharides, and unmethylated cytosine-phosphate diester–guanine Cpg DNA found in prokaryotic genomes and DNA viruses act as ligand for the intracellular receptor, TLR9.[4,5] Once activated, TLRs elicit an intracellular signaling cascade leading to the production of proinflammatory cytokines. However, the physiologic function of TLRs in the GI tract includes maintaining hyporesponsiveness to innocuous luminal commensals, inhibition of allergic responses to food allergens and protection of mucosal barrier function.[4,5] Polymorphisms in the genes encoding TLR1, TLR2, TLR4, and TLR6 are associated with an increased risk for development of IBD in human patients and in murine animal models.[4,5]

NOD and TLRs are also a focus of attention in canine chronic enteropathies. Cultured primary canine colonocytes can express NOD2, TLR2, and TLR4 when stimulated by their respective ligands.[6] In a study investigating TLR expression profiles in endoscopic biopsies, it was found that dogs with chronic enteropathies that needed steroid treatment to keep their symptoms controlled had increased levels of TLR2, TLR4, and TLR9 messenger RNA (mRNA) expression compared with healthy dogs.[7] However, no difference in TLR expression was detected between biopsies sampled before and after clinically successful therapy, regardless of whether dogs had been treated with diet or steroids.[7,8] Another study identified a correlation between clinical severity of disease and expression of TLR mRNA. Duodenal mucosal mRNA expression of TLR2 was markedly increased in dogs with clinically severe IBD when compared with healthy controls, and TLR2 expression was correlated with clinical severity of diseases in a linear fashion.[8] Breed differences in TLR expression profiles have been reported in dogs with IBD. German Shepherd Dogs (GSD) with IBD have increased levels of TLR4 mRNA and decreased levels of TLR5 mRNA in the intestine compared to healthy greyhounds.[8a] Differences in TLR expression mimic those reported in people with Crohn's disease and have prompted genetic investigations into polymorphisms of pattern recognition receptors in dogs with IBD. In GSDs, single-nucleotide polymorphisms (SNPs) in TLR4 and TLR5 have been associated with an increased incidence of IBD.[8b] SNPs in TLR5 are associated with increased risk of development of IBD in 38 other breeds, and have been shown to be functionally hyper-responsive in GSD. This particular mutation may play a role in the pathogenesis of IBD in dogs in general.[8b] Finally, although it does not appear that food antigens play a direct role in the pathogenesis of human IBD, various dietary components can exert deleterious or beneficial effects on the intestinal microflora and on the intestinal mucosa, making it plausible that dietary changes could influence the inflammatory process in the mucosa of dogs with IBD.[9] To date, the effects of dietary antigens on canine and feline IBD have not been studied in detail. However, dietary treatment is viewed by most as an integral part of the therapeutic approach to chronic inflammatory GI diseases.

A number of studies have investigated the inflammatory process associated with canine and feline colitis. Immunohistochemical studies have shown T and B lymphocytes, as well as IgG-positive plasma cells to be increased in the colonic mucosa of dogs with IBD.[9-11] Semiquantitative RT-PCR has been used to evaluate cytokine mRNA expression in colonic mucosal biopsies. Human ulcerative colitis patients typically show a Th2 dominated inflammatory response.[2] In one study the prevailing cytokine mRNA expression pattern in dogs was that of a Th1 immune response.[12] Nevertheless, the accuracy of these results has since been questioned, at least in the duodenal mucosa, where the more reliable quantitative real-time RT-PCR showed a lack of difference in cytokine mRNA expression between healthy dogs and dogs with IBD.[13] However, colonic cytokine mRNA expression has not been investigated again using the more accurate amplification techniques, and it is prudent not to overinterpret the results from the initial study. To date there are no published data about cytokine expression in feline colitis, but duodenal mucosa of cats with IBD revealed a complex pattern of cytokine mRNA expression with a possible increase in Th1 cytokine mRNA expression.[14,15]

Table 58-4 Efficacy of Various Treatments for Chronic Colitis in Dogs and Cats Based on Published Case Series

Source	Number of Animals	Treatment Evaluated	Success Rate
Cats			
Nelson et al., 1984[29]	6 Cats	Homemade diet (boiled lamb and rice), then switched to highly digestible commercial diet. SS × 3 weeks in 1 cat with NR to commercial diet.	CR in 6 cats fed homemade diet. Rec in 2 cats when switched to highly digestible diet. Both controlled with homemade diets, 1 required SS for 3 wk.
Dennis et al., 1993[30]	13 Cats available for follow up	F (high F diet or addition of F to diet) in 8 of 10 cats with CR or PR, highly digestible diet in 2/7. CR cats received T and/or P initially, which was then d/c. All cats with CR maintained on diet alone. Cats with PR on P or SS as needed.	CR in 7 cats within 6 to 50 mo. PR in 3 cats. No change in one cat. Two cats with severe disease euthanized without treatment.
Dogs			
Nelson et al., 1988[39]	13 Dogs	Diet, initially homemade (cottage cheese and rice), followed by commercial novel antigen or low-residue diet. No medication.	CR to homemade diet in all dogs within 3 days to 6 wk. Rec in 2 of 13 after switch to commercial novel antigen or low-residue diet. Rec in 9 of 11 after exposure to pretreatment diet.
Simpson et al., 1994[40]	11 Dogs	Diet (commercial restricted antigen), initially SS in 9 dogs, d/c after resp of clinical signs. No F supplementation.	SS could be d/c after 1 mo in 3 of 9, 2 mo. in 8 of 9 but had to be resumed in 1 dog. Improvement in stool consistency, fecal mucus, and fecal blood, but not in frequency of defecation in all dogs.
Leib, 2000[31]	27 Dogs available for follow up	F (psyllium) added to various commercial or homemade (low-fat, low-residue or novel protein) diet.	Response excellent in 17, very good in 6, good in 3, and poor in 1 dog. Fiber could be d/c in 5 of 11 dogs, and special diet could be d/c in 5 of 7 dogs.
Allenspach et al., 2007[28]	30 Dogs	Diet (commercial novel antigen), P if NR to diet after 10 days.	CR in 28, NR or PR in 2. No data about resp to P in these 2 dogs.

CR, complete remission; D, diet; d/c, discontinued; F, fiber; NR, no response; P, prednisone; PR, partial remission; rec, recurrence; resp, response; SS, sulfasalazine; T, tylosin

Influence of Diet

A high proportion of dogs and cats with colitis respond to dietary therapy alone (Table 58-4); however, it is important to distinguish the various reasons for diet-responsive colitis. In humans, as well as in dogs and cats, adverse reactions to food can result from immunologic (food allergy) and nonimmunologic (food intolerance) mechanisms.[16] So far, in small animals, the clinical differentiation between food allergy and food intolerance relies heavily on restricted antigen dietary trials.[17,18] All dogs and cats with GI manifestations of adverse reaction to food get better when fed a novel diet, especially if it is designed to avoid antigens from their original diet. When challenged with their original food, they all show a relapse of GI signs. However, only food-allergic dogs and cats also relapse when their low-allergen diet is supplemented with proteins from a single source such as beef, chicken, milk, or any protein that was part of their original offending food.[17] Finally, a number of animals with colitis may simply benefit from being fed a highly digestible diet. These dogs and cats may have mild IBD that responds to the novel diet, which usually also offers additional benefits, such as an improved ratio of n6-to-n3 fatty acids or the presence of prebiotics. These animals usually do not experience a relapse when fed their original diet.

Effects of Inflammation on Colonic Function

The main functions of the colon include absorption of water and electrolytes (proximal colon) and storage of feces (distal colon). Colonic inflammation disrupts these normal events. It may decrease the total absorptive capacity of the mucosa through loss of functional colonocytes, increased epithelial permeability and disturbance of sodium and chloride transport.[19] Additionally, colitis has direct effects on colonic motility. The colon exhibits three types of contractions: While the individual phasic contractions and the migrating and nonmigrating motor complexes produce extensive mixing and kneading of fecal material and slow net distal propulsion, the giant motor complexes (GMCs) produce mass movements and expel feces during defecation.[20] In an experimental model, dogs with acute colitis had a decrease in nonpropulsive motility and an increase in GMCs, resulting in frequent defecation and tenesmus.[21] Decreased nonpropulsive motility may be explained by disturbances of the circular colonic smooth muscle cells associated with inflammation. These include impairment of calcium mobilization,[22-24] changes in expression of key signaling molecules for excitation–contraction coupling,[25] inhibition of muscarinic signaling,[26] and increased transcription of nuclear factor kappa B (NF-κB).[27] Finally, absorptive and motility disorders may change the composition of the luminal commensal flora, which plays an important role in the maintenance of colonic function, and therefore contribute to further deterioration.

Differential Diagnoses

Other colonic diseases that may lead to similar clinical signs include infectious diseases (e.g., parasite infestation with nematodes or

protozoa), infections with systemic fungi, oomycetes, algae, and bacteria. Histiocytic ulcerative colitis (HUC), another chronic inflammatory disease, can only be distinguished from lymphoplasmacytic IBD histologically. Moreover, lymphoma or other neoplasia can infiltrate the large intestine and cause identical clinical signs to those of inflammatory diseases. Finally, cecal intussusception, although rare, is another differential diagnosis of chronic noninfectious colitis. In cats with clinical signs of colitis, it is generally recommended to search for concomitant involvement of the small bowel as enterocolitis appears to occur more frequently than isolated colitis in that species.

Evaluation of the Patient

History

Dogs with IBD tend to be middle-aged (mean age: 6 to 6.5 years with a wide age range)[1,28] and older than those with diet-responsive enterocolitis (mean age: 3.5 years; range: 0.6 to 7.6).[28] In cats with lymphoplasmacytic colitis, the mean age of onset of clinical signs is similar (around 5.2 years; range: 0.5 to 10 years).[29,30] A predilection for purebred cats was noticed in one study,[30] but no canine breed appeared more frequently affected. There is no sex predilection. Signs of chronic colitis are characterized by large bowel diarrhea with frequent defecation of small volumes of soft to watery stool, often mixed with mucus and/or fresh blood (hematochezia). Urgency to defecate and tenesmus are often noticed by the owners, especially in dogs. Although occasional vomiting is often reported, abdominal pain, weight loss, anorexia, and/or lethargy are infrequently part of the history. They may occur during severe episodes, in severely affected animals, or in those with concurrent involvement of stomach and/or small intestine.[31] Clinical signs are often intermittent, although they may be continuous in some animals.[31] A gradual deterioration to more severe disease may be observed over weeks to months.

Physical Examination

Most dogs and cats with large intestinal IBD are in good general condition. Their nutritional status is unchanged by the disease. However, low body condition score and lethargy may be present in severe cases, or in animals with gastroenterocolitis. Without small intestinal involvement, abdominal palpation is often unrewarding, but may help ruling out space-occupying lesions affecting the colon (e.g., intussusception, neoplasia). Rectal palpation may be painful because of anal and rectal inflammation associated with colitis. The rectum may appear empty, or contain blood, mucus, and/or diarrheic stool. Abnormal surface of the rectal wall may be noticeable on rectal palpation.

Ancillary Tests and Laboratory Investigation

Generally, complete blood cell count, serum biochemistry, and urinalysis do not reveal significant abnormalities in dogs and cats with large intestinal IBD. This may be different in animals with generalized GI inflammation: leukocytosis with neutrophilia and left shift, hypoproteinemia with hypoalbuminemia and hypoglobulinemia, and mildly to moderately increased liver enzymes can all be present in such patients. Evaluation of acute phase reactants such as C-reactive protein in the serum has delivered mixed results,[1,28,32] and is not specific for GI inflammation. The precise clinical relevance of serum markers of autoimmunity such as perinuclear antineutrophil cytoplasmic antibodies still remains to be determined in dogs with IBD, but they may be suggestive of diet-responsive disease.[33] A parasitologic examination of one or several fecal samples is necessary to rule out parasite infestation. Alternatively, empirical treatment with broad-spectrum parasiticides such as fenbendazole (50 mg/kg PO daily for 3 days) will eliminate most GI nematodes and protozoa. Cytologic examination of rectal scrapings can reveal the presence of *Histoplasma capsulatum*, large numbers of neutrophils, a sign of inflammation, or increased numbers of Gram-positive rods (suggestive of overgrowth with *C. perfringens*).[34] Usually, diagnostic imaging (radiographs and ultrasonography) is not very helpful in cats and dogs with colitis. It may however yield useful information if the disease extends to the small intestine.

When the diagnostic elimination process confirms the possibility of large intestinal IBD, evaluation of the disease severity is desirable and best performed by colonoscopy (preceded by gastroduodenoscopy in cases with small and large bowel involvement). Full endoscopic examination of the colon requires general anesthesia but remains a safe diagnostic procedure.[35] Flexible colonoscopy allows full visualization of the rectum and descending and ascending colon, as well as cecum and ileocolic junction. Additionally, it is often possible to pass the endoscope into the ileum. Changes noticed during colonoscopy may include an increase in friability, granularity, or hyperemia; changes in the numbers of lymphoid follicles; decreased visualization of submucosal blood vessels; localized colonic spasms; and localized erosions.[31] Significant edema and inflammatory infiltrate may give the mucosa a honeycomb appearance (Figure 58-7); however, the colonic mucosa may also appear normal.[31] The endoscopic procedure also makes it possible to collect mucosal biopsies to evaluate the histopathologic appearance of the mucosa. As the colon can usually be easily distended, it is advisable to use an endoscope with a large-bore biopsy channel that makes the use of large biopsy forceps possible (≥2.8 mm diameter). Rigid proctoscopy/colonoscopy is an alternative method for procuring good size colonic mucosal samples.

Histopathology allows identification of neoplastic processes and differentiation between the various types of colonic inflammation. Recently, criteria for the scoring of colonic inflammation in dogs and cats have been proposed[36]; however, there is currently no universally approved grading system. Consequently, various pathologists may give different interpretations when evaluating the same mucosal sample.[37] Lymphoplasmacytic colitis is the most common form of chronic colitis. It may occur in young dogs (often associated with diet-responsive disease) as well as in older dogs (often associated with IBD). Eosinophilic inflammation may occur in association with IBD, or result from parasite infestation. Pyogranulomatous colitis is uncommon and associated with proliferative masses (millimeters to centimeters in diameter) visible during colonoscopy or palpable rectally. Affected dogs show severe clinical signs.[38] Suppurative colitis has been reported as a probable variant of IBD in cats and often responds to the empirical treatment of colitis.

Treatment and Management

In many instances, treatment of colonic IBD can be initiated after known causes of large intestinal disease have been ruled out. Empirical treatment should focus on a dietary approach and the use of several drugs with limited side effects. A precise assessment of the disease with colonoscopy and histopathologic evaluation of mucosal samples is required prior to using glucocorticoids or other immunosuppressive drugs. These drugs can have multiple side effects and may also hamper the success of further diagnostic efforts.

Several clinical reports describe the dietary approach to dogs and cats with histologically documented chronic colitis and large intestinal IBD (see Table 58-4).[28-31,39,40] Diets recommended for patients with chronic colitis include elimination diets (based on a novel

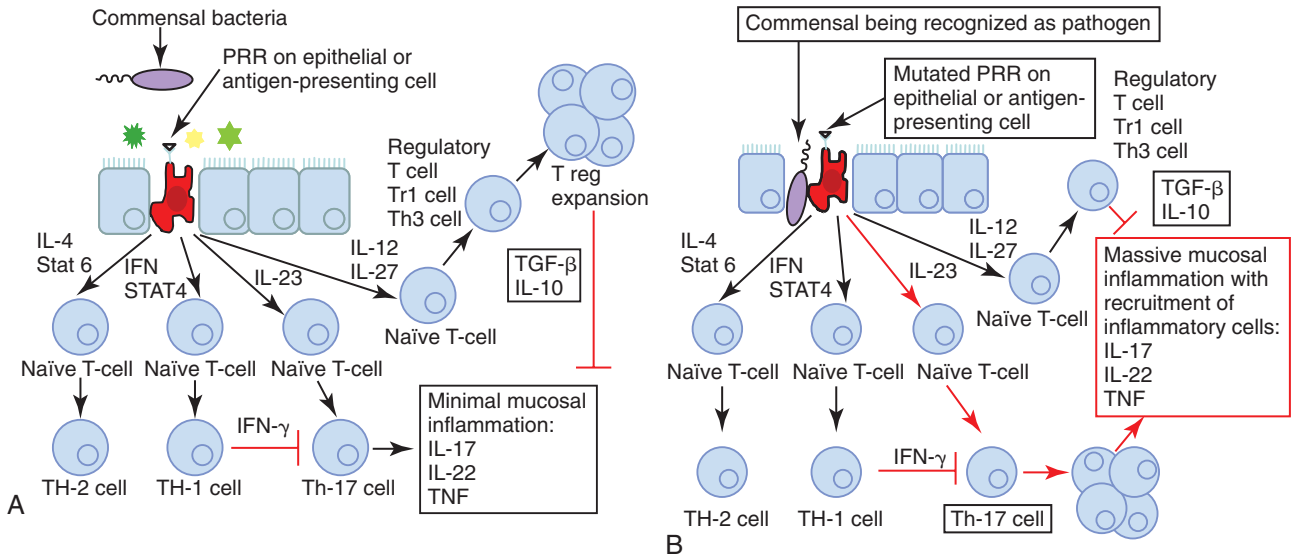

Figure 58-7 Proposed mechanism of oral tolerance against commensal organisms and pathogenesis of IBD. **A,** The pathogenesis of IBD involves three factors: the mucosal barrier, including an intact epithelial cell lining; the host immune system consisting of innate immunity and adaptive immunity; and microbes and food antigens in the intestinal lumen. The interplay of these three factors is important to maintain intestinal homeostasis. In the normal case scenario, antigen-presenting cells continuously sample antigens from the intestinal lumen through pattern recognition receptors (PRRs). Depending on the nature of these antigens, the signals elicited by the antigen-presenting cells drive the adaptive immune response in the appropriate direction to eradicate a pathogen. For example, in the case of a parasite, naive T cells are preferentially driven to differentiate into T-helper (Th) 2 cells that recruit eosinophils, basophils, and mast cells to kill the parasites. In the case of a pathogenic virus, the naive T cells preferentially differentiate into Th1 cells that produce cytokines such as interferon (IFN)-γ. These cytokines recruit macrophages that phagocytose and kill intracellular viruses. In the case of pathogenic bacteria being recognized, naive T cells preferentially differentiate into Th17 cells to produce proinflammatory cytokines such as interleukin (IL)-17 and IL-22. This recruits T cells and neutrophils to kill extracellular bacteria. In the case of commensal bacteria being recognized through PRRs, naive T cells preferentially differentiate into T-regulatory cells that counteract the effect of proinflammatory cytokines produced by Th17 cells. **B,** In the case of IBD, a primary defect in the recognition of commensals or certain pathogens by innate immune receptors may play a causative role. Mutations in PRRs lead to misrepresentation of commensals as pathogens, leading to the massive production of IL-23, driving naive T cells to differentiate into Th17 cells. These Th17 cells then produce large amounts of proinflammatory cytokines, such as IL-17, IL-22, and tumor necrosis factor (TNF). This leads to tissue destruction and epithelial cell injury, letting even more antigens pass through to the lamina propria. This inflammatory response cannot be counterregulated by regulatory T cells, leading to the characteristic inflammatory pattern seen in IBD.

protein or on hydrolyzed peptides),[28,40] and highly digestible, low-residue diets.[29,39] Most dogs and cats with colitis respond within 2 weeks to a diet change, some however may require up to 6 weeks. It is important to communicate the importance of exclusive feeding of the diet to the animal's owner, especially if an elimination diet is chosen. Recommendations regarding the required duration of dietary therapy after clinical remission diverge significantly. Although in one study most dogs relapsed after being fed their original pretreatment diet again,[39] many of the dogs could be switched again to their pretreatment diet after varying time periods in another study.[28] Consequently, it is important to discuss the risks and benefits of a reexposure to the regular diet with the patient's owners in each case to enable them to make an informed decision about their pet.

Dietary fiber consists of nondigestible complex carbohydrates. The addition of soluble fiber to the diet has provided additional benefits in clinical studies of canine and feline chronic colitis.[30,31] Fermentable fibers are metabolized to short-chain fatty acids by the large intestinal flora and provide a useful source of energy to the colonocytes. Overall, they enhance structure and function of the intestinal epithelium.[41] Examples of fermentable fibers include beet pulp, psyllium, and fructooligosaccharides. Fructooligosaccharides are oligosaccharides that resist digestion in the small intestine and are fermented by the colonic bacterial flora. Their beneficial effects on the large intestine include proliferation of colonocytes by increasing blood flow to the colonic mucosa and promotion of epithelial cell differentiation into fully functional colonocytes.[41] Additionally, fructooligosaccharides are prebiotics and therefore are able to influence the composition of the large bowel commensal flora. In cats, they were reported to increase colonic fecal concentrations of *Bacteroides* and *Lactobacillus* spp. and decrease those of *E. coli* and *C. perfringens*.[42] Finally, dietary fibers also have beneficial effects on colonic motility. As a tradeoff, addition of fiber to the diet may have a negative impact on nutrient digestibility, depending on the specific fiber type. Some fibers may also delay gastric emptying time and slow small intestinal transit time.[41] Psyllium is a soluble fiber derived from the seed of *Plantago ovata*. It has great water-holding capacities and forms gels in water, two properties that can contribute to improvement of fecal consistency. Psyllium was very efficient when added to a highly digestible diet in the treatment of chronic idiopathic colitis using the following initial daily dosage: 0.5 tablespoons (T) for toy breeds, 1 T for small dogs, 2 T for medium dogs, and 3 T for large dogs.[31] The fiber supplement should be administered with each meal, and the dose adapted to effect.

Probiotics are live microorganisms that may be beneficial to the host GI tract. Canine- and feline-specific probiotic cocktails are available commercially. However, the achievable benefits of modification of the large intestinal flora by administration of probiotics are subject to controversy. To date, no clinical study has been able to document positive effects of probiotics in dogs and cats with chronic GI diseases,[43] even though in vitro experiments yielded promising results.[44]

Table 58-5 Pharmaceutical Therapy of Large Bowel Inflammation

Drug Category and Name	Dosage Recommendation	Indication
Antimicrobials		
Enrofloxacin	5 mg/kg PO once daily (D)	HUC
Metronidazole	10 to 15 mg/kg PO BID (D, C) to TID (D) For metronidazole benzoate increase above dose by approximately 50%	Acute and chronic colitis
Antiinflammatory Drugs		
Sulfasalazine	10 to 30 mg/kg PO TID for 4 to 6 weeks, max 1 g total dose (D) 5 to 12.5 mg/kg PO TID for 2 to 4 weeks (C) Administer with food; slowly decrease in 10- to 14-day steps to BID, then half the dose BID, then once daily; regularly measure tear production	Colonic IBD refractory to diet and metronidazole
Immunosuppressive Drugs		
Prednisone	1 to 2mg/kg PO bid for 10 to 14 days, then slow tapering over several weeks	Colonic IBD refractory to diet and antibiotics
Azathioprine (D)	Starting dose 2 mg/kg PO once daily for 2 weeks, then 2 mg/kg every other day for 2 to 4 weeks, then 1 mg/kg PO every other day May take 2 to 4 weeks to take effect	Steroid-refractory colonic IBD
Chlorambucil (C)	Cats weighing >4 kg: 2 mg per cat PO every other day for 2 to 4 weeks then tapered to the lowest effective dose (2 mg/kg PO per cat every 3 to 4 days) Cats weighing <4 kg are started at 2 mg/kg per cat every third day	Refractory or severe feline IBD, combined with prednisolone
Cyclosporine (D)	5 mg/kg PO once daily for 10 weeks	Steroid-refractory chronic colonic IBD

C, cat; D, dog.

Pharmacologic intervention (Table 58-5) is required if dietary therapy fails to control clinical signs or may be initiated simultaneously to dietary changes in severe cases. Among antimicrobials, metronidazole is frequently used in the initial management of dogs and cats with colitis. Beside its antimicrobial effects against a variety of obligate anaerobic bacteria, metronidazole is also effective against *Giardia* spp. Furthermore, metronidazole has immunomodulatory effects.[45] It is used in dogs and cats with colitis to modify the intestinal flora (decrease in obligate anaerobes) and decrease inflammation. If a suspension is administered to a cat, metronidazole HCl is not a palatable formulation and may elicit ptyalism and anorexia. Metronidazole benzoate is the preferable formulation for feline patients, but it contains only 62% metronidazole and therefore requires a dose adjustment. Other side effects of metronidazole are rare, although cats may be more susceptible because of the probable increased half-life of the drug, and include vomiting and diarrhea. Hepatotoxicity and neurotoxicity have been reported at higher dosages.[45]

Sulfasalazine consists of 5-aminosalicylic acid (5-ASA; also called mesalamine [United States] or mesalazine [Europe]) linked by an azo bond to sulfapyridine, a sulfonamide compound.[46] Most of the orally administered sulfasalazine reaches the distal small intestine and colon unchanged. There, the microbial flora breaks the azo bond and liberates both molecules. Sulfapyridine is essentially a carrier molecule and is not thought to unfold any therapeutic effect. It is absorbed, metabolized in the liver, and filtered through the kidneys. The antiinflammatory effects of 5-ASA on the colonic mucosa are associated with inhibition of cyclooxygenase and a decrease in prostaglandin and leukotriene synthesis. Moreover, 5-ASA is an activator of peroxisome proliferator-activating receptor (PPAR)-γ.[46] In dogs, PPAR-γ are expressed at a high level in gastric, duodenal, and colonic mucosal epithelial cells.[47] They inhibit pathways leading to increased NF-κB transcription and hence to production of inflammatory cytokines and chemokines.[46] However, recent data do not support a decrease in PPAR in the colonic mucosa of dogs with colitis.[48] The main side effect of sulfasalazine is keratoconjunctivitis sicca (KCS). Although the exact mechanism of action is unknown, sulfapyridine is likely responsible for damaging lacrimal glands.[49] Early detection followed by treatment discontinuation is necessary to prevent the onset of irreversible KCS. Consequently, tear production must be measured at regular intervals in all dogs receiving sulfasalazine. Vomiting may also occur, and can be prevented if the drug is administered with food. Other drugs with the same mechanism of action are available and include olsalazine (two molecules of mesalamine linked by an azo bond) and other formulations of mesalamine coated with an acrylic resin that release the compound in the distal small bowel or colon. Although these drugs have not been extensively tested in small animals, KCS has been reported with their use in dogs.

Glucocorticoids are used as a second line of treatment in dogs with colonic IBD that are refractory to dietary modifications and treatment with metronidazole and sulfasalazine. Their antiinflammatory effects are partly a result of the lipocortin-mediated inhibition of phospholipase A that inhibits the cascade leading to formation of proinflammatory prostaglandin and leukotriene synthesis. Their therapeutic interest also relies on the multiple effects they have on both the innate and adaptive immune response.[50] However, because of their multiple side effects, immunosuppressive doses of prednisone should be reserved for dogs that have undergone colonoscopy, and for which a histologic diagnosis confirms the existence and type of the inflammatory infiltrate. Cats do not appear to develop as many side effects from glucocorticoid therapy as dogs. Additionally, cats may not tolerate TID medication with sulfasalazine, and are more susceptible to mesalamine toxicity. Moreover, many cats with colitis also have lesions in the small intestine (enterocolitis) on which sulfasalazine has no effect. This combination of facts makes glucocorticoids a treatment option that is often considered earlier in feline than in canine colitis patients.

In cases refractory to immunosuppressive doses of glucocorticoids, additional immunosuppressive drugs such as azathioprine (dogs only), chlorambucil (cats), and cyclosporine[51] may be helpful. Because of potential side effects and financial considerations, these drugs should be reserved for patients with well-documented colonic inflammatory disease that showed no response to any other treatment.

Prognosis

The prognosis for IBD is generally better when only the colon is affected. However, one retrospective study of dogs with IBD failed to find any association between localization of disease and outcome.[52] Nevertheless, the various clinical studies summarized in Table 58-4 demonstrate that a majority of dogs and cats with colitis will respond completely to dietary modification and/or to sulfasalazine treatment. If sulfasalazine is used, it can often be discontinued after a few weeks. However, there is a risk of recurrence when the animals are switched back to their original diet or a commercial diet. Therefore, the owners of dogs and cats with colitis should be prepared to feed their pets a special diet in the long-term, and consider the financial implications of the prolonged treatment. In a few cases, colitis may be refractory to treatment. This is probably most common in cats showing predominantly large bowel diarrhea, while in reality they have a general involvement of their GI tract (enterocolitis). In dogs with IBD, several negative prognostic factors have been identified that all reflect severe involvement of the small intestine, including hypoalbuminemia, hypocobalaminemia, severe duodenal lesions, and a high clinical disease score.[28,52] Therefore, they do not appear to apply to colonic IBD.

Histiocytic Ulcerative Colitis

Definition

HUC is a form of IBD that occurs most frequently in young Boxer dogs, also known as granulomatous colitis of Boxer dogs. It was first described 30 years ago[53] and has since been reported to occur in many countries, including the United States,[54-56] Australia,[57,58] Japan, and continental Europe and the United Kingdom.[59,60] HUC also occurs infrequently in other breeds, such as Mastiffs, Alaskan Malamutes,[61] French Bulldogs,[62] and English Bulldogs,[56] and has also been described in one cat.[63]

Pathophysiology and Mechanism

The mechanisms involved in the pathogenesis of HUC in dogs have been debated for decades. The recent success of antibiotic treatment raises the question of an infectious origin; however, this hypothesis has been investigated previously. The role played by macrophages containing cytoplasmic material stained by periodic acid-Schiff (PAS) is intriguing, and early electron microscopic studies have demonstrated so-called residual bodies, which resemble bacteria-like organisms in granules of PAS-positive macrophages.[64] These particles contained parallel pairs of membranes and electron-dense particles ranging in size from 100 to 500 nm, and may have represented bacterial cell membranes. Therefore, specific infectious agents, such as *Mycobacteria*, *Mycoplasma*, *Chlamydia*, and *Rickettsiales* ssp. have all been proposed to play a role in the pathogenesis of the disease.[55] However, attempts to reproduce the disease by infecting dogs with *Mycoplasma* spp. have failed.

Some reports have compared human Whipple disease with canine HUC. Whipple disease is caused by *Tropheryma whipplei* and mainly affects the small intestine. There is a striking histologic resemblance between both diseases involving severe granulomatous inflammation and distortion of the intestinal lamina propria. The causative organism in Whipple disease is susceptible to a variety of antibiotics, such as penicillin, chloramphenicol, and tetracycline, but seems to be resistant to fluoroquinolones. *T. whipplei* has not yet been identified in dogs with HUC, but the recent treatment success with enrofloxacin seems to make this organism less likely to be causally involved.

In a recent publication investigating the possibility of an infectious cause for canine HUC, large numbers of coccobacilli were found in the colonic mucosa by fluorescence in-situ hybridization (FISH) in Boxers affected with HUC but not in histologically normal tissues or in the mucosa of dogs with other types of colitis.[65] Further studies using culture, cloning, and sequencing of the colonic flora from Boxers with HUC identified the bacteria to be *E. coli*. Electron microscopy of HUC lesions allowed identification and localization of the bacteria to the intracellular compartment of PAS positive macrophages.[65] Additionally, the intracellular material found in PAS-positive macrophages from dogs with HUC was positively labeled with polyclonal antibodies against *E. coli*.[66] Further classification of the virulence genes and biologic behavior of these bacteria in coculture with epithelial cells and macrophages revealed specific adhesive and invasive properties.[65] The *E. coli* strains associated with HUC have a similar phenotype with adhesive and invasive behavior resembling *E. coli* isolates that were recently associated with Crohn's disease in people.[65] In several studies, a particular strain of *E. coli* (LF82) could be detected in biopsies of 20% to 35% of ileal lesions in Crohn's disease, but only in 6% of ileal samples from healthy controls or other colonic inflammatory diseases.[67] Crohn's disease affects primarily the mucosa and submucosa of the ileum and colon. It resembles canine HUC in its histologic appearance, as granulomas are the main feature of the disease. As in canine HUC, some cases of Crohn's disease are responsive to treatment with antibiotics. The *E. coli* strain LF82 that has increasingly been associated with Crohn's disease is unusual because it adheres to and invades intestinal epithelial cells in culture[68] and has been shown to replicate within the phagolysosomes of macrophages in the granulomatous lesions[69] instead of being cleared by the adaptive immune system. There is evidence that the adhesive and invasive *E. coli* associated with HUC are taken up by endosomes and persist in the macrophages instead of being cleared.[65] These findings support the hypothesis that genetics play a major role in the pathogenesis of Crohn's disease, and has led to recent genome-wide association studies in canine HUC. Certain defects in pattern-recognition receptors (PRRs) of the innate immune system have long been known to be associated with the development of Crohn's disease.[70] These receptors are important for the interaction of the mucosal innate immune system with the microflora of the intestinal lumen. The default response of the gut-associated lymphoid tissue is to clear offending pathogens, but to tolerate commensal organisms from the intestinal lumen.[71] Recent evidence confirms that polymorphisms in certain PRRs, such as NOD2, result in a disturbed response of human monocytes to *E. coli* LF82, linking genetics with functional disease for the first time.[72] Preliminary results from genetic studies in Boxers with HUC and healthy controls point to a defect in a protein in neutrophils that leads to defective clearance in *E. coli* in macrophages.

The inflammatory response normally only occurs as a reaction toward pathogenic bacteria breaching the intestinal barrier, and resembles the lesions observed in the mucosa of people affected with Crohn's disease and dogs with HUC. It is therefore possible that similar defects in PRRs occur in people with IBD and in dogs with HUC. A genetic predisposition for HUC is suspected due to the

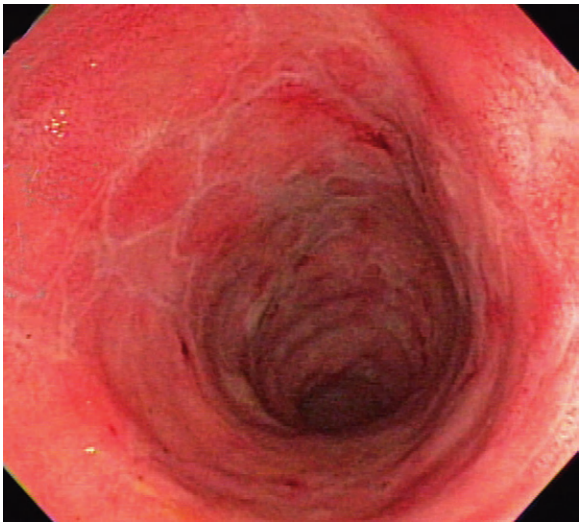

Figure 58-8 Endoscopic view of the descending colon from a dog with severe lymphoplasmacytic colitis. Note the honeycomb pattern that reflects mucosal edema and inflammation.

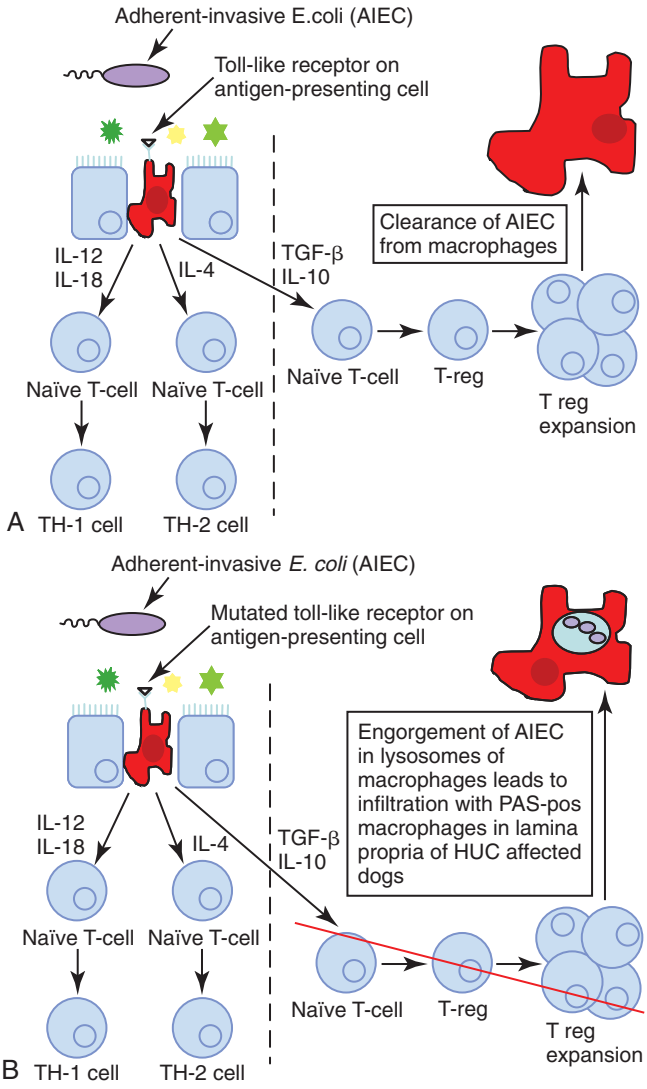

Figure 58-9 **A,** In the normal case scenario, various pathogens in the intestinal lumen, such as bacteria, viruses, and fungi, bind to PRRs on the surface of antigen-presenting cells, such as TLRs. To prevent infection, the innate immune system activates adaptive immune processes by promoting proinflammatory cytokine expression of T cells, such as tumor necrosis factor (TNF), interferon (IFN)-γ, and interleukin (IL)-17. This results in appropriate expansion of the relevant T cells to clear the infection, such as T-helper (Th) 1 cells for viruses and Th2 cells for parasites. In the case of normal commensals and adhesive–invasive *E. coli* (AIEC) in an animal not affected by HUC, T-regulatory cells will produce antiinflammatory cytokines such as IL-10 and transforming growth factor (TGF)-β, which leads to suppression of an inflammatory adaptive immune response and tolerance toward these bacteria. **B,** Hypothetical explanation for the pathogenesis of HUC. Mutations in pathogen recognition receptors, such as TLRs, lead to inappropriate activation of the adaptive immune system. In the case of AIEC, there is no expansion of T-regulatory cells, which results in engorgement of macrophages with AIEC within their lysosomes. The colonic lamina propria in dogs with HUC is filled with macrophages which stain positive for intracellular AIEC.

preponderance of cases in young boxer dogs. In the first report of the disease in 1965, most of the affected dogs could be traced to a single ancestor.[53] Confirmation and identification of mutations in PRRs such as TLRs or NODs in boxers with HUC is still lacking. However, it seems likely that a defect in innate immunity renders dogs with HUC more susceptible to infections with specific bacteria, such as the adhesive and invasive *E. coli* strains described previously (Figure 58-8).

Differential Diagnoses

Typically, HUC is characterized by chronic large intestinal diarrhea in relatively young dogs. Differential diagnoses include parasitic diseases such as infestation with *Trichuris vulpis* or *Giardia* spp., bacterial infections with *Campylobacter* or *Clostridia*, infections with oomycetes (*Pythium* spp.) and fungal microorganisms (*H. capsulatum*), as well as diet-responsive diseases such as food intolerance or food allergy. Further differentials include IBD other than HUC, such as lymphoplasmacytic and eosinophilic colitis. Rectal and colonic polyps as well as neoplastic disorders, such as lymphoma or adenocarcinoma, are less likely to occur in younger animals.

Evaluation of the Patient

History

The onset of disease occurs predominantly before 2 years of age. The clinical signs are those of severe chronic large intestinal inflammation and comprise diarrhea, hematochezia, increased frequency of defecation, tenesmus, and presence of excessive mucus in the feces.

Physical Examination

Physical examination findings are normal in many cases of HUC. However, weight loss and inappetence can be seen in severe cases, and should prompt further more invasive investigations. Fresh blood and mucus can be seen upon rectal examination.

Diagnostic Investigation

The diagnostic approach to cases with HUC is as described for chronic colitis. Typically, colonoscopy reveals sites of severe colonic hemorrhage and ulceration interspersed with stretches of normal appearing mucosa (Figure 58-9). Ten to 15 biopsies should be taken for histopathological analysis. Early lesions can consist of a mixed inflammatory infiltrate in the lamina propria, subjacent to degenerative epithelium.[53,55,73,74] With more extensive lesions and chronic disease, the ulcers become more visible on histology with severe infiltration of the lamina propria and the submucosal regions with

neutrophils, macrophages, lymphocytes, plasma cells and mast cells. There is also usually marked loss of the epithelial surface in biopsies from lesions and loss of goblet cells in the entire colon. Accumulation of large PAS-positive macrophages is pathognomonic for HUC[54,73,75] and remains the best way to confirm the diagnosis (Figure 58-10). In immunohistochemical studies HUC lesions are characterized by an increased number of L1-positive cells (Figure 58-11), as well as major histocompatibility complex (MHC) class II-positive cells, CD3-positive cells, and IgG-positive plasma cells.[60] L1 is a cytosolic calcium-binding protein, the function of which has not been described in detail in the dog. In humans, it is expressed by macrophages and neutrophils at an early stage in their differentiation and is lost when macrophages migrate into tissues and mature. It is possible that in canine HUC recently emigrated blood monocytes progressively differentiate into tissue macrophages, and become eventually filled with PAS-positive material, while L1 expression is downregulated.[55] MHC class II molecules are normally present on macrophages. Therefore it is not surprising to find an increased MHC class II expression associated with PAS-positive macrophages in HUC. Increased T-cell numbers were observed in HUC and are reminiscent of increased numbers of CD3-positive cells seen in other forms of canine IBD, particularly lymphoplasmacytic IBD.[60] Confirmation of the presence of *E. coli* using FISH analysis on formalin-fixed biopsies is now recommended as part of the detailed diagnostic work-up for dogs with suspected HUC.[75a] Up to 43% of dogs with HUC develop enrofloxacin resistance early in the disease process and may be refractory to treatment if they are treated without taking bacterial culture results into account.[75b]

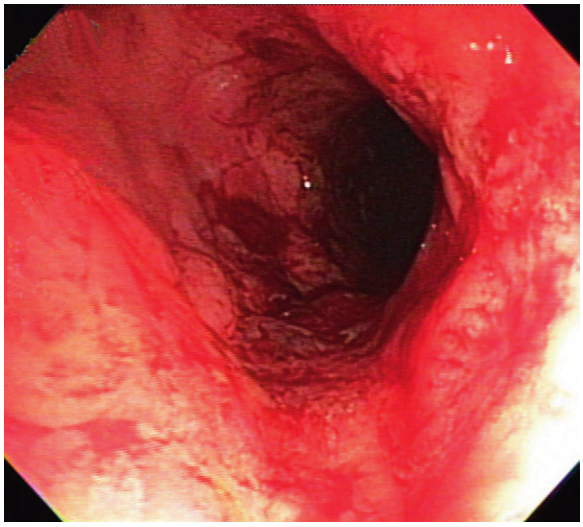

Figure 58-10 Endoscopic view of the descending colon in a young Boxer dog with histiocytic ulcerative colitis (HUC). The mucosa is very irregular, with discolored swollen areas interspersed with fistulae and spontaneous bleeding is observed. The final diagnosis was made after histopathologic evaluation of colonic mucosal biopsies.

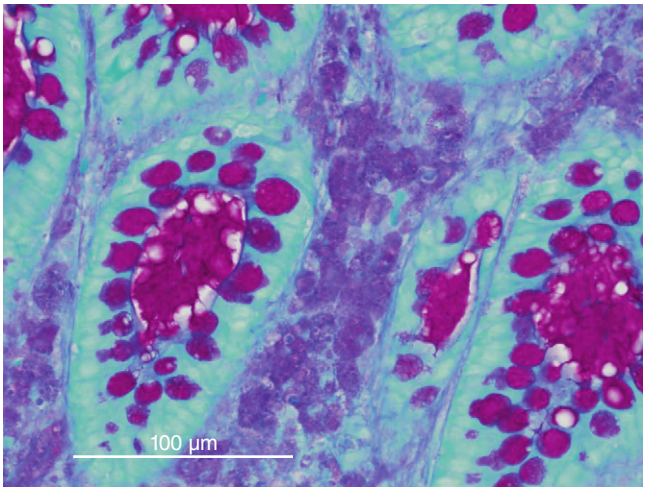

Figure 58-11 Photomicrograph of the colonic mucosa from a Boxer dog with HUC (PAS). The transversely cut colonic crypts have dark magenta-colored mucus in their goblet cells and lumen. There is an inflammatory infiltrate in between the crypts with large mononuclear cells with purple, heterogeneous material in their cytoplasm. This material represents in part phagocytosed *E. coli*. The granulomatous infiltrate and the PAS staining of infiltrating macrophages are diagnostic of HUC.

Treatment and Management

The prognosis for HUC was considered to be guarded to poor until recently. Management of HUC used to consist of various combinations of dietary modification (e.g., increasing fiber content and specific elimination diets), and antiinflammatory or immunosuppressive treatment with sulfasalazine, prednisone, and azathioprine, as described previously for the treatment of chronic colitis. Typically these strategies were not successful, and most cases had to be euthanized because of refractoriness to treatment. In recent years two reports have sparked hope for treatment of HUC: a total of 35 cases have been described and have shown a dramatic response to treatment with enrofloxacin (5 mg/kg PO once daily), or a combination protocol with enrofloxacin, amoxicillin (20 mg/kg PO twice daily), and metronidazole (10 to 15 mg/kg PO twice daily).[56] Reports of the disease almost 30 years ago also occasionally described a good response to treatment with antibiotics, namely chloramphenicol and tetracycline.[76] The response to treatment with enrofloxacin in the more recent reports was dramatic, with all dogs responding within 3 to 12 days of initiating therapy. It is particularly encouraging that several dogs were reportedly disease-free after the drug had been discontinued following a 4- to 6-week course of treatment.[56]

This implies that HUC can be cured in some cases. Five dogs were rebiopsied when they were in clinical remission after completion of the antibiotic treatment. A dramatic improvement in the histologic lesions was evident in all cases, with disappearance of PAS-positive macrophages in three dogs and marked reduction in the number of macrophages in the other two cases.[56]

However, care must be taken to treat dogs with HUC long enough to avoid relapse after discontinuation of treatment. In addition, it may be prudent to send intestinal biopsies for culture and sensitivity before starting treatment, so that the use of antibiotics can be tailored to the specific sensitivity profile of the cultured *E. coli*.[75a,77]

Colitis Associated with Anal Furunculosis

Anal furunculosis (AF) is a chronic and painful disease of the anorectum in dogs that preferentially affects German Shepherd dogs and is characterized by inflammation, ulceration, and sinus tract formation. Clinical signs include a painful ulcerated perineal region that may cause tenesmus, hematochezia, and even anorexia and weight loss. Histologic evidence of colitis has been documented in several cases of AF.[78,79] This association is interesting because

chronic fistulation is frequently observed in people with Crohn disease. Moreover, PRRs are thought to play an important role in the pathogenesis of IBD in people and dogs, and have been the object of recent research in dogs with AF. One study found dysfunctional NOD2 responses in German Shepherd dogs with AF.[80] Moreover, a restricted allelic variation in TLR1, TLR5, and TLR6 was found in German Shepherd dogs. However, there were no significant associations between these PRR polymorphisms and AF. Nevertheless, these polymorphisms may influence innate immune responses in German Shepherd dogs and may be an important predisposing factor for the development of AF in that breed.[81] In other studies, increased prevalence of a specific haplotype of alleles of genes encoding class II molecules of the canine MHC was shown in German Shepherd dogs with AF, suggesting a possible defect in antigen presentation associated with the disease.[82] Finally, it is noteworthy that feeding a restricted antigen diet maintained more than 80% of dogs with AF in complete remission after en bloc surgical excision and anal sacculectomy,[83] and that both AF and IBD respond to treatment of immunosuppressive drugs such as prednisone and cyclosporine.[84] These similarities underline the possibility of a comparable pathomechanism for both diseases.

Typhlitis

Definition

Typhlitis refers to inflammation of the cecum and is a rare condition in small animals.

Pathophysiology and Mechanism

There are few case reports that describe typhlitis in association with concurrent inflammation of the ileum and/or colon in dogs. The inflammation has been reported to be predominantly eosinophilic in one dog. Little is known about the pathomechanism of disease, but it is likely that the pathogenesis is similar to lymphoplasmacytic and/or eosinophilic IBD in the small and large intestine.

Differential Diagnoses

Typhlitis usually presents in combination with enteritis or colitis, and the clinical signs are associated with small and/or large intestinal chronic diarrhea. In addition, the anatomical location of the cecum makes it more likely that severe inflammation could result in signs of intestinal obstruction or pseudoobstruction. Consequently, differential diagnoses include infectious and inflammatory causes of enteritis and colitis such as *T. vulpis*, as well as causes for obstruction, such as foreign bodies, abscesses, inversion of the cecum into the colon, fecaliths, or neoplasia.

Evaluation of the Patient

History and physical examination in patients with typhlitis resemble those for chronic small intestinal and/or large intestinal diarrhea.[85] In some cases, ileus or pseudoileus can occur as a consequence of obstruction of the cecum, which results in acute or chronic vomiting.[86,87] Radiography may reveal signs of partial or complete ileus. Abdominal ultrasound may show thickening of the cecal mucosa or evidence of obstruction in the cecal lumen. Endoscopy is recommended in all cases of suspected nonobstructive typhlitis as it allows direct visualization of the mucosa and collection of multiple endoscopic biopsies.

Management

If typhlitis occurs secondary to enteritis or colitis, the management consists of treatment of these diseases. If chronic typhlitis has led to obstruction or abscessation, surgical typhlectomy is the treatment of choice and usually results in a favorable prognosis.[86,87]

INFECTION

Jody L. Gookin

Infectious diseases of the canine and feline gastrointestinal tract are numerous and commonly affect function of the small and large bowel. The infectious agents included in this section are those for which the colon is a primary target of injury or for which signs of large intestinal disease are a dominant clinical feature.

Helminths

Heterobilharzia americana

Etiology

Heterobilharzia americana, a fluke parasite, is the causative agent of canine schistosomiasis in North America.[1-5] Infection is enzootic in the Southeastern and Gulf Coast of the United States. Raccoons are considered the most important reservoir host of the parasite. Domestic and wild canid infections are uncommon, but clinically significant. The major intermediate hosts are the freshwater lymnaeid snails, *Lymnaea cubensis* and *Pseudosuccinea columella*.

Pathophysiology

Infection is acquired when free-swimming cercaria, released from the snail intermediate host, penetrate skin. The cercaria migrate through the lung and liver where they mature into adult flukes and then to the terminal mesenteric veins to reproduce. Ova are deposited in the terminal branches of the mesenteric veins and work their way through the intestinal mucosa to the bowel lumen by secretion of proteolytic enzymes. When ova are excreted in feces and come into contact with water, they give rise to miracidia that penetrate susceptible snails to reinitiate the cycle. The presence of ova in the submucosa of the small intestine and colon elicits an intense granulomatous tissue reaction.[2] Lesions are characterized by epithelioid macrophages, usually surrounding parasitic ova, admixed with varying amounts eosinophils, neutrophils, lymphocytes, and plasma cells.[1,2] Ova that do not make it to the intestinal lumen may be hematogenously disseminated to distant sites, particularly via the portal vein to hepatic venules where ova-induced chronic inflammation can lead to hepatic fibrosis and organ failure. Ova and associated granulomatous inflammation may also be found in the pancreas and lungs.

Clinical Examination

Clinical signs range from profuse acute to chronic mucoid diarrhea and tenesmus. Signs of inappetence, weight loss progressing to cachexia, and bloody diarrhea of small bowel (melena) or large bowel (hematochezia) origin are common. Physical examination findings may include thickened loops of intestine, abdominal effusion, peripheral edema, and mild generalized lymphadenopathy. Dermatitis caused by cercarial penetration of the skin or coughing because of lung migration are uncommonly reported. Clinicopathologic abnormalities include anemia, hyperglobulinemia, hypoalbuminemia, eosinophilia, and proteinuria. Dogs with *Heterobilharzia* infection may present with clinical signs arising from moderate to severe hypercalcemia.[1,6] In 2 dogs with *Heterobilharzia* infection, and lack of evidence for malignancy, hypercalcemia was attributed to elevated parathyroid hormone-related peptide concentrations.[6]

Diagnosis

Diagnosis of *H. americana* is made by performing saline sedimentation of feces to observe ova containing miracidia and by the observation of motile miracidia released from ova when exposed to water.[7] In cases where infection is suspected, but ova are not observed in feces, diagnosis may be attempted by detection of circulating anodic antigen in serum by enzyme-linked immunosorbent assay (ELISA).[2]

Treatment

Treatment with high-dose praziquantel (25 mg/kg per os BID-TID for 2 to 3 days)[2,6] or fenbendazole (40 mg/kg per os once a day for 10 days)[8] is reportedly effective is resolving ova shedding and clinical signs.

Prognosis

The prognosis for acute infection is good. Chronic infections may result in liver fibrosis and organ failure.

Strongyloides tumefaciens

Etiology

Strongyloides tumefaciens is a feline threadworm parasite. Infections are rare and observed primarily in temperate regions of the United States Gulf Coast. Infections are more common in tropical and semitropical climates wherein favorable conditions for the free-living stages of the lifecycle can be obtained.

Pathophysiology

Infective larvae penetrate oral-esophageal mucosa or skin and are carried in the circulation to the lungs. Larvae break into alveoli, migrate up the airways, and are subsequently swallowed. Adult parasites are comprised exclusively of parthenogenetic female worms that burrow into the submucosa of the large intestine. Worms, eggs, and larvae reside in submucosal, epithelial-lined cavities where they elicit adenomatous proliferation and infiltration of macrophages, neutrophils, lymphocytes, plasma cells, and connective tissue resulting in visible nodules on the mucosal surface of the colon.

Clinical Examination

Infection is usually asymptomatic, but in clinical cases the parasite causes intractable diarrhea, particularly in young cats and kittens.[9-12] Adult parasites residing in the submucosa are associated with formation of whitish-colored, raised nodules and mucus on the mucosal surface of the colon. Each nodule has a central depression corresponding to an epithelial-lined pore through which the cavities communicate with the lumen of the colon. Coalescence of nodules may give the appearance of adenomatous tumors.

Diagnosis

Embryonated ova are identified in fresh feces by fecal flotation. Larvae may be identified in feces by the Baermann technique and must not be confused with larvae of *Aelurostrongylus abstrusus*. Adult worms, eggs, and larvae may be observed in biopsy specimens of colonic mucosal nodules.

Treatment

Fenbendazole 50 mg/kg once a day for 5 days.

Prognosis

Good.

Trichuris spp.

Etiology

T. vulpis, the parasite responsible for whipworm infection, is likely one of the most common causes of chronic large bowel diarrhea in dogs. In cats, infections are rare and caused by *Trichuris campanula* and *Trichuris serrata*.

Pathophysiology

Worms of the genus Trichuris are parasites of large intestinal mucosa. Infection is transmitted by the fecal–oral route. Eggs are ingested and develop into larvae that hatch in the small intestine where they burrow into the epithelial crypts. Larvae subsequently migrate to the cecum and colon where they develop into adults. Adult worms tunnel their thread-like anterior body into the mucosa and use a mouth spear to puncture and shred tissue, blood vessels, and epithelial cells upon which they feed.[12,13] Heavy infections may produce severe typhlitis and colitis. Cecal inversion is uncommonly reported. Factors contributing to pathogenicity and clinical severity include the number and location of adult worms, degree of mucosal inflammation, severity of anemia or hypoproteinemia, nutritional status of the host, and presence of other GI parasites and microorganisms.[14]

Clinical Examination

Trichuris spp. can infect dogs of all ages. Many, if not most, infections are asymptomatic. Characteristic clinical signs are those of mucoid large bowel diarrhea with tenesmus and hematochezia. Signs may be acute, chronic, or intermittent. Severe infections may be accompanied by eosinophilia, anemia, and hypoproteinemia. Rarely, infected dogs have serum electrolyte abnormalities consistent with hypoadrenocorticism (hyponatremia and hyperkalemia). When tested, these dogs are normoresponsive to adrenocorticotropic hormone stimulation.[15]

Diagnosis

Characteristic bipolar operculated, thick-walled, unembryonated ova are identified by routine fecal flotation. Immature adults can cause severe disease and adults are sporadic egg producers. Accordingly, repeated fecal examination may be necessary to identify ova and negative fecal examinations do not rule out infection. Empirical treatment for occult *Trichuris* infection should always be performed before moving on to a more detailed, costly, and unnecessary medical investigation. Ova of the feline trichurids, *T. campanula* and *T. serrata*, may be easily confused with pseudoparasites, for example, ova of *Trichuris* or *Capillaria* spp. that parasitize feline prey and pass unaltered into feline feces.

Treatment

Drugs effective for treatment of *Trichuris* spp. infections include fenbendazole and febantel. The latter drug is partially metabolized to fenbendazole and oxibendazole. Regular use of milbemycin oxime for heartworm prevention is also effective for treatment and prevention of *T. vulpis* infection.[16] Immature worms are less susceptible to drug treatment and it takes approximately 3 months for larval stages to mature to egg-laying adults. Therefore, treatment should be repeated in 3 weeks and again in 3 months. Whipworm ova survive for prolonged periods of time in the environment and dogs housed in areas that are difficult to decontaminate (e.g., on dirt) may need to be retreated every 2 to 3 months. When possible, feces should be collected and removed.

Prognosis

Excellent.

Protozoa

Balantidium coli

Balantidium coli is a ciliated protozoan that primarily infects swine and nonhuman primates.[17] The infection is rare in dogs[18-22] and is frequently associated with exposure to swine. Trophozoites reside in the colon and result in ulcerative colitis.[19] Dogs are frequently coinfected with *T. vulpis*.[18,20] Clinical signs consist of chronic hemorrhagic colitis. Diagnosis is based on demonstration of large ciliated protozoa with prominent macronuclei in fresh saline smears of diarrheic feces or cysts in feces following zinc sulfate flotation. The distinctive macronuclei of the trophozoite and cyst can only be seen after staining. Treatment for any concurrent helminth infection may alone be curative in some cases.[20] Because of their effectiveness in people, specific therapy for *B. coli* is likely to be attained with tetracycline or metronidazole.

Entamoeba histolytica

Entamoeba histolytica is the causative agent of human amebic dysentery. Infection in dogs[23,24] and cats is rare and acquired by ingestion of food or water contaminated by human or nonhuman primate feces containing infective cysts. Trophozoites dwell in the lumen of the colon and invade the submucosa by secreting lytic factors that allow them to undermine and ulcerate the mucosa. These pathogenic effects result in ulcerative to necrotic colitis and bloody, mucoid large bowel diarrhea. Rarely, trophozoites disseminate to other organs.[24] Diagnosis is made by finding ameboid trophozoites in wet-mount preparations of fresh diarrheic feces, quadrinucleated cysts in feces following zinc sulfate flotation, or trophozoites in colonic biopsy specimens. Treatment with metronidazole alleviates clinical signs of colitis, but dogs may continue to shed trophozoites.[25]

Tritrichomonas foetus

Etiology

T. foetus is a flagellated protozoan characterized by three anterior flagella and an undulating membrane. Trichomonads are obligate parasites of warm, moist and anaerobic sites within the gastrointestinal or genitourinary tract of their hosts. Trichomonads do not form cysts, reproduce by binary fission, and are transmitted directly from host to host in the form of trophozoites. *T. foetus* was first identified as a cause of chronic large bowel diarrhea in cats in 2003 and the duration of its existence in cats prior to that time is unknown.[26] The prevalence of *T. foetus* infection is high among densely housed cats (31% of 117 cats from 89 catteries sampled at an international cat show).[27]

Pathophysiology

In cats, *T. foetus* colonizes the distal ileum and colon where trophozoites can be found in close proximity to the surface of the mucosa or in the lumen of colonic crypts.[28] Less commonly, subepithelial invasion of trichomonads may also be observed. Inflammatory infiltrates consist of plasma cells, lymphocytes, and neutrophils.[29]

Clinical Examination

Cats with symptomatic *T. foetus* infection are generally young. Asymptomatic infection in older cats may be common. Cats originating from a cattery (e.g., purebred) or shelter appear to be at increased risk for infection because of a history of dense housing. A true breed predisposition has not been shown.[27] Clinical signs are characterized by a waxing and waning large bowel diarrhea with occasional fresh blood and mucus. Diarrhea is semiformed to cow pie in consistency and malodorous. The anus may appear inflamed and painful; involuntary dribbling of feces or rectal prolapse may be present. Despite these clinical signs, most cats maintain good health, and normal appetite and body condition.

Diagnosis

Feline *T. foetus* infection may be diagnosed by identifying the organism in feces by direct saline smear examination, selective protozoal culture, PCR using species-specific primers, or by observation of trichomonads in colonic mucosal biopsy specimens. The sensitivity of direct fecal smear examination for diagnosis of *T. foetus* is low (2% in cats with experimentally induced infection and 14% in cats with spontaneous disease). *T. foetus* trophozoites are often misdiagnosed as *Giardia* and can be difficult to distinguish from nonpathogenic trichomonads such as *Pentatrichomonas hominis*. If repeated direct microscopic examination results are negative for *T. foetus*, feces may be cultured in commercially available pouches marketed for diagnosis of *T. foetus* infection in cattle (In Pouch TF, Biomed Diagnostics, White City, OR). Neither *Giardia* spp. nor *P. hominis* organisms survived in In Pouch TF for longer than 24 hours in one study; consequently, positive cultures are strongly suggestive of *T. foetus* infection.[30] A sensitive and specific single-tube nested PCR based on amplification of a conserved portion of the *T. foetus* ribosomal RNA (rRNA) gene unit from feline feces is commercially available (http://www.JodyGookin.com). Nested PCR assays are believed to be superior to fecal culture for diagnosis of infected cats.[31] Histopathology should not be relied upon to make a diagnosis of *T. foetus* infection, although a diagnosis can be attained if organisms are identified.[29]

Treatment

Ronidazole has been demonstrated to be effective at killing feline isolates of *T. foetus* in vitro and eradicated *T. foetus* from experimentally infected cats (on the basis of PCR).[32] The recommended dose is 30 mg/kg q24h PO for 14 days. Ronidazole is not registered for human or veterinary use in the United States and is currently banned for use in food-producing animals because of human hazards. Neurotoxicosis may be a common and serious side effect. Therefore, treatment with ronidazole should only be considered in cases of confirmed *T. foetus* infection where informed consent has been obtained. Follow-up testing by PCR is recommended if diarrhea persists longer than 2 weeks post treatment. Importantly, negative results should be interpreted with caution as PCR cannot prove the absence of infection and prolonged asymptomatic carriage of the organism after antimicrobial therapy may be common.

Prognosis

For single-cat households where reinfection is improbable, the prognosis for eradication of *T. foetus* infection with ronidazole is generally good. When left untreated, 88% of cats with *T. foetus* infection had spontaneous resolution of diarrhea within 2 years (median: 9 months; range: 5 months to 2 years). Time to resolution of diarrhea was significantly longer for cats from multiple-cat households, and those receiving a variety of different diets and antimicrobial drugs in an attempt to treat the condition. Importantly, spontaneous resolution of diarrhea does not imply recovery from infection, as 57% of these cats remain infected with *T. foetus* as determined by PCR when performed 2 to 5 years after diagnosis.[33]

Fungi

Histoplasma capsulatum

Etiology

H. capsulatum is a dimorphic fungus whose free-living mycelial stage flourishes in warm, moist, and nitrogen-rich (contaminated with bird or bat excrement) soil. Although sporadic cases may occur throughout the United States, most infections are diagnosed in animals living or traveling in the Ohio, Missouri, and Mississippi River valleys.

Pathophysiology

Fungal spores (macro- and microconidia) are inhaled and develop into yeast in the lung parenchyma. The yeast are ingested by macrophages wherein they reproduce by budding and may be disseminated via the blood and lymphatics to organs rich in mononuclear phagocytes including the GI tract, lymph nodes, liver, spleen, and bone marrow. Intestinal involvement in the absence of lung disease in many cases suggests that ingestion may also be a route of infection, however experimental studies have failed to produce GI disease reliably after oral administration of *H. capsulatum* spores.[34] Intestinal infection results in a granulomatous inflammatory response, mucosal ulceration, and blood loss.

Clinical Examination

Dogs with intestinal histoplasmosis are typically young, large breed, and have chronic diarrhea, inappetence, weight loss, pale mucous membranes, and fever that is unresponsive to antibiotics.[35] Although signs of large bowel diarrhea (tenesmus, mucus, and fresh blood in the feces) predominate, the small bowel is invariably involved and may result in a voluminous, watery stool, melena, and accompanying protein-losing enteropathy. Clinical signs of intestinal involvement are identified less commonly in cats.[36] Other historical and physical examination findings will depend on organ and tissue involvement.

Diagnosis

Definitive diagnosis of intestinal histoplasmosis is made by demonstrating *Histoplasma* organisms within mononuclear phagocytes by exfoliative cytology, intestinal biopsy, or tissue aspirates. Rectal mucosal scrapings, imprints of colonic biopsy specimens, and aspirates of liver, lung, spleen, and bone marrow are most productive in the dog.[34] For formalin-fixed, paraffin-embedded biopsy specimens, special staining (PAS, Gomori methenamine silver) is needed to demonstrate the organisms. Fungal culture is not recommended as this fosters growth of the mycelial phase, thereby increasing the risk of human inhalation of infective microconidia. Serologic and intradermal skin tests to diagnose histoplasmosis currently lack suitable sensitivity and specificity for clinical use.

Treatment

Itraconazole (10 mg/kg PO q12-24h) is the drug of choice for treatment of systemic histoplasmosis.[34,37] Amphotericin B may be combined with itraconazole in cases of severe or fulminating infection. In general, treatment is continued for 2 to 3 months beyond remission of clinical signs and for a minimum of 4 to 6 months. Symptomatic treatment may alleviate clinical signs of intestinal disease. Recommended therapies have included dietary modification (highly digestible diet for small intestinal disease, increased fiber diet for large intestinal disease), antibiotics for control of intestinal bacterial overgrowth, direct antidiarrheal drugs, and antiinflammatory drugs such as the 5-aminosalicylates.[38,39]

Prognosis

Depending on severity of clinical signs and systemic involvement, prognosis can vary from guarded to good.

Oomycetes

Pythium insidiosum

Etiology

P. insidiosum is an aquatic oomycete.

Pathophysiology

In an aquatic environment, *P. insidiosum* releases motile biflagellate zoospores that cause infection by penetrating and encysting in damaged skin and gastrointestinal mucosa. Gastrointestinal pythiosis is characterized by eosinophilic and pyogranulomatous inflammation and necrosis that localizes predominantly in the submucosal and muscular layers of the intestine[40] resulting in severe, segmental thickening that most frequently involves the gastroduodenal and ileocolic sections of the GI tract. However, multisegmental lesions and diffuse involvement of the GI tract have been described.[40-43] Infection may extend directly to adjacent tissues including the mesenteric lymph nodes, blood vessels, pancreas, uterus, and prostate.[40,41,44]

Clinical Examination

Pythium is identified most often in young, male, large breed dogs with recurrent exposure to warm freshwater habitats.[40,45] Gastrointestinal or cutaneous disease may be present, but are rarely found together in the same patient.[45] Gastrointestinal pythiosis in cats appears to be rare.[45] In dogs, GI pythiosis typically results in clinical signs of weight loss, vomiting, diarrhea, and hematochezia in association with a palpable abdominal mass on physical examination.[45] Hematologic and serum biochemistry abnormalities may include anemia, eosinophilia, hyperglobulinemia, and hypoalbuminemia. Cutaneous lesions consist of nonhealing wounds and invasive masses that contain ulcerated nodules and draining tracts.[45]

Diagnosis

A tentative diagnosis of gastrointestinal pythiosis is made by deep wedge biopsy of affected segments of intestine wherein broad, sparsely septate, and occasionally branching hyphae are demonstrated after staining with Gomori methenamine silver or anti–*P. insidiosum* antibodies.[45] Definitive diagnosis of *P. insidiosum* can be made using a species-specific nested PCR assay applied to DNA extracted from cultured isolates, appropriately preserved tissue samples (frozen at −70°C (−94°F) and stored in 95% ethanol at room temperature), or paraffin-embedded specimens.[45-47] Alternatively, a soluble mycelial antigen-based ELISA or Western analysis may be used to detect anti–*P. insidiosum* antibodies in the serum.[48]

Treatment

The treatment of choice for *P. insidiosum* infection is aggressive surgical resection. In the GI tract, 3- to 4-cm surgical margins (beyond tissue pathology) are recommended.[45] Because of frequent postoperative recurrence, postsurgical medical therapy with itraconazole (10 mg/kg PO q24h) and terbinafine (5 to 10 mg/kg PO q24h) is recommended.[45] Medication should be continued for 2 to 3 months at which time ELISA serology should be performed and compared with presurgical values. Medical therapy should be continued until serologic results (checked at 2- to 3-month intervals) are negative for *P. insidiosum* antibodies.[45] Medical therapy alone for treatment of pythiosis is unrewarding; this may be attributed to the

absence of cell membrane ergosterol (the target of most available antifungal drugs) in oomycetes.

Prognosis

Most dogs with GI pythiosis are presented late in the course of infection when complete excision is not possible. The anatomic site of the lesion may also preclude complete resection. Accordingly, the prognosis in most patients is guarded to grave.

Algae

Prototheca zopfii

Etiology

P. zopfii and *P. wickerhamii* are achlorophyllous algae that are ubiquitous to raw and treated sewage, slime flux of trees, and animal wastes with secondary contamination of the environment. *P. zopfii* is responsible for disseminated infections in dogs, whereas *P. wickerhamii* is responsible for cutaneous infections. Only the cutaneous form of infection has been described in cats.

Pathophysiology

It is presumed that *P. zopfii* is ingested by susceptible hosts, passes through the GI tract, replicates by endosporulation in the colon, and is subsequently disseminated to other organ systems via the blood and lymph. The kidney, liver, heart, brain, and eye are the most common sites of systemic dissemination. Inflammatory infiltrates are minimal in active lesions. Less commonly, however, pronounced granulomatous or pyogranulomatous inflammation may be observed.

Clinical Examination

Prototheca infection is predominantly identified in immunocompromised hosts. The most frequently reported clinical sign is intermittent and protracted bloody large bowel diarrhea. Other clinical signs depend on the organ systems involved and include acute renal failure, central vestibular disease, and posterior granulomatous uveitis.

Diagnosis

Diagnosis of protothecosis requires identification of the organisms by cytology, histopathology, or culture for *Prototheca* spp. High-yield, minimally invasive samples for diagnosis of disseminated disease include rectal scrapings, and urine for sediment examination and standard aerobic culture.[49] More invasive samples obtained by vitreocentesis, cerebrospinal fluid tap, or biopsy may be required as indicated by the existence of disseminated disease.

Treatment

Based on previous reports, and in the absence of susceptibility data, *P. zopfii* infection in dogs should be treated with amphotericin B alone or in combination with itraconazole. Aminoglycosides or tetracyclines should also be considered.[50]

Prognosis

The prognosis for disseminated *P. zopfii* infection is guarded to grave. Treatment may prolong the course of infection, but the outcome is uniformly fatal.

Bacteria

Bacterial causes of large intestinal disease in dogs are numerous and increasingly recognized with the advent of molecular diagnostics. Problematic to diagnosis of disease causation is the high prevalence of many of these "pathogens" in healthy animals. Table 58-6 summarizes the bacterial agents to which large intestinal disease have been attributed, their prevalence in normal dogs, clinical signs in symptomatic dogs, diagnostic approaches to their recognition, and efficacy of available tests for determining disease causation.

Anaerobiospirillum

Anaerobiospirillum spp. are small, Gram-negative, spiral bacteria that can be isolated from the throat and feces of normal dogs and cats. In a small number of cats, infection is associated with subacute to acute ulcerative or necrotizing ileocolitis with secondary sepsis. In histologic sections of intestine, *Anaerobiospirillum* were observed in intestinal crypts after staining with Giemsa or Steiner stains, and identified by 16S rRNA gene PCR.[51] Treatment in cats has not been described.

Brachyspira pilosicoli

Etiology

Infection of the mammalian large intestine by diverse populations of spirochetes has been recognized for many decades. Their role in causation of disease is still poorly understood. In dogs, three major groups of spirochetes have been identified in feces on the basis of selective culture, multilocus enzyme electrophoresis, and 16S rRNA gene sequence data: *B. pilosicoli*, *Brachyspira canis*, and *Brachyspira alvinipulli*.[52,53]

Pathophysiology

Pathogenic spirochetes intimately attach to the apical membrane of cecal and colonic epithelial cells. The mechanism(s) by which their cellular interaction results in diarrhea remains unclear. Spirochetes can be found in large numbers in the colonic crypts of normal dogs. In dogs with diarrhea, spirochetes can appear in the feces in large numbers. Whether the spirochetes are causal to the diarrhea or alternatively, mechanically dislodged from the crypts by diarrhea induced by other etiologic factors, remains an area of active debate. In a small number of cases, it has been observed that *B. pilosicoli* can be isolated from dogs with diarrhea and intestinal spirochetosis, whereas *B. canis* were commonly isolated from healthy dogs.[53,54] Furthermore, *B. pilosicoli* will attach to cecal epithelial cells from chicks, whereas *B. canis* will not.[55] Accordingly, the current presumption is that *B. pilosicoli* may be pathogenic and *B. canis* commensal. A characteristic, but not invariable feature of *B. pilosicoli* infection is the attachment of one pole of the spirochete to the intestinal epithelium, resulting in a dense "false brush-border."[53,56] Other pathologic changes include colonic inflammation, thickening of the colonic mucosa, and enlarged Peyer patches and lymphoid follicles.

Clinical Examination

Limited descriptions of diarrhea attributed to *B. pilosicoli* have been reported in dogs housed in pet shops and research colonies.[54,57] Diarrhea has been variably characterized as mucohemorrhagic, watery, or mucoid.[58] Diarrhea appears to be more common in puppies or when intestinal function is compromised by concurrent disease.

Diagnosis

A diagnosis of *B. pilosicoli* infection can be based on anaerobic culture of feces in selective media for isolation of spirochetes and multilocus enzyme electrophoresis, or demonstration of *B. pilosicoli* 16S rRNA genes in fecal samples or cultures by means of PCR.

Table 58-6 Bacterial Causes of Large Intestinal Disease in Dogs, Prevalence of Isolation From Feces of Normal Animals, Clinical Signs of Symptomatic Infection, and Diagnostic Approaches to Infection and Their Efficacy for Determining Disease Causation

Bacterial Agent	Prevalence in Normal Dogs	Clinical Signs	Diagnostic Tests	Utility for Diagnosis of Disease Causation
Brachyspira pilosicoli	6% to 66%	Watery, mucoid, or mucohemorrhagic large bowel diarrhea	Fecal culture in selective media and multilocus enzyme electrophoresis for identification of *B. pilosicoli*	Disease causation of *B. pilosicoli* unclear
			Polymerase chain reaction (PCR) identification of *B. pilosicoli* 16S rRNA in feces	
Campylobacter jejuni	≤90%	Watery, mucoid to bloody diarrhea	Characteristic darting motility observed in fecal wet mounts	None
			Fecal culture in selective media for *Campylobacter*	
			PCR-restriction fragment length polymorphism demonstration of *Campylobacter* genes in feces	
Clostridium perfringens	≥80%	Acute, nosocomial large bowel diarrhea	Fecal culture for *C. perfringens*	None
			Fecal cytology ≥3 endospores per high-power field	Poor
			PCR identification of *cpe* gene	Fair to good (in combination)
			Immunodetection of *C. perfringens* enterotoxin (CPE) in feces	
Clostridium difficile	≤40%	Mixed small and large bowel diarrhea ± acute hemorrhagic gastroenteritis	Fecal culture for *C. difficile*	None
			PCR identification of toxin A or B genes	None
			Immunodetection of toxin A ± toxin B in feces	Fair
			Immunodetection of toxin A ± toxin B in culture isolate of *C. difficile*	Good
Enteropathogenic *Escherichia coli* (EPEC)	≤7%	Acute-to-chronic, watery, sometimes hemorrhagic, diarrhea	Demonstration of attaching and effacing intestinal lesions by electron microscopy or immunofluorescence and absence of *Shiga*-like toxins	Good
			Demonstration of locus of enterocyte effacement (LEE)-associated genes (e.g., *eae*) in fecal extracts or bacterial cultures by PCR or DNA hybridization	Fair
Enterotoxigenic *Escherichia coli* (ETEC)	<3%	Nonbloody, watery, small bowel diarrhea	Demonstration of enterotoxin in fecal extracts or bacterial cultures by (a) Y-1 cell cytotoxicity assay or (b) enzyme-linked immunosorbent assay (ELISA)	Good (in combination)
			Demonstration of enterotoxin genes in fecal cultures by PCR and Southern blot hybridization	
Enterohemorrhagic *Escherichia coli* (EHEC)	≤5% (25% Greyhounds)	Watery or mucoid to hemorrhagic diarrhea	Demonstration of *Shiga*-like toxin in fecal extracts or bacterial cultures by (a) Vero cell cytotoxicity assay or (b) ELISA	Good (in combination)
			Demonstration of *Shiga*-like toxin encoding genes in fecal extracts or bacterial cultures by (a) PCR or (b) in-situ hybridization	
Salmonella	1% to 36%	Watery or mucoid to hemorrhagic diarrhea	Culture or PCR identification of *Salmonella* in feces	Poor
			Culture or PCR identification of *Salmonella* in sterile body fluids	Good

Treatment
The best treatment for *Brachyspira* spp. infection has not been identified.

Prognosis
Likely good, although specific treatment outcomes in dogs with confirmed infection have not been reported.

Campylobacter

Etiology
Campylobacter spp. (*C. jejuni*, *Campylobacter coli*, *Campylobacter helveticus*, and *Campylobacter upsaliensis*) are Gram-negative, microaerophilic, gullwing-shaped and motile, bacterial rods. *Campylobacter* can be cultured from the feces of up to 90% of normal dogs and cats, especially in young animals housed in dense populations such as breeding facilities and shelters.

Pathophysiology
Campylobacter is acquired from contaminated food and water sources and transmitted in contaminated facilities by a fecal–oral route. *Campylobacter* replicate in the lumen of the GI tract, penetrate the mucus lining of the intestine, adhere to the intestinal epithelium, and are variably internalized into the host epithelial cells. Virulence factors are expressed by different *Campylobacter* isolates and include enterotoxins, cytotoxins (e.g., cytolethal distending toxin), and adherence/invasion proteins. Lesions induced by *Campylobacter* infection include typhlitis and colitis characterized by epithelial cell death and attenuation, loss of the microvillus brush-border, depletion of goblet cells, and infiltration of colonic crypts by neutrophils culminating in the formation of microabscesses. The factors responsible for inciting resident *Campylobacter* to become invasive have yet to be determined, although changes in intestinal microflora, the presence of concurrent enteric pathogens, immunoincompetence, and poor environmental hygiene likely play contributory roles.

Clinical Examination
Dogs and cats with *Campylobacter*-associated diarrhea are typically young puppies or kittens, stressed by hospitalization, travel, concurrent disease, or dense housing conditions. Diarrhea ranges from mild loose feces, to watery diarrhea, to bloody mucoid diarrhea. Inappetence, vomiting, fever, and leukocytosis may also be present. Concurrent infections with other enteric pathogens, such as parvovirus, *Giardia*, and *Salmonella*, may play a synergistic role and worsen clinical signs.

Diagnosis
As a result of the high prevalence of *Campylobacter* in normal and diarrheic dogs and cats, demonstration of the organisms in feces is not indicative of disease causation. Methods used to demonstrate *Campylobacter* include (a) phase-contrast or darkfield examination of fresh wet mount preparations of feces for characteristic darting motility; (b) bacterial culture of feces in selective media; or (c) molecular identification of *Campylobacter* in feces on the basis of PCR and restriction fragment length polymorphism of specific genes. The morphologic appearance of *Campylobacter* cannot be adequately differentiated from *Helicobacter* spp. on the basis of Gram staining.

Treatment
Erythromycin is the drug of choice for treatment of *C. jejuni* infections in people and has been shown to decrease fecal shedding within 24 to 48 hours when administered to dogs.[59] Dogs and cats are an important reservoir for *Campylobacter* infection in people, where the infectious dose can be as low as a few hundred organisms. Veterinarians should alert owners of the zoonotic risk of *Campylobacter* infection and stress the importance of appropriate hygienic measures, particularly when pets have diarrhea.

Prognosis
Generally good.

Clostridium difficile

Etiology
Clostridium difficile is a Gram-positive, anaerobic, spore-forming bacillus. These bacteria are the most common cause of nosocomial and antibiotic-associated diarrhea in people. *C. difficile* can be cultured from the feces of up to 40% of normal dogs and cats, with most of these isolates being toxigenic (containing toxin genes).[60-64]

Pathophysiology
Diarrhea is mediated by toxigenic strains of *C. difficile*; that is, those that produce cytotoxic proteins of which toxin A (an enterotoxin) and toxin B (a cytotoxin) are best characterized. Both toxins mediate glycosylation and inactivation of Rho-GTPases (guanosine triphosphatases), resulting in depolymerization of F-actin, loss of epithelial integrity, and cell death. In the lamina propria, toxin A stimulates the synthesis of prostaglandins by macrophages, release of substance P, and degranulation of mast cells. Collectively these effects promote intestinal fluid loss and inflammation. There have been no studies to date evaluating the sensitivity of canine intestinal epithelia to either toxin A or B.

Clinical Examination
Reports clearly attributing diarrhea to *C. difficile* infection are uncommon and experimental infections have not produced diarrhea to date. Although antibiotic administration is a predisposing factor for *C. difficile*–associated disease in humans and horses, this does not appear to be a predisposing factor for dogs, although carriage of *C. difficile* may be more common in a hospital setting.[62,65,66] Dogs with suspected *C. difficile*–associated diarrhea commonly have signs consistent with concurrent involvement of the small and large intestine and occasionally, hemorrhagic gastroenteritis.[65]

Diagnosis
In dogs, there has been no significant association between isolation of *C. difficile* (toxigenic or nontoxigenic) and the presence of diarrhea.[62,64,66,67] Toxigenic *C. difficile* can be isolated from up to 94% of neonatal dogs in the absence of clinical signs of disease.[68] An association has been documented between immunodetection of toxin A in feces and clinical signs of diarrhea in the dog,[66,67] although toxin A was also detected in some dogs without diarrhea. In general, a diagnosis of *C. difficile*–associated diarrhea is supported by laboratory detection of toxin A or B by ELISA. Commercially available assays for detection of toxin A and B have unacceptably low sensitivity when applied to feces, but have reasonably good sensitivity and specificity when applied to culture isolates.[64]

Treatment
Metronidazole is the drug of choice for treatment of dogs and cats with *C. difficile*–associated diarrhea.[69,70] Metronidazole resistance among canine isolates appears to be absent or low.[71]

Clostridium perfringens

Etiology

C. *perfringens* is a Gram-positive, anaerobic, spore-forming bacillus. These bacteria also are members of the normal intestinal flora and can be cultured from 80% or greater normal and diarrheic dogs.[66,67] Most isolates obtained from dogs are biotype A, approximately 15% of which carry the gene encoding C. *perfringens* enterotoxin (CPE).[72]

Pathophysiology

The pathophysiology of C. *perfringens* infection remains poorly understood. It is speculated that in response to changes in diet, antibiotic administration, or coinfection with other intestinal pathogens, commensal enterotoxigenic strains are somehow triggered to undergo massive sporulation and synthesis of CPE. CPE binds to intestinal epithelial cells, forming pores in the plasma membrane that initiate cell death signaling pathways. Subsequent access of CPE to the basolateral epithelium induces structural damage to intercellular tight junctions resulting in increased epithelial permeability.[73] When administered orally or directly into the intestinal lumen of dogs, CPE induces fluid secretion and diarrhea.[74] CPE is one of numerous polypeptide enterotoxins that may be produced by C. *perfringens*. CPE-negative strains of C. *perfringens* may mediate diarrhea by virtue of other virulence factors (e.g., β_2 toxin).

Clinical Examination

The clinical spectrum of GI disease attributed to C. *perfringens* varies considerably and ranges from mild self-limiting diarrhea to fatal acute hemorrhagic gastroenteritis. C. *perfringens* is believed to be a major cause of acute, nosocomial large bowel diarrhea that begins with 1 to 5 days of boarding or kenneling. Clinical signs of large intestinal diarrhea including mucus, increased frequency, tenesmus and hematochezia are most often attributed to C. *perfringens*. However, acute and chronic diarrhea of both large and small bowel origin have been described.

Diagnosis

Diagnosis of C. *perfringens* as a causative agent of diarrhea remains highly problematic. At present, the optimum diagnostic approach is demonstration of CPE (protein) in feces by ELISA (C. *perfringens* Enterotoxin Test, TECHLAB, Blacksburg, VA) in conjunction with PCR, performed on culture isolates, for the presence of the *cpe* gene. Although immunodetection of CPE has been significantly associated with diarrhea in dogs, CPE is also detected in dogs without diarrhea,[66,67] and available methods for immunodetection of CPE have poor sensitivity and specificity. Fecal culture or endospore enumeration are unreliable tests for establishing C. *perfringens* infection in the dog because the bacteria are commensal and there appears to be no association between fecal endospore numbers and presence of diarrhea or between spore counts and detection of CPE.[66,67,75]

Treatment

Drugs commonly used for treatment of C. *perfringens* diarrhea include ampicillin, erythromycin, metronidazole, and tylosin. Because of a high incidence of resistance, the use of tetracyclines is discouraged.[71]

Prognosis

The prognosis for recovery is excellent.

Enterohemorrhagic *Escherichia coli*

Etiology

Enterohemorrhagic *E. coli* (EHEC) mediate disease by production of *Shiga*-like toxins (Stx). These toxins are uniquely characterized by cytotoxic effects on cultured Vero (African green monkey kidney) cells and are therefore also referred to as *Verotoxins*. *E. coli* of a broad range of O:H serotypes are capable of producing Stx, of which *E. coli* O157:H7 is but one member. Verotoxigenic *E. coli* may be isolated from 2% to 13.8% and 0% to 4.8% of healthy cats and dogs, respectively.[76-80] Carriage of EHEC may be greater in Greyhound dogs, where 25% of normal animals in one study were found to be infected. A higher prevalence of EHEC in Greyhounds may be attributed to the common practice of feeding raw meat.[81] Most EHEC recovered from dogs and cats are *not* serotype O157:H7.

Pathophysiology

EHEC colonize the colon and produce Stx, which is translocated from the lumen of the intestine, across the intestinal epithelial cells, and into the bloodstream. The bacteria do not invade the intestinal epithelium, nor are they suspected to directly mediate toxic effects on the intestine. Rather, Stx is disseminated in the bloodstream and binds to glycolipid receptors that are expressed in abundance by the kidney and intestine. At these sites, Stx interacts with endothelial cells to disable 28S rRNA, inhibit protein translation, and thereby mediate cell death. When experimentally injected into the bloodstream of Greyhound dogs, *Shiga* toxins mediate severe bloody diarrhea and hemolytic uremic syndrome within 48 to 52 hours.[82]

Clinical Examination

Intestinal manifestations of EHEC infection range from asymptomatic disease, to watery or mucoid diarrhea with slight blood,[83] to anorexia, vomiting, and hemorrhagic diarrhea.[84-86] Extraintestinal sequelae of EHEC infection in dogs are reported rarely[84-86] and have not been reported in the cat. In these cases, hemorrhagic diarrhea is followed by a hemolytic uremic syndrome characterized by a triad of acute renal failure, microangiopathic hemolytic anemia, and thrombocytopenia.

Diagnosis

A diagnosis of EHEC infection is based on demonstration of Stx (ELISA) and/or Stx genes (PCR or in-situ hybridization) in extracts of feces or in culture isolates of *E. coli* obtained from the feces. Sensitivity is improved by demonstrating both the toxin and gene and by performing such assays on culture isolates, rather than feces. There is little information on potential sequence heterogeneity of Stx in the dog and cat, and accordingly, the sensitivity and specificity of commercially available tests used for demonstration of Stx genes or antigen. In Greyhound dogs, a significant association was found between the presence of diarrhea and demonstration of the *stx1* gene or *Shiga* toxin in fecal cultures.[81] Although *Shiga* toxin was demonstrated in 43% of Greyhound dogs with diarrhea in the study, 25% of dogs without diarrhea also had *Shiga* toxin-producing *E. coli* present. In cats, *E. coli* strains isolated from feces of diarrheic animals produced verotoxin more frequently than did *E. coli* strains isolated from those without diarrhea.[80]

Treatment

Too few cases in dogs and cats have been described to make solid recommendations on the appropriateness or choice of antibiotic

treatment for EHEC infection. In people, treatment with antibiotics is contraindicated because of increased risk of developing hemolytic uremic syndrome as a consequence of lysis of bacteria with release of additional toxin into the lumen of the intestine. Accordingly, treatment of infection may be limited largely to supportive care.

Prognosis

The prognosis is likely good for hemorrhagic diarrhea alone. The prognosis is guarded for cases characterized by hemolytic uremic syndrome.

Enteropathogenic *Escherichia coli*

Etiology

Enteropathogenic *E. coli* (EPEC), also termed *attaching and effacing E. coli* (AEEC), possess key attributes that enable them to intimately attach to intestinal epithelial cells, into which they inject bacterial proteins, and initiate intracellular signaling pathways leading to diarrhea.

Pathophysiology

EPEC adhere, in part, to intestinal epithelial cells by virtue of an adherence factor plasmid that contains genes encoding bundle-forming pili. The EPEC genome also contains a "pathogenicity island," called the *locus of enterocyte effacement* (LEE), which contains genes encoding a type III secretory system, multiple EPEC-secreted proteins, a bacterial adhesin called *intimin* (*eae*), and a translocated intimin receptor called *Tir*. EPEC use the type III secretory system as a "molecular syringe" to inject Tir into the host cell whereupon it is translocated to the host cell membrane and serves as a receptor for the bacterial-expressed adhesin intimin. Bacterial attachment results in considerable cytoskeletal reorganization leading to the effacement of microvilli, the formation of pedestals beneath the attached bacteria and disruption of epithelial barrier function. Diarrhea is attributed to a combination of malabsorption, water and electrolyte secretion, increased permeability of tight junctions, and epithelial synthesis of cytokines and chemokines that promote mucosal inflammation.

Clinical Examination

Dogs in which EPEC infection has been described are typically younger than 1 year of age, have acute to chronic, sometimes hemorrhagic, diarrhea, and are often concurrently infected with other diarrheal agents such as distemper virus, parvovirus, coccidia, *Giardia*, or *Cryptosporidium*.[78,87] Fatal EPEC infection has been documented in a 2-month-old kitten and an adult cat in which attaching and effacing lesions and acute mucosal inflammation were present in the ileum and colon.[88]

Diagnosis

Diagnosis of EPEC infection is based on documentation of attaching and effacing histologic lesions, and absence of Stx. The latter is important as some strains of enterohemorrhagic *E. coli* can also cause attaching and effacing lesions. Attaching and effacing lesions are characterized by accumulation of F-actin beneath the adherent bacteria and can be demonstrated by transmission electron microscopy or by staining of F-actin with fluorescent-labeled phalloidin. In dogs, attaching and effacing lesions have been reported in both the small and large intestine. Studies seeking to diagnose EPEC by demonstration of LEE-associated genes in feces have found such genes to be commonly present in the flora of both healthy and diseased individuals.[89]

Treatment

Treatment consists of supportive care, parenteral fluid therapy, and administration of antimicrobial drugs with Gram-negative activity including amoxicillin-clavulanate, first- or second-generation cephalosporins, or enrofloxacin.

Prognosis

Prognosis depends on the cause and severity of concurrent intestinal infectious disease. Death in puppies with EPEC and concurrent enteric infection is common.

Table 58-7 discusses the section of intestine most commonly affected, type of intestinal lesion(s), invasiveness, virulence characteristics, and mechanism of diarrhea of enteric *E. coli* infecting dogs.

Salmonella

Etiology

Salmonella are motile, non–spore-forming, Gram-negative bacterial rods. The species most commonly isolated from diseased animals and people is *Salmonella typhimurium*. *S. typhimurium* is ubiquitous in the environment because of direct or indirect fecal contamination of food, water, or fomites. In dogs, infection is most commonly acquired through the practice of feeding raw,[90,91] dehydrated (e.g., dog chews made from animal hide[92]), or improperly cooked meat products. *Salmonella* spp. were isolated from 80% of samples taken from a bones-and-raw-food diet and from 30% of fecal samples from dogs fed the diet.[91] A conservative prevalence of *Salmonella* infection in clinically healthy or hospitalized dogs is 1% to 36% and from healthy cats is 1% to 18%.[93]

Pathophysiology

Following ingestion, *Salmonella* adhere via fimbriae to intestinal epithelial cells and M cells. *Salmonella* translocates bacterial proteins into these host cells by virtue of a type III secretion system. The translocated proteins interact with Rho-family guanosine triphosphate–binding proteins to facilitate internalization of the bacteria into host cell vesicles and stimulate host cell secretion of cytokines such as interleukin-8. A resulting influx of neutrophils transmigrate across the epithelium resulting in loss of barrier integrity. A fraction of *Salmonella*-containing vesicles are transported to the basolateral membrane where released *Salmonella* enters macrophages in which they multiply and disseminate systemically. Factors contributing to susceptibility to *Salmonella* infection include young age, nutritional deficiency, impaired immune defense, concurrent GI infection, and disruption of the normal intestinal flora (e.g., antibiotics) leading to loss of colonization resistance. Intestinal lesions are usually confined to the distal small bowel, cecum, and colon, and consist of mucosal inflammation and epithelial sloughing.

Clinical Examination

Clinical signs of salmonellosis are most severe in puppies and kittens younger than 1 year of age and geriatric animals. Diarrhea varies from watery to mucoid, with fresh blood present in severe cases. In addition to diarrhea, other clinical signs, such as fever, anorexia, vomiting, and abdominal pain, may be present. Patients developing bacteremia or endotoxemia may be obtunded, weak, have pale mucous membranes, tachycardia, hypothermia, and vascular collapse. The clinical and pathologic features of salmonellosis may be indistinguishable from those of canine parvovirus and feline panleukopenia infection.

Table 58-7 Section of Intestine Most Commonly Affected, Type of Intestinal Lesion(s), Invasiveness, Virulence Characteristics, and Mechanism of Diarrhea of Enteric *Escherichia coli* Infecting Dogs

	Disease Localization	Intestinal Lesions	Invasion of Intestinal Epithelial Cells	Virulence Characteristics	
Enteropathogenic *E. coli* (EPEC)	Small and large intestine	Effacement of microvilli and pedestal formation Mucosal inflammation	Variable	Adherence factor plasmid contains genes encoding bundle-forming pili Locus for enterocyte effacement contains bacterial genes encoding intimin (*eae*), a type III secretory apparatus, translocated intimin receptor, and EPEC-secreted proteins	Malabsorption, water and electrolyte secretion, increased permeability of tight junctions, and mucosal inflammation
Enterotoxigenic *E. coli* (ETEC)	Small intestine	Minimal histologic changes or inflammation	Noninvasive	Heat-labile toxins stimulate adenylyl cyclase activity by activational adenosine diphosphate-ribosylation of $G_{s\alpha}$, thereby increasing the synthesis of cyclic adenosine monophosphate Heat-stabile toxins bind to and activate membrane-bound guanylyl cyclase, thereby increasing the synthesis of cyclic guanosine monophosphate	Secretory diarrhea ("traveler's diarrhea" in people): stimulate Cl^- secretion by crypt epithelium and inhibit NaCl absorption by villous epithelium
Enterohemorrhagic *E. coli* (EHEC) and *E. coli* 0127:H7	Large intestine	Edema and submucosal hemorrhage, arteritis, and microvascular thrombosis of intestinal arterioles	Noninvasive	*Shiga*-like verotoxins inhibit protein synthesis resulting in cell death	Hemorrhagic colitis Hemolytic uremic syndrome

Diagnosis

Isolation of *Salmonella* organisms is the most definitive means of confirming infection. Because of the high prevalence of asymptomatic carriage of *Salmonella*, isolation from normally sterile samples (e.g., urine, blood) may allow a definitive diagnosis and indicate disseminated disease. In addition, failure to isolate *Salmonella* does not rule out infection because of the fastidious nature of *Salmonella* in culture. Use of PCR for identification of *Salmonella* in dogs has been described[94] but is not yet widely applied.

Treatment

Treatment varies according to the severity of the clinical signs. Acute gastroenteritis, without clinical signs of systemic disease may be treated with fluid therapy and supportive care. Antibiotic therapy may prolong fecal shedding and induce drug resistance and is therefore reserved for patients with severe hemorrhagic diarrhea, history of immunosuppression, suspected or documented septicemia, evidence of systemic inflammatory response syndrome, or a combination of these symptoms.

Antibiotics reported to be effective for treatment of *Salmonella* include chloramphenicol, amoxicillin, trimethoprim-sulfa, and enrofloxacin. Posttreatment cultures should be performed to confirm eradication, and pet owners should be advised of the public health importance of the disease.

Prognosis

The prognosis for enteritis alone is generally good. The prognosis for patients with disseminated disease, endotoxemia, or sepsis is more guarded. Some patients may remain chronic carriers with recrudescence during periods of stress or unrelated disease.

Yersinia enterocolitica

Y. enterocolitica and *Yersinia pseudotuberculosis* are motile, Gram-negative, coccobacilli that can be isolated from the feces of clinically normal dogs and cats. *Yersinia* has been cultured on rare occasions from the feces of dogs and cats with abdominal discomfort or bloody diarrhea.[95-97]

Viruses

Feline Enteric Coronavirus

Although uncommon, colonic disease may be a primary manifestation of feline infectious peritonitis (FIP) infection in the cat.[98,99] Clinical signs of diarrhea or constipation may be present. Physical examination reveals a palpable abdominal mass of the colon or ileocecocolic junction. Histopathology is consistent with pyogranulomatous inflammation with intralesional feline coronavirus demonstrable by immunohistochemistry. In the majority of cases reported,

cats were euthanized or died from the effects of multisystemic FIP infection.

OBSTRUCTION

Robert J. Washabau

Intussusception

Etiology

Intussusception is an invagination of one segment of the gastrointestinal tract into the lumen of an adjoining segment. The intussusceptum is the invaginated segment of the alimentary tract, whereas the intussuscipiens is the enveloping segment. Invagination may occur in an antegrade (aborad) or retrograde (orad) direction, but is most commonly in the antegrade direction. Any portion of the alimentary tract may be involved, but enterocolic intussusceptions account for almost two-thirds of the published cases in dogs and cats. Enterocolic intussusceptions can be further divided into three types: cecocolic (or cecal inversion), with the inverted cecum forming the apex[1]; ileocolic, with the ileum forming the apex; and ileocecal, with the ileocecal junction forming the apex.[2] Of these three forms of enterocolic intussusception, the ileocolic intussusception is the one most frequently encountered in clinical practice. A number of conditions are reported to predispose to intussusception, including intestinal parasitism, viral enteritis, foreign bodies, and masses, but in dogs and cats most intussusceptions are idiopathic.[3-5]

Pathophysiology

The initiating events in an intussusception are often difficult to identify retrospectively, but all intussusceptions appear to share three important features: (a) inhomogeneity in a bowel segment, a region in which the gastrointestinal tract undergoes a sudden anatomic change in diameter (e.g., ileocolic junction) or a bowel segment that is either flaccid or indurated; (b) mechanical linkage of nonadjacent segments, which can be intraluminal (e.g., linear foreign bodies or parasites) or extramural (e.g., fibrous adhesions or bands); and (c) peristaltic activity of the gut.[2] Invagination begins as a result of peristaltic contraction. Once the invagination has begun, its progress may be rapid, involving as much as several centimeters of intestinal tract within just a few hours. Invagination and intussusception result in luminal obstruction, which may be partial or complete. Obstruction usually results in distention of the bowel segment proximal to the intussusception. The degree of distention is dependent upon the completeness and duration of the obstruction, volume of fluid secretion, degree of vascular compromise, and volume of gas production from bacterial fermentation. Because the mesentery and blood supply are included in the invaginating segment, vascular compromise can occur, which initially leads to intramural hemorrhage and edema and eventually to ischemia and necrosis of the bowel. Full-thickness necrosis may ensue but perforations are rare.

Clinical Examination

The most important clinical signs with ileocolic intussusceptions are intermittent vomiting, progressive loss of appetite, mucoid bloody diarrhea, and a palpable cylinder-shaped mass in the cranial abdomen. Abdominal pain is not a consistent finding in affected animals. Clinical signs may persist for several weeks and affected animals eventually succumb to the effects of starvation rather than dehydration, electrolyte imbalances, or acid–base disturbances.

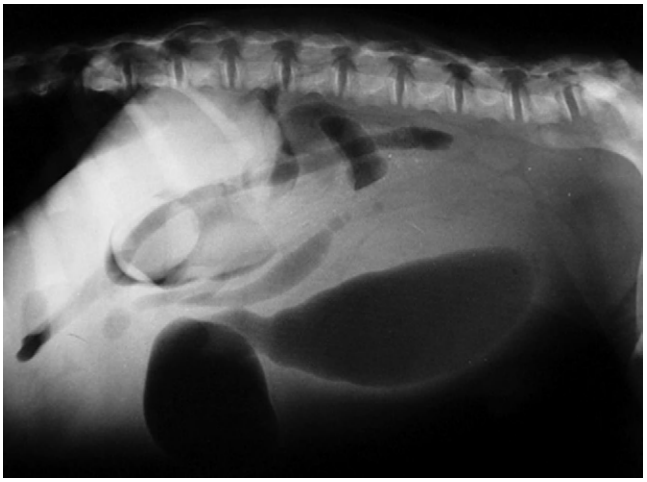

Figure 58-12 Abdominal survey radiographic evidence of intussusception.

Diagnosis

With some ileocolic intussusceptions, the intussuscepted bowel may protrude through the anus and must be differentiated from a rectal prolapse. This is accomplished by passing a blunt probe between the protruding segment and the anal sphincter. If the probe can be passed cranial to the pubis without reaching a fornix, then the protruding bowel is the apex of an intussusception rather than rectal prolapse.

Survey abdominal radiographs are often nondiagnostic, but may reveal distention and obstruction proximal to the intussusception (Figure 58-12). Barium-contrast studies (barium enema or upper GI series) are often diagnostic, but abdominal ultrasonography is the preferred method of diagnosis. The appearance of a target-like mass consisting of two or more hyperechoic and hypoechoic concentric rings in transverse section or the appearance of multiple hyperechoic and hypoechoic parallel lines in longitudinal section is virtually diagnostic of an intussusception (Figure 58-13).[6] The ultrasound scan might also identify a mass associated with the intussusception. Endoscopy may be performed in suspected cases of suspected neoplasia, otherwise endoscopy does not confer any additional benefits over abdominal ultrasound or CT scanning.

Treatment

The surgical management of ileocolic intussusception involves either reduction or resection, and anastomosis, or both.[7,8] Secretory diarrhea may persist following relief of the obstruction and affected animals may need continuous crystalloid and colloidal therapy. If possible, the ileocecal sphincter should be preserved to reduce reflux and contamination of the distal small bowel. Cecocolic intussusceptions or inversions should also be treated with surgical resection. Surgical resection of the cecocolic intussusceptions is generally curative. Enteroplication procedures have been recommended,[9] but they do not appear to reduce recurrence rates.[7,8]

Prognosis

The most common complications following treatment of intussusception are recurrence, dehiscence of the anastomosis, ileus, intestinal obstruction, peritonitis, and short bowel syndrome. The

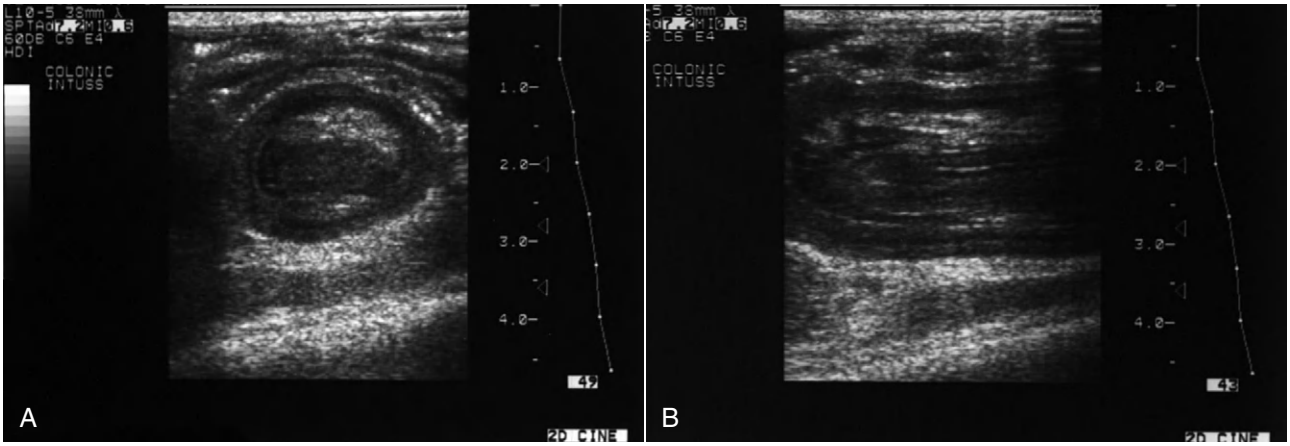

Figure 58-13 Abdominal ultrasonographic appearance of intussusception. Target-like mass consisting of two or more hyperechoic and hypoechoic concentric rings in transverse section (**A**) and the appearance of multiple hyperechoic and hypoechoic parallel lines in longitudinal section (**B**) are virtually diagnostic of an intussusception.

recurrence rate in dogs is reported to be between 11% and 20%. In dogs in which no surgical procedure was performed to prevent recurrence, intussusception recurred in 25% of dogs that underwent manual reduction alone and in 19% of dogs that underwent resection and anastomosis. Enteroplication does not appear to reduce recurrence rates any further.[7,8] Indeed, 19% of dogs undergoing enteroplication in one study experienced severe complications that required a second surgery. Intestinal obstruction was a complication of the enteroplication in those patients.[8]

Pyogranulomatous Inflammation

Histoplasma capsulatum

Etiology

Histoplasmosis is a systemic fungal disease of dogs and cats caused by *H. capsulatum*. In the environment, *H. capsulatum* organisms are mycelial, saprophytic soil fungi. In infected tissue or when cultured at 30°C (86°F) to 37°C (98.6°F), the organism is a yeast. The fungus is endemic throughout most of the temperate and subtropical regions of the world. Most cases of histoplasmosis in the United States occur in the central states, with the geographic distribution following the Mississippi, Ohio, and Missouri Rivers.[10,11]

Pathophysiology

Infection is probably via inhalation or ingestion of infective conidia from the environment. The respiratory system is thought to be the primary route of infection in cats and dogs, although the gastrointestinal tract may also be an important route in the dog. After inhalation or ingestion, conidia transform from the mycelial phase and are phagocytized by macrophages, where they grow as facultative intracellular organisms. Hematogenous and lymphatic dissemination results in multisystemic disease. Organisms can be disseminated to any organ system, but the lungs, gastrointestinal tract, lymph nodes, liver, spleen, bone marrow, eyes, and adrenal glands are the most common organs of dissemination in the dogs; lungs, liver, lymph nodes, eyes, and bone marrow are most commonly affected in cats. Cell-mediated immunity induces a granulomatous inflammatory response in most infection.[12]

Clinical Examination

Dogs with gastrointestinal histoplasmosis are typically presented with mild fever, anorexia, lethargy, weight loss, vomiting, diarrhea, hematochezia, and tenesmus. Cachexia is a common physical examination finding. Other historical and physical examination findings (dyspnea, cough, ascites, lameness, oropharyngeal ulcerations, chorioretinitis, neuropathy) will depend upon organ and tissue involvement. The small intestinal form of histoplasmosis is described in more detail in Chapter 57.

Diagnosis

Organism identification is required for definitive diagnosis. The most common means of organism identification is cytology. Cytology from affected tissue reveals pyogranulomatous inflammation, often with numerous small, round to oval intracellular yeast cells (2 to 4 μm in diameter) characterized by a basophilic center and a light halo. Exfoliative cytology during colonoscopy is particularly useful in diagnosing the disease. Histopathology is helpful if cytology is nondiagnostic or inconclusive. Multiple endoscopic colonic biopsies are usually sufficient to diagnose the disease. The yeast form does not stain well with routine hematoxylin and eosin stains, so special stains such as PAS and Gomori methenamine silver stain are often used to demonstrate organisms. Fungal culture from affected tissue can be used for diagnosis but is rarely needed in clinical cases. Currently available serologies have poor specificity and sensitivity.[12]

Treatment

Itraconazole (5 mg/kg PO BID for 2 to 4 months) is considered the treatment of choice for feline histoplasmosis. In one study, itraconazole therapy cured histoplasmosis infections in all eight study cats.[13] Ketoconazole and amphotericin B have been described as the treatments of choice for canine histoplasmosis. With colonic involvement, additional gastrointestinal therapy may be useful in affected dogs, for example, dietary modification, treatment for small intestinal bacterial overgrowth, and direct antidiarrheal therapy. Corticosteroids may have been used successfully in the treatment of airway obstruction secondary to hilar lymphadenopathy in chronically infected dogs.[14]

Prognosis

There may be important species differences in prognosis although the paucity of reports, especially of prospective clinical trials, makes it difficult to generalize. It would seem that the prognosis is guarded in dogs, but fair to good in cats.

Pythium insidiosum

Etiology

P. insidiosum is an aquatic oomycete that causes severe gastrointestinal pathology in a range of hosts in the tropical and subtropical climates.[15] Based on ribosomal RNA gene sequence data, members of the class *Oomycetes* are phylogenetically distinct from the kingdom *Fungi*, and are more closely related to algae than to fungi.[16] The oomycetes differ from fungi in two important properties: cell wall and cell membrane composition. Chitin is an essential component of the fungal cell wall, but it is generally lacking in the oomycete cell wall. Oomycetes also differ from fungi in that ergosterol is not a principal sterol in the oomycete cell membrane. This difference may explain why ergosterol-targeting drugs like itraconazole are less effective in the medical treatment of pythiosis.[16]

Pathophysiology

The infective state of *P. insidiosum* is thought to be the motile zoospore, which is released into stagnant water in warm environments, and likely causes infection either by encysting in the skin, or by being ingested into the gastrointestinal tract. Ingested zoospores encyst and adhere to the gastric, jejunal, and colonic epithelium with a polarity oriented toward the submucosa for rapid tissue penetration following germ tube eruption. *Pythium* induces a chronic pyogranulomatous response in the gastrointestinal tract and mesenteric lymph nodes. The gastric outflow tract and ileocolonic junction are the most frequently affected portions of the GI tract, and it is not uncommon to find two or more segmental lesions in the same patient.[17] Inflammation in affected regions is typically centered on the submucosa, with variable mucosal ulceration and occasional extension of disease through serosal surfaces, resulting in adhesion formation and peritonitis.

Clinical Examination

Weight loss, vomiting, diarrhea, and hematochezia are the most important clinical signs. Physical examination often reveals emaciated body condition and a palpable abdominal mass. Signs of systemic illness such as lethargy and depression are not typically present unless intestinal obstruction, infarction, or perforation occurs.

Diagnosis

Ileocolonic wall thickening, obliteration of the normal layered appearance, and regional lymphadenopathy are common ultrasonographic features of canine intestinal pythiosis.[18] Of course, these findings cannot be readily differentiated from those associated with intestinal malignancy. Definitive diagnosis requires histologic demonstration or immunohistochemical staining of the organism and/or positive ELISA or PCR assays. The histologic findings associated with pythiosis generally are characterized by eosinophilic granulomatous to pyogranulomatous inflammation with fibrosis. Affected tissue typically contain multiple foci of necrosis surrounded and infiltrated by neutrophils, eosinophils, and macrophages. Discrete granulomas composed of epithelioid macrophages, plasma cells, multinucleate giant cells, and neutrophils and eosinophils may also be observed. *Pythium* zoospores may be cultured directly from affected tissue in antibiotic-containing (e.g., streptomycin and ampicillin) media. More recently, sensitive and specific ELISA and PCR assays have been developed for the accurate diagnosis of pythiosis in dogs.[19-21]

Treatment

Aggressive surgical resection remains the treatment of choice for pythiosis in dogs. Because it provides the best opportunity for long-term cure, complete resection of infected tissue should be pursued whenever possible. Segmental lesions of the GI tract should be resected with 3- to 4-cm margins whenever possible. Medical therapy for the oomycetes has not been very promising. This may relate to the absence of ergosterol (cell membrane target of most currently available antifungal drugs) in the oomycete cell membrane. Clinical and serologic cures have been obtained in a small number of dogs following therapy with amphotericin B lipid complex (2 to 3 mg/kg QOD administered to a cumulative dose of 24 to 27 mg/kg) or itraconazole (10 mg/kg q24h for 6 to 9 months).

Prognosis

Unfortunately, most dogs with GI pythiosis are not presented to the veterinarian until late in the course of the disease, when complete excision is not possible. The anatomic site of the lesion (e.g., pylorus or ileocolic sphincter) may also prevent complete excision. Consequently, the prognosis is usually grave in most animals.[16]

Feline Infectious Peritonitis

FIP is a well-known and widely distributed coronavirus-induced systemic disease in cats, characterized by fibrinous to granulomatous serositis with protein-rich effusions in body cavities and granulomatous inflammatory lesions in multiple organs. One of its morphologic hallmarks is a granulomatous to necrotizing phlebitis and periphlebitis.[22,23] Affected cats develop signs caused by granulomatous lesions in target organs (central nervous system, eyes, and parenchymatous organs) and vasculitis leading to fluid redistribution into third spaces with fluid accumulation in body cavities.[22] In addition to the well-known multisystemic condition, some unusual problems have been described, including focal pyogranulomas of the gastrointestinal tract. In a survey of 156 cats with disseminated FIP, 26 had solitary mural intestinal lesions.[24] Predominant clinical signs included diarrhea and vomiting for 3 months or less before intestinal biopsy. All cats had a mass, believed to be a neoplasm, in the colon or ileocecocolic junction. Affected intestine was markedly thickened, nodular, firm, and white, with multifocal pyogranulomas extending throughout the wall of the intestine, and the regional lymph nodes were uniformly involved. Most cats were euthanized or died within 9 months of histologic findings, many with signs of multisystemic FIP.[24]

Nonneoplastic Stricture

The etiologies for nonneoplastic colonic strictures include foreign bodies, postoperative complications, inflammatory disease (e.g., IBD, diffuse perianal fistula disease), and congenital malformation.[25] Postoperative complications are probably the most important cause of colonic strictures in dogs and cats,[25] which emphasizes the importance of good surgical principles in performing colonic surgery.[26] Nonneoplastic strictures of the colon are fairly rare. Nonneoplastic strictures of the rectum are more common (see Chapter 59).

DYSMOTILITY

Robert J. Washabau

Constipation

Etiology

The etiopathogenesis of idiopathic megacolon is still incompletely understood. Several reviews have emphasized the importance of

Table 58-8 Causes of Constipation

Type	Cause
Mechanical obstruction	
Intraluminal	Bones, hair, neoplasia, rectal diverticulum, stricture, deviation/sacculation associated with perineal hernia
Intramural	Neoplasia
Extramural	Pelvic fractures, neoplasia, prostatic disease
Inflammation	Perianal fistula, anal sac disease, perineal wounds
Neuromuscular dysfunction	Lumbosacral disease, cauda equina syndrome, sacral spinal cord deformities (Manx cat)
	Hypogastric or pelvic nerve disorders–trauma, neoplasia, dysautonomia
	Colonic smooth muscle–idiopathic megacolon
Metabolic, endocrine	Dehydration, hypokalemia, hypocalcemia
	Hypothyroidism, nutritional secondary hyperparathyroidism, obesity
Pharmacologic	Opioids, atropine, anticholinergics, diuretics, barium sulfate, phenothiazines, β-agonist drugs
Environmental	Soiled/absent litterbox, inactivity, hospitalization, multicat households, competition

Adapted from Washabau RJ, Hasler AH: Constipation, obstipation, and megacolon. In: August JR, editor: Consultations in Feline Internal Medicine, ed 3. Philadelphia, 1997, Saunders, p 106.

considering an extensive list of differential diagnoses (e.g., neuromuscular, mechanical, inflammatory, metabolic/endocrine, pharmacologic, environmental, and behavioral causes) for the obstipated cat (Table 58-8). A review of published cases suggests that 96% of cases of obstipation are accounted for by idiopathic megacolon (62%), pelvic canal stenosis (23%), nerve injury (6%), or Manx sacral spinal cord deformity (5%).[1,2] A smaller number of cases are accounted for by complications of colopexy (1%) and colonic neoplasia (1%); colonic hypo- or aganglionosis was suspected, but not proved, in another 2% of cases. A definitive case of colonic hypoganglionosis was reported in an 11-week-old female domestic shorthaired cat.[3] Inflammatory, pharmacologic, and environmental/behavioral causes were not cited as predisposing factors in any of the original case reports. Endocrine factors (e.g., obesity and hypothyroidism) were cited in several cases, but were not necessarily impugned as part of the pathogenesis of megacolon. It is important to consider an extensive list of differential diagnoses in an individual animal, but it should be kept in mind that most cases are idiopathic,[1,2] orthopedic,[1,2] or neurologic[4] in origin. Behavioral (e.g., stress) and/or environmental (e.g., competition for the litterbox) factors very likely play an important role in the development of this lesion, but this has been poorly studied in retrospective or prospective studies.

Pathophysiology

Megacolon develops through two pathologic mechanisms: *dilation* and *hypertrophy*. *Dilated megacolon* is the end stage of colonic dysfunction in idiopathic cases. Cats affected with idiopathic dilated megacolon have permanent loss of colonic structure and function. Medical therapy may be attempted in such cases, but most affected cats eventually require colectomy. *Hypertrophic megacolon*, on the other hand, develops as a consequence of obstructive lesions (e.g., malunion of pelvic fractures, tumors, foreign bodies). Hypertrophic megacolon may be reversible with early pelvic osteotomy or it may progress to irreversible dilated megacolon if appropriate therapy is not instituted.[5]

Constipation and *obstipation* are earlier manifestations of the same problem. Constipation is defined as the infrequent difficult evacuation of feces but does not necessarily imply a permanent loss of function. Many cats suffer from one or two episodes of constipation without further progression. Intractable constipation that has become refractory to cure or control is referred to as *obstipation*. The term *obstipation* implies a permanent loss of function. A cat is assumed to be obstipated only after several consecutive treatment failures. Recurring episodes of constipation or obstipation may culminate in the syndrome of *megacolon*.

The pathogenesis of idiopathic dilated megacolon appears to involve functional disturbances in colonic smooth muscle. In vitro isometric stress measurements have been performed on colonic smooth muscle obtained from cats suffering from idiopathic dilated megacolon.[6,7] Megacolonic smooth muscle develops less isometric stress in response to neurotransmitter (acetylcholine, substance P, cholecystokinin), membrane depolarization (potassium chloride), or electrical field stimulation, when compared with healthy controls.[6,7] Differences have been observed in longitudinal and circular smooth muscle from descending and ascending colon. No significant abnormalities of smooth muscle cells or of myenteric neurons were observed on histologic evaluation. These studies initially suggested that the disorder of feline idiopathic megacolon is a generalized dysfunction of colonic smooth muscle, and that treatments aimed at stimulating colonic smooth muscle contraction might improve colonic motility. The lesion begins in the descending colon and appears to progressively involve the ascending colon over time.[8]

Clinical Examination

History

Constipation, obstipation, and megacolon may be observed in cats of any age, sex, or breed, however, most cases are observed in middle aged (mean: 5.8 years), male cats (70% male, 30% female) of domestic shorthair (46%), domestic longhair (15%), or Siamese (12%) breeding.[1] Affected cats are usually presented for reduced, absent, or painful defecation for a period of time ranging from days to weeks or months. Some cats are observed making multiple, unproductive attempts to defecate in the litterbox, while other cats may sit in the litterbox for prolonged periods of time without assuming a defecation posture. Dry, hardened feces are observed inside and outside of the litterbox. Occasionally, chronically constipated cats have intermittent episodes of hematochezia or diarrhea as a result of the mucosal irritant effect of fecal concretions. This may give the pet owner the erroneous impression that diarrhea is the primary problem. Prolonged inability to defecate may result in other systemic signs, including anorexia, lethargy, weight loss, and vomiting.

Physical Examination

Colonic impaction is a consistent physical examination finding in affected cats. Other findings depend upon the severity and pathogenesis of constipation. Dehydration, weight loss, debilitation, abdominal pain, and mild to moderate mesenteric lymphadenopathy may be observed in cats with severe idiopathic megacolon. Colonic impaction may be so severe in such cases as to render it difficult to differentiate impaction from colonic, mesenteric, or other

abdominal neoplasia. Cats with constipation caused by dysautonomia may have other signs of autonomic nervous system failure, such as urinary and fecal incontinence, regurgitation as a consequence of megaesophagus, mydriasis, decreased lacrimation, prolapse of the nictitating membrane, and bradycardia. Digital rectal examination should be carefully performed with sedation or anesthesia in all cats. Pelvic fracture malunion may be detected on rectal examination in cats with pelvic trauma. Rectal examination might also identify other unusual causes of constipation, such as foreign bodies, rectal diverticula, stricture, inflammation, or neoplasia. Chronic tenesmus may be associated with perineal herniation in some cases. A complete neurologic examination with special emphasis on caudal spinal cord function should be performed to identify neurologic causes of constipation, for example, spinal cord injury, pelvic nerve trauma, or Manx sacral spinal cord deformity.

Diagnosis

Although most cases of obstipation and megacolon are unlikely to have significant changes in laboratory data (e.g., complete blood cell count, serum chemistry, urinalysis), these tests should nonetheless be performed in all cats presented for constipation. Metabolic causes of constipation, such as dehydration, hypokalemia, and hypercalcemia may be detected in some cases. Basal serum T_4 (thyroxine) concentration and other thyroid function tests should also be considered in cats with recurrent constipation and other signs consistent with hypothyroidism. Although hypothyroidism was documented in only one case of obstipation and megacolon, obstipation is a frequent clinical sign in kittens affected with congenital or juvenile-onset hypothyroidism.[1] Constipation could also theoretically develop following successful treatment of feline hyperthyroidism.

Abdominal radiography should be performed in all constipated cats to characterize the severity of colonic impaction, and to identify predisposing factors such as intraluminal radiopaque foreign material (e.g., bone chips), intraluminal or extraluminal mass lesions, pelvic fractures, and spinal cord abnormalities (Figure 58-14). The radiographic findings of colonic impaction cannot be used to distinguish between constipation, obstipation, and megacolon in idiopathic cases. First or second episodes of constipation in some cats may be severe and generalized but may still resolve with appropriate treatment.

Ancillary studies may be indicated in some cases. Extraluminal mass lesions may be further evaluated by abdominal ultrasonography and guided biopsy, whereas intraluminal mass lesions are best evaluated by endoscopy. Colonoscopy may also be used to evaluate the colon and anorectum for suspected inflammatory lesions, strictures, sacculations, and diverticula. Barium enema contrast radiography may be used if colonoscopy is not possible. Both colonoscopy and barium-contrast enema radiography require general anesthesia and evacuation of impacted feces. Cerebrospinal fluid analysis, CT or magnetic resonance imaging (MRI), and electrophysiologic studies should be considered in animals with evidence of neurologic impairment. Finally, colonic biopsy or anorectal manometry will be necessary to diagnose suspected cases of aganglionic megacolon.

Treatment

The specific therapeutic plan will depend upon the severity of constipation and the underlying cause.[2] Medical therapy may not be necessary with first episodes of constipation. First episodes are often transient and resolve without therapy. Mild to moderate or recurrent episodes of constipation, on the other hand, usually require some medical intervention. These cases may be managed, often on an outpatient basis, with dietary modification, water enemas, oral or suppository laxatives, and/or colonic prokinetic agents (Table 58-9). Severe cases of constipation usually require brief periods of hospitalization to correct metabolic abnormalities and to evacuate impacted feces using water enemas, manual extraction of retained feces, or both. Followup therapy in such cases is directed at correcting predisposing factors and preventing recurrence. Subtotal colectomy will become necessary in cats suffering from obstipation or idiopathic dilated megacolon. These cats, by definition, are unresponsive to medical therapy. Pelvic osteotomy without colectomy may be sufficient for some cats suffering from pelvic canal stenosis and hypertrophic megacolon.[9] Figure 58-15 provides an algorithm for the therapeutic approach to the constipated, obstipated, and megacolonic cat.

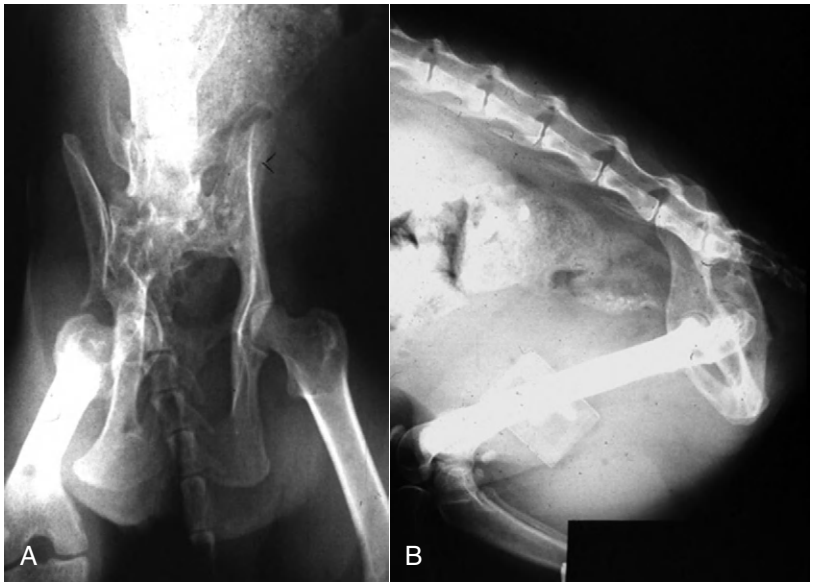

Figure 58-14 Lateral and ventrodorsal radiographs of the pelvis of a cat with megacolon. Note the healed malaligned fracture of the ilium obstructing the pelvic canal.

Table 58-9 Mechanisms, Sites of Activity, Indications, and Doses of Currently Available Gastrointestinal Prokinetic Agents

Drug Classification/ Mechanism	Sites of Activity	Indications	Dose	Other properties
Dopaminergic D_2 Antagonist Drugs				
Metoclopramide	GES, stomach, intestine, CRTZ	Vomiting disorders, gastroesophageal reflux, delayed gastric emptying, ileus/pseudoobstruction	0.2 to 0.5 mg/kg PO, IV TID; 0.01 to 0.02 mg/kg/h infusion	α_2-Adrenergic antagonist β_2-Adrenergic antagonist 5-HT_4 serotonergic agonist 5-HT_3 serotonergic antagonist
Domperidone	GES, CRTZ	Vomiting disorders, gastroesophageal reflux	0.05 to 0.10 mg/kg PO BID	α_2-Adrenergic antagonist β_2-Adrenergic antagonist
Serotonergic 5-HT_4 Agonist Drugs				
Mosapride	Stomach	Delayed gastric emptying	0.25 to 1.0 mg/kg PO BID	None
Prucalopride	Stomach, colon	Delayed gastric emptying, constipation	0.01 to 0.20 mg/kg PO BID	None
Cisapride*	GES, stomach, intestine, colon, CRTZ	Gastroesophageal reflux, delayed gastric emptying, ileus/pseudoobstruction, constipation, chemotherapy-induced vomiting	0.1 to 0.5 mg/kg PO TID (doses as high as 0.5 to 1.0 mg/kg have been used in some dogs)	5-HT_3 serotonergic antagonist 5-HT_1 serotonergic antagonist 5-HT_2 serotonergic agonist
Tegaserod*	Intestine, colon	Constipation, ileus/ pseudoobstruction	0.05 to 0.10 mg/kg PO or IV, BID	5-HT_1 serotonergic antagonist
Motilin-Like Drugs				
Erythromycin	GES, stomach, intestine, colon	Gastroesophageal reflux, delayed gastric emptying, constipation (dogs)	0.5 to 1.0 mg/kg PO IV TID	5-HT_3 serotonergic antagonist
Acetylcholinesterase Inhibitors and Cholinomimetic Agents				
Ranitidine	Stomach, colon	Delayed gastric emptying, constipation	1 to 2 mg/kg PO BID-TID	H_2 histaminergic antagonist
Nizatidine	Stomach, colon	Delayed gastric emptying, constipation	2.5 to 5.0 mg/kg PO SID	H_2 histaminergic antagonist
Bethanechol	Esophagus	Canine idiopathic megaesophagus	Dog: 5 to 15 mg/dog PO TID	
Nitric Oxide Donors				
AMU-301	Stomach	Diabetic gastroparesis	Not yet established	
Prostanoids				
Misoprostol	Colon	Constipation	Dog: 2 to 5 µg/kg PO TID-QID	

*Removed from many international markets.
CRTZ, chemoreceptor trigger zone; GES, gastroesophageal sphincter.

Removal of Impacted Feces

Removal of impacted feces may be accomplished through the use of rectal suppositories, enemas, or manual extraction.

Rectal Suppositories. A number of pediatric rectal suppositories are available for the management of mild constipation. These include dioctyl sodium sulfosuccinate (emollient laxative), glycerin (lubricant laxative), and bisacodyl (stimulant laxative). The use of rectal suppositories requires a compliant pet and pet owner. Suppositories can be used alone or in conjunction with oral laxative therapy.

Enemas. Mild to moderate or recurrent episodes of constipation may require administration of enemas and/or manual extraction of impacted feces. Several types of enema solutions may be administered, such as warm tap water (5 to 10 mL/kg), warm isotonic saline (5 to 10 mL/kg), dioctyl sodium sulfosuccinate (5 to 10 mL/cat), mineral oil (5 to 10 mL/cat), or lactulose (5 to 10 mL/cat). Enema solutions should be administered slowly with a well-lubricated 10 to 12 rubber catheter or feeding tube. Enemas containing sodium phosphate are contraindicated in cats because of their propensity for inducing severe hypernatremia, hyperphosphatemia, and hypocalcemia in this species.[10]

Manual Extraction. Cases unresponsive to enemas may require manual extraction of impacted feces. Cats should be adequately rehydrated and then anesthetized with an endotracheal tube in place to prevent aspiration should colonic manipulation induce vomiting. Water or saline is infused into the colon while the fecal mass is manually reduced by abdominal palpation. Sponge forceps may also be introduced rectally (with caution) to break down the fecal mass. It may be advisable to evacuate the fecal mass over a period of several days to reduce the risks of prolonged anesthesia and perforation of a devitalized colon. If this approach fails,

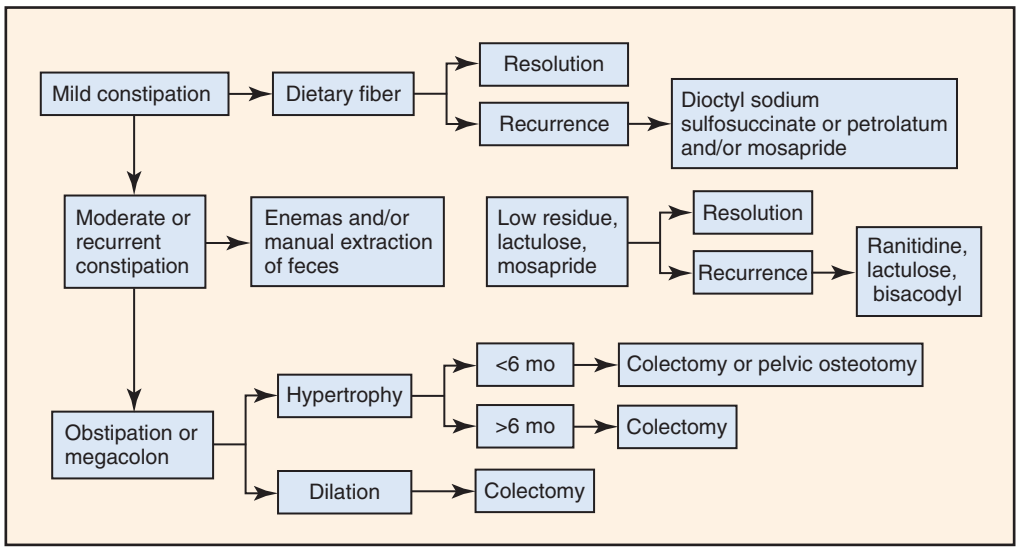

Figure 58-15 Suggested management of mild, moderate, or recurrent constipation and obstipation or megacolon.

colotomy may be necessary to remove the fecal mass. Laxative and/or prokinetic therapy may then be instituted once the fecal mass has been removed.

Established Laxative Agents

Laxatives promote evacuation of the bowel through stimulation of fluid and electrolyte transport or increases in propulsive motility. They are classified as bulk-forming, emollient, lubricant, hyperosmotic, or stimulant laxatives according to their mechanism of action. There are literally hundreds of products available for the treatment of constipation. Chapter 50 provides more detail about laxative agents.

Bulk-Forming Laxatives. Most of the available bulk-forming laxatives are dietary fiber supplements of poorly digestible polysaccharides and celluloses derived principally from cereal grains, wheat bran, and psyllium. Some constipated cats will respond to supplementation of the diet with one of these products, but many require adjunctive therapy (e.g., other types of laxatives or colonic prokinetic agents).[11] Fiber supplemented diets are available commercially, or the pet owner may wish to add psyllium (1 to 4 tsp per meal), wheat bran (1 to 2 tblsp per meal), or pumpkin (1 to 4 tblsp per meal) to canned cat food. Cats should be well hydrated before commencing fiber supplementation to maximize the therapeutic effect. Fiber supplementation is most beneficial in mildly constipated cats, prior to the development of obstipation and megacolon. In obstipated and megacolon cats, fiber may in fact be detrimental. Low-residue diets may be more beneficial in obstipated and megacolonic cats.

Emollient Laxatives. Emollient laxatives are anionic detergents that increase the miscibility of water and lipid in digesta, thereby enhancing lipid absorption and impairing water absorption. Dioctyl sodium sulfosuccinate and dioctyl calcium sulfosuccinate are examples of emollient laxatives available in oral and enema form. Dioctyl sodium sulfosuccinate at a dosage of 30 mg/kg/day had no effect on fecal consistency in Beagle dogs.[12]

Lubricant Laxatives. Mineral oil and white petrolatum are the two major lubricant laxatives available for the treatment of constipation. The lubricating properties of these agents impede colonic water absorption, as well as permit greater ease of fecal passage. These effects are usually moderate, however, and, in general, lubricants are beneficial only in mild cases of constipation.

Hyperosmotic Laxatives. This group of laxatives consists of the poorly absorbed polysaccharides (e.g., lactose, lactulose), the magnesium salts (e.g., magnesium citrate, magnesium hydroxide, magnesium sulfate), and the polyethylene glycols. Lactose is not effective as a laxative agent in all cats.[13] Lactulose is the most effective agent in this group. The organic acids produced from lactulose fermentation stimulate colonic fluid secretion and propulsive motility. Lactulose administered at a dosage of 0.5 mL/kg of body weight every 8 to 12 hours fairly consistently produces soft feces in the cat. Magnesium salts are not currently recommended in the treatment of feline constipation and idiopathic megacolon. Anecdotal reports of therapeutic successes have been reported with the polyethylene glycols.

Stimulant Laxatives. The stimulant laxatives (bisacodyl, phenolphthalein, castor oil, cascara, senna) are a diverse group of agents that have been classified according to their ability to stimulate propulsive motility. Bisacodyl, for example, stimulates nitric oxide–mediated epithelial cell secretion and myenteric neuronal depolarization.[14] Diarrhea results from the combined effect of increased mucosal secretion and colonic propulsion. Bisacodyl, at a dosage of 5 mg every 24 hours PO, is the most effective stimulant laxative in the cat. It may be given individually or in combination with fiber supplementation for long-term management of constipation. Daily administration of bisacodyl should probably be avoided, however, because of injury to myenteric neurons with chronic usage.[14]

Newer Laxative Agents

Chloride Channel Activators. Chloride channels are voltage-gated anion channels that allow the transport of chloride ions across cell membranes and play a critical role in fluid transport, maintenance of cell volume, and intracellular pH.[15,16]

Lubiprostone. Lubiprostone is a member of a group of compounds referred to as *prostones*.[17] Prostones are naturally occurring

bicyclic fatty acids formed by enzymatic oxidation of the 15-hydroxyl group of prostaglandins to the keto form. Lubiprostone is approved by the U.S. Food and Drug Administration for the treatment of chronic idiopathic constipation in humans. Lubiprostone activates type 2 chloride channels in the apical membrane of intestinal epithelial cells. This activity stimulates chloride secretion, followed by passive secretion of sodium and water (see Figure 1-17 in Chapter 1). The fluid-induced bowel distention secondarily induces peristalsis, but lubiprostone has no direct stimulatory effect on gastrointestinal smooth muscle. Insufficient safety and efficacy data are currently available to recommend the routine use of lubiprostone in dogs and cats.

Guanylate Cyclase Activators. Activation of the guanylate cyclase-C receptor increases cyclic guanosine monophosphate, thereby inducing signaling pathways that stimulate chloride and bicarbonate secretion through CFTR chloride channel–dependent mechanisms and, to a lesser extent, CFTR chloride channel–independent mechanisms, and inhibit sodium absorption by a sodium-proton exchanger.[15,16]

Linaclotide is a guanylate cyclase-C receptor agonist and intestinal secretagogue that improves bowel symptoms and accelerates colonic transit in chronic constipation.[18,19] Linaclotide has also been shown to attenuate nociceptive reflexes in response to colonic distention in three rodent models of visceral hypersensitivity.[18] Insufficient safety and efficacy data are currently available to recommend the routine use of linaclotide in dogs and cats.

μ-Opioid Antagonists. Postoperative ileus has multiple pathogenetic mechanisms. A dominant theme is the activation of enteric μ-opioid receptors resulting in inhibition of enteric nerve activity.[15,16]

Methylnaltrexone is a quaternary derivative of the μ-opioid receptor antagonist naltrexone.[20] N-terminal methylation reduces lipid solubility and prevents the drug from crossing the blood–brain barrier. Methylnaltrexone's reversal of opioid-induced inhibition of enteric nerve activity increase propulsion and secretory activity. Methylnaltrexone is clearly beneficial in the treatment of opioid-induced constipation; its efficacy in the treatment of postoperative ileus has not yet been definitively established. Insufficient safety and efficacy data are currently available to recommend the routine use of methylnaltrexone in dogs and cats.

Alvimopan has all of the same properties as methylnaltrexone; additionally, alvimopan accelerates colonic transit in healthy individuals, suggestive of a direct prokinetic effect.[20] Insufficient safety and efficacy data are currently available to recommend the routine use of alvimopan in dogs and cats.

Colonic Prokinetic Agents

Previous studies of feline colonic smooth muscle function have suggested that stimulation of colonic smooth muscle contraction might improve colonic motility in cats affected with idiopathic dilated megacolon.[6,7,21] Unfortunately, many gastrointestinal prokinetic agents have not proved useful in the therapy of feline constipation either because of significant side effects (e.g., bethanechol), effects limited to the proximal gastrointestinal tract (e.g., metoclopramide, domperidone, erythromycin), or market withdrawal because of cardiac 5-HT_4 effects. Some of the 5-HT_4 serotonergic agonists (e.g., cisapride, prucalopride, tegaserod) appear to have the advantage of stimulating motility from the gastroesophageal sphincter to the descending colon with relatively few side effects. Cisapride, for example, increases gastroesophageal sphincter pressure, promotes gastric emptying, and enhances small intestinal and colonic propulsive motility.[12,22] Cisapride enhances colonic propulsive motility through activation of colonic neuronal or smooth muscle 5-HT receptors in a number of animal species.[23,24] In vitro studies show that cisapride stimulates feline colonic smooth muscle contraction,[7,24] although it has not yet been conclusively shown that cisapride stimulates feline colonic propulsive motility in vivo. Anecdotal experiences suggest that cisapride is effective in stimulating colonic propulsive motility in cats affected with mild to moderate idiopathic constipation; cats with long-standing obstipation and megacolon are unlikely to show much improvement with cisapride therapy. Cisapride was widely used in the management of feline colonic motility disorders throughout most of the 1990s,[22,25,26] until it was withdrawn from the American, Canadian, and certain Western European markets in July 2000 following reports of untoward cardiac side effects in human patients. Cisapride causes QT interval prolongation and slowing of cardiac repolarization via blockade of the rapid component of the delayed rectifier potassium channel (I_{Kr}).[27] This effect may result in a fatal ventricular arrhythmia referred to as *torsades de pointes*. Similar effects have been characterized in canine cardiac Purkinje fibers,[28] but in vivo effects have not yet been reported in dogs or cats. The withdrawal of cisapride has created a clear need for new GI prokinetic agents although cisapride continues to be available from compounding pharmacies throughout the United States and other countries. A recent evidence-based data review of cisapride's efficacy in the treatment of human constipation and constipation-predominant irritable bowel syndrome (IBS) was carried out by the Cochrane Collaboration.[29] The authors concluded that "no clear benefit could be demonstrated with cisapride."[29]

Tegaserod is a potent partial nonbenzamide agonist at 5-HT_4 receptors and a weak agonist at 5-HT_{1D} receptors.[30,31] Tegaserod has definite prokinetic effects in the canine colon, but its effects in the feline colon are not known. Intravenous doses of tegaserod (0.03 to 0.3 mg/kg) accelerate colonic transit in dogs during the first hour after intravenous administration.[30] Tegaserod at doses of 3 to 6 mg/kg PO has also been shown to normalize intestinal transit in opioid-induced bowel dysfunction in dogs,[32] suggesting it could prove useful in other disorders of intestinal ileus or pseudoobstruction. Eventually, tegaserod was also shown to prolong the QT interval and delay cardiac repolarization as had been reported with cisapride. Tegaserod was marketed under the trade name of Zelnorm in the United States in September 2002 and subsequently removed from American and other markets in 2006. As with many other drugs in companion animal medicine, tegaserod was not licensed for the treatment of canine or feline gastrointestinal motility disorders.

Prucalopride is a potent 5-HT_4 receptor agonist that stimulates GMCs and defecation in the dog and cat.[33,34] Prucalopride also appears to stimulate gastric emptying in the dog.[35] In lidamidine-induced delayed gastric emptying in dogs, prucalopride (0.01 to 0.16 mg/kg) dose-dependently accelerates gastric emptying of dextrose solutions. Prucalopride is marketed as Resolor by Movetis in Europe.

Mosapride citrate, a substituted benzamide, is a novel 5-HT_4 receptor agonist that increases gastric emptying in rats and dogs, and increases electrically evoked contractions in the isolated guinea pig ileum.[36,37] Mosapride stimulates acetylcholine release from the myenteric plexus via activation of 5-HT_4 receptors, but has no real affinity for D_2 dopamine, 5-HT_1, 5-HT_2 receptors, or α_1-adrenoceptors. Mosapride restores gastric motility in dogs with vincristine-induced gastric hypomotility,[38] and therefore may be clinically useful in other

gastric emptying disorders. Mosapride is apparently without effect on distal gastrointestinal tract motility, and therefore may not prove useful in disorders of constipation. Mosapride is marketed as Pronamid by DS Pharma Animal Health in Japan.

Misoprostol is a prostaglandin E_1 analogue that reduces the incidence of nonsteroidal antiinflammatory drug-induced gastric injury. The main side effects of misoprostol therapy are abdominal discomfort, cramping, and diarrhea. Studies in dogs suggest that prostaglandins may initiate a giant migrating complex pattern and increase colonic propulsive activity.[39] In vitro studies of misoprostol show that it stimulates feline and canine colonic smooth muscle contraction.[40] Given its limited toxicity, misoprostol may be useful in cats (and dogs) with severe refractory constipation.

Ranitidine and nizatidine, classic histamine H_2 receptor antagonists, may also stimulate canine and feline colonic motility. These drugs stimulate contraction apparently through inhibition of tissue acetylcholinesterase and accumulation of acetylcholine at the motor endplate. It is not yet clear how effective these drugs are in vivo, although both drugs stimulate feline colonic smooth muscle contraction in vitro.[41] Cimetidine and famotidine, members of the same classification of drug, are without this effect.

Surgery

Colectomy should be considered in cats that are refractory to medical therapy. Cats have a generally favorable prognosis for recovery following colectomy, although mild to moderate diarrhea may persist for weeks to months postoperatively in some cases.[42,43] Pelvic osteotomy without colectomy has been recommended for cats with pelvic fracture malunion and hypertrophic megacolon of less than 6 months duration.[44] Symphyseal distraction-osteotomy with spirally fashioned orthopedic wire has also been used in the surgical management of this disorder.[45] Pathologic hypertrophy may be reversible with early pelvic or symphyseal distraction osteotomy in such cases. Some surgeons still prefer colectomy in this instance because of the technical difficulty of some pelvic osteotomies.[46]

Subtotal colectomy is an effective treatment for feline idiopathic megacolon or megacolon secondary to the mechanical obstruction created by old, healed pelvic fractures. Recommendations for removal of the ileocolic valve and ileum vary in cats with megacolon. The ileocolic blood vessels tether the distal ileum and proximal ascending colon, preventing anastomosis to the distal colon; thus if a complete colectomy is performed, these vessels must be sacrificed. This necessitates removing the ileum, which has important normal functions in water, vitamin B_{12}, and bile salt resorption, and performing a jejunocolic anastomosis. In spite of this concern, postoperative intestinal function was normal in four cats evaluated after subtotal colectomy and jejunocolic anastomosis.[43,47] The ileocolic valve also minimizes colonic bacterial access to the small intestine,[44] so preservation of the valve would be ideal to minimize small intestinal bacterial overgrowth and deconjugation of bile salts. However, preservation of the ileocolic junction necessitates leaving several centimeters of the ascending colon to ensure a tension-free anastomosis, possibly predisposing these cats to recurrent constipation. To evaluate these concerns, cats with megacolon treated with colectomy were studied retrospectively. Cats with excision of the ileocolic junction had significantly looser stool on long-term followup.[43] However there was no difference in the incidence of constipation between cats with preservation versus excision of the ileocolic junction.[48] This is perhaps explained by in vitro experiments with ascending and descending colonic smooth muscle from cats with clinical megacolon showing that smooth muscle dysfunction is less severe in the ascending colon.[8]

When the ileocolic junction is preserved, the ascending colon is transected approximately 3 cm distal to the ileocolic junction to ensure a tension-free anastomosis. An end-to-end colocolostomy is performed using single interrupted sutures of 4-0 polydioxanone.[47] The successful use of a biofragmentable anastomosis ring has also been reported.[46] The omentum is wrapped around the anastomotic site and the abdomen is thoroughly lavaged with a warm, balanced electrolyte solution. All lavage fluid is aspirated from the peritoneal cavity before the incision is closed.

Cats recovering from colectomy are maintained on intravenous fluids until they commence eating and drinking. Electrolytes are supplemented if necessary. Bowel movements may be soft or loose and more frequent than normal. A highly digestible, low-residue diet is fed. In cats with profuse postoperative diarrhea in which small intestinal bacterial overgrowth is suspected, a short course of antibiotics is administered.

Prognosis

Many cats have one or two episodes of constipation without further recurrence, although others may progress to complete colonic failure. Cats with mild to moderate constipation generally respond to conservative medical management (e.g., dietary modification, emollient or hyperosmotic laxatives, colonic prokinetic agents). Early use of colonic prokinetic agents (in addition to one or more laxative agents) is likely to prevent the progression of constipation to obstipation and dilated megacolon in these cats. Some cats may become refractory to these therapies, however, as they progress through moderate or recurrent constipation to obstipation and dilated megacolon. These cats eventually require colectomy. Cats have a generally favorable prognosis for recovery following colectomy, although mild to moderate diarrhea may persist for 4 to 6 weeks postoperatively in some cases.

Irritable Bowel Syndrome

IBS is a human chronic gastrointestinal tract disorder of unknown origin that is characterized by abdominal pain and altered bowel habits in the absence of detectable biochemical or structural abnormalities.[49] IBS is one of the most common functional GI disorders with an estimated prevalence of 10% to 15% in Western adult populations. Direct and indirect costs of IBS reach up to $30 billion per year in the United States alone.[49] IBS is commonly subdivided into different phenotypes depending upon the most prevalent bowel habit: diarrhea-predominant IBS (IBS-D), constipation-predominant IBS (IBS-C), and mixed features IBS (IBS-M).[50] Because of the inability of animal species to describe clinical symptoms such as abdominal pain and discomfort, IBS is not a very-well-defined syndrome in veterinary medicine. Nonetheless, recurring vomiting and diarrheal disorders are seen in companion animal species that are unaccompanied by mucosal morphologic change, and are presumed therefore to be of functional or physiological origin.[51] The reader is referred to Chapter 41 for a more detailed discussion of IBS and its management.

A fiber-responsive large bowel diarrheal syndrome similar to IBS in humans has been characterized in dogs.[51] Affected animals have a chronic idiopathic large bowel-type diarrhea characterized by excessive fecal mucus, hematochezia, and tenesmus. Abdominal pain and weight loss are occasionally reported by pet owners. Multiple diet changes and empirical medications fail to relieve clinical signs. Medical investigation is negative for bacterial and other pathogen infections, colitis, and colonic neoplasia, and the term chronic large bowel diarrhea is applied to the patient's disorder. Dogs

affected with this syndrome may respond to the feeding of a highly digestible diet that is supplemented with soluble fiber.[51]

The reader is referred to Chapter 41 for more detailed discussion of IBS and its management.

NEOPLASIA

Robert J. Washabau

Etiology

In dogs, tumors of the large intestine are more common than tumors of the stomach and small intestine. The mean age of dogs affected with colonic neoplasia is variably reported between 7 and 11 years of age.[1] Most colonic tumors of dogs are malignant and include the adenocarcinomas, lymphosarcomas, and gastrointestinal stromal tumors (Table 58-10). Other reported tumors include leiomyosarcoma, neurofibrosarcoma, fibrosarcoma, and ganglioneuroma.[2-11] Leiomyosarcomas are the most common (91%) of the gastrointestinal stromal tumors.[12-15] Most colonic neoplasia develop in the descending colon and rectum, although leiomyosarcomas more frequently develop in the cecum.[4,6] Local tumor invasion apparently occurs at a slower rate with canine colonic neoplasia, and metastasis to distant sites is relatively uncommon. Benign colonic neoplasia (e.g., adenomas, adenomatous polyps, and leiomyomas) also occur, although they are less common than malignant tumors. Malignant transformation of adenomatous polyps to carcinoma in situ and invasive adenocarcinoma has been demonstrated in the dog just as it has in humans.[1,16,17] Extramedullary plasmacytomas are uncommon tumors of the gastrointestinal tract, but many of these occur in the large intestine and rectum.[12,13] All of the aforementioned tumors are associated with signs of inflammation and obstruction (e.g., hematochezia, tenesmus, and dyschezia). Carcinoids (rare 5-hydroxytryptamine [5-HT] secreting tumors) are occasionally associated with diarrhea because of the effects of 5-HT on secretion and motility.

In cats, adenocarcinoma (46%) is the most common tumor of the large intestine (see Table 58-10), followed by lymphosarcoma (41%) and mast cell tumors (9%).[14,15,18] The mean age of cats affected with colonic neoplasia is 12.5 years. The descending colon (39%) and the ileocolic sphincter (28%) are the most common sites of colonic neoplasia in the cat. Unlike colonic tumors in the dog, feline colonic tumors have a high rate (63%) of metastasis and, of course, metastasis is associated with decreased survival time. Metastatic sites include colonic lymph nodes, mesenteric lymph nodes, liver, spleen, bladder, urethra, omentum, mesocolon, lungs, duodenum, and peritoneum.

Table 58-10 Distribution of Colonic Neoplasia in Dogs and Cats

Tumor Type	Dog	Cat
Adenocarcinoma	43%	46%
Lymphosarcoma	19%	41%
Mast cell tumors	<1%	9%
Stromal tumors	19%	2%
Adenomas/polyps	17%	1%
Plasmacytomas	2%	<1%

Alimentary lymphoma is less common in dogs than in cats, representing only 7% of all canine lymphomas.[19] Lymphoma is the most common malignancy in cats, and the GI tract is the most common predilection site for this tumor. Feline alimentary lymphoma may affect any component of the digestive system (stomach, intestine, colon, liver, biliary tract, and pancreas), but it most commonly involves the small intestine.[19-25] Lymphoma can be classified histologically into small cell (lymphocytic; low grade; well differentiated) or large cell (lymphoblastic; high grade; undifferentiated) types.[19] Low-grade lymphocytic lymphoma has a higher reported incidence than high-grade lymphoblastic lymphoma in most case series.[20-25] Large granular lymphoma is a subtype that is characterized by the presence of natural killer T lymphocytes with intracytoplasmic granules. Clinically, these types of lymphoma are distinct entities with different clinical presentations, therapies, and outcomes.[19]

Although infection with FeLV and FIV are major risk factors for the development of feline lymphoma, cats with GI lymphoma are usually serologically negative for both infections.[19] Feline gastrointestinal lymphoma has been associated with *Helicobacter* infection[26] and exposure to household cigarette smoke.[27]

Pathophysiology

Mechanical obstruction is the most common pathophysiologic consequence of locally invasive colonic tumor. Other nonneoplastic processes such as intussusception, FIP granuloma, fibrosing stricture, linear and nonlinear foreign bodies, hematoma, and phycomycosis lesions also cause intraluminal obstruction. Prolonged obstruction induces smooth muscle hypertrophy proximal to the site of the obstruction.[28] Other pathophysiologic consequences of intestinal obstruction are pronounced fluid secretion and malabsorption of water and solutes; fluid, electrolyte, and acid–base disturbances; proliferation and translocation of luminal bacteria; and inflammation, devitalization, and perhaps even perforation of the colon. Secretory diarrheas have been reported with carcinoids of the rectum, colon, and intestine.

Clinical Examination

Most affected dogs have signs of hematochezia, mucoid feces, tenesmus, and dyschezia of varying severity. Importantly, the clinical signs observed with colorectal neoplasia are often indistinguishable from other causes of obstruction or chronic colitis. Hematochezia is infrequently reported with leiomyosarcomas or leiomyomas presumably because these tumors do not typically involve the mucosa. Other clinical signs depend on the tumor type and location. Vomiting, malabsorption, and cachexia may be observed, for example, when multifocal or diffuse tumors (e.g., lymphosarcoma) involve the proximal portions of the gastrointestinal tract. Gastrointestinal stromal tumors, particularly the leiomyomas, have been associated with hypoglycemia and the resulting clinical signs of muscular weakness and seizure activity.[29] Functional plasmacytomas secrete a single class of immunoglobulin and affected animals may go on to develop hyperviscosity syndrome, for example, retinal bleeding and epistaxis. If colonic perforation has occurred, animals may be presented moribund with fever, lethargy, anorexia, vomiting, abdominal pain, and collapse.

Vomiting (65%), diarrhea (52%), and weight loss (46%) are common clinical signs in cats with colonic neoplasia.[16] Most cats with colonic (and alimentary) lymphosarcoma are FeLV-negative. These lymphomas are still believed to be caused by FeLV,

Table 58-11 Characteristics of Feline Alimentary Lymphocytic and Lymphoblastic Lymphoma

Feature	Lymphocytic Lymphoma	Lymphoblastic Lymphoma
Clinical signs	Gradual weight loss, vomiting, diarrhea, decreased appetite	Rapid weight loss, anorexia, vomiting, diarrhea
Duration of clinical signs	Typically prolonged (weeks to months)	Typically acute (days to weeks)
Physical examination and ultrasonographic findings	May be normal; thickened bowel loops; palpable masses uncommon	Palpable mass lesions common
Diagnostic workup	Aspiration cytology, endoscopy, full-thickness surgical biopsy	Aspiration cytology, endoscopy, full-thickness surgical biopsy
Pitfalls of diagnostic testing	False negatives on aspiration cytology; differentiation of LSA from IBD	False negatives on aspiration cytology, differentiation of LSA from IBD
Surgical intervention	Useful for definitive biopsy	Therapeutic if obstructing mass lesions are present
Therapy	Chemotherapy–prednisone and chlorambucil; radiation therapy–may prolong survival	Chemotherapy–CHOP, CCNU, MOPP; radiation therapy–may prolong survival
Response to therapy	75% to 90% response rate	50% to 60% response rate
Outcome	Most cats live >2 years and are managed long-term with chemotherapy	Median survival 6 to 7 months; if complete response to therapy 40% chance of living a year or longer

CHOP, cyclophosphamide, doxorubicin, vincristine, prednisone ± L-asparaginase ± methotrexate; CCNU, lomustine; IBD, inflammatory bowel disease; LSA, lymphosarcoma; MOPP, mustargen, vincristine, prednisone, procarbazine.
Adapted from Gieger T: Alimentary lymphoma in cats and dogs. Vet Clin North Am Small Anim Pract 41:419–432, 2011; with permission.

with integrated virus causing neoplastic transformation in the absence of viral replication. Although most lymphomas in cats appear to be comprised of malignant T lymphocytes, most colonic (and alimentary) lymphomas are of B-cell origin. Alimentary and colonic lymphomas originate primarily from submucosal lymphocytes and/or mucosal lymphoid follicles, although two studies reported an epitheliotropic form of T-cell intestinal lymphomas.[30,31] Epitheliotropic T-cell lymphomas have not yet been reported in the feline colon. Feline lymphocytic lymphoma is typically a slowly progressive disease with a protracted history, whereas lymphoblastic lymphoma is more often characterized by an acute onset (Table 58-11).[19]

Diagnosis

Canine rectal adenocarcinomas are palpable in 60% to 80% of clinical cases, but colonic and cecal lesions are not as readily apparent on physical examination.[1,13,28,32,33] More than 50% of cats with colonic masses have a palpable abdominal mass.[16]

Survey and contrast radiographic and ultrasonographic studies have been employed with varying levels of success in the diagnosis of canine and feline colonic neoplasia. Annular stenotic lesions associated with adenocarcinoma of the colon may manifest as proximal colonic dilation on survey radiographs. Radiographic contrast material more precisely outlines the narrowing of the lumen at the site of the tumor. Although still of some clinical utility, contrast studies have been largely superseded by ultrasonography and other imaging modalities. Ultrasonography is presently considered to be the most effective means of diagnosing colonic tumors in dogs and cats and appears to be useful in evaluating mural lesions and associated abdominal changes such as lymphadenopathy (Figure 58-16).[33] Ultrasonography was reported to be useful 84% of the time in localizing feline colonic neoplasia in one study.[16] Ultrasonographic features of colonic tumors include transmural wall thickening with complete loss of the normal wall layering, fluid accumulation proximal to the lesion, and reduced regional motility.[33] Transabdominal fine-needle aspiration, peritoneal fluid cytology, and endoscopic

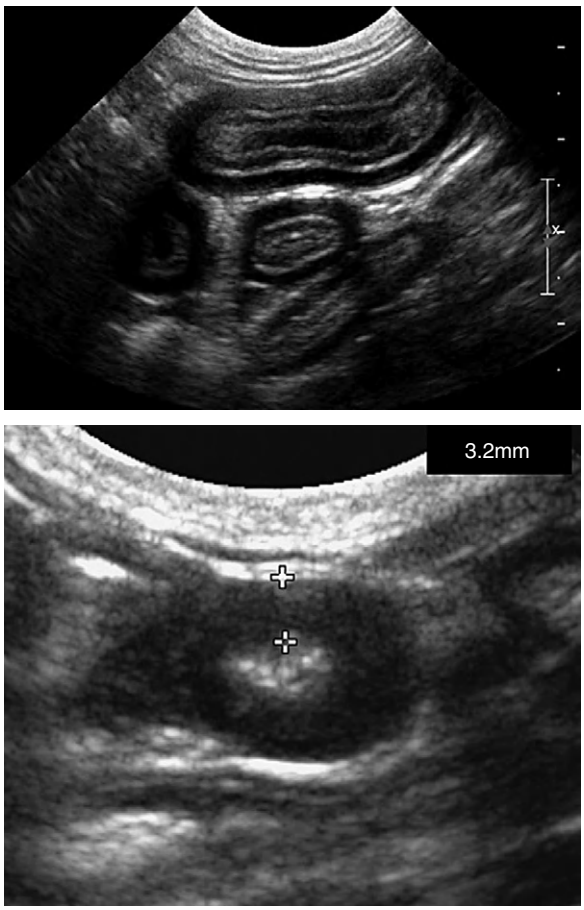

Figure 58-16 Abdominal ultrasonogram of a cat with lymphocytic lymphoma. (Reprinted with permission from Gieger T: Alimentary lymphoma in cats and dogs. Vet Clin North Am Small Anim Pract 41:419–432, 2011.)

exfoliative cytology may be useful in the diagnosis of lymphoma, but histopathology is generally required for a definitive diagnosis of other colonic neoplasia. CT and MRI scanning have not been sufficiently evaluated for reasonable comparisons to be made with ultrasonography.

Flexible colonoscopy with mucosal biopsy is the preferred method of diagnosis for colonic neoplasia. Endoscopic abnormalities may include mass effect, mucosal bleeding, increased mucosal friability, erosions and ulcers, and circumferential luminal narrowing with submucosal infiltrative lesions. Multiple biopsy specimens should always be taken from diseased tissue, adjacent healthy tissue, as well as the transition zone between healthy and diseased tissue. With tumor necrosis, the pathologist has a much better chance of diagnosing and staging the disease by evaluating nonnecrotic tissue.

Treatment

The treatment of colonic neoplasia will depend upon tumor type, anatomic location, and presence and extent of metastases (Box 58-2; see Tables 58-12 and 58-13). Complete surgical excision is the recommended therapy for focal adenocarcinomas, cecal leiomyosarcomas, and obstructive lymphomas. Multiagent chemotherapy (prednisone, vincristine, cyclophosphamide) has been used to treat colonic lymphoma, but it does not appear to alter survival time in affected cats.[16] Cyclooxygenase (COX)-2 upregulation may contribute to the growth characteristics of some canine colonic neoplasia.[34-36] Consequently, selective COX-2 inhibitors (e.g., piroxicam, meloxicam) may be useful in the treatment of some canine colonic neoplasia. Plasmacytomas may be managed with adjuvant chemotherapy (e.g., prednisone and melphalan) following surgical excision. Radiation therapy has been used to palliate recurrent adenocarcinomas with varying results and complications; however, postradiation peritonitis and perforation have been reported in some cases.[37]

Surgery

Preoperative Considerations

In dogs with rectal or colonic tumors, appropriate staging is vital to determine the extent of local and systemic disease. In many cases, a careful digital rectal examination can delineate the extent of local disease in the rectum and provide subjective information on the enlargement of regional lymph nodes. Thoracic radiographs are

Box 58-2 Treatment of Colonic Neoplasia in Dogs and Cats

Colonic tumors	→	Surgical excision
Lymphoma	→	Chemotherapy
Carcinomas	→	Cyclooxygenase-2 inhibitors
Plasmacytomas	→	Prednisone, melphalan
Recurrences	→	Radiation therapy

Table 58-12 Chemotherapy Protocols for Feline Alimentary Lymphocytic Lymphoma

Chlorambucil Dose (PO)	Prednisone Dose (PO)	Response Rate	Median Response Duration (Months)	Median Survival Time (Months)	References
2 mg q48-72h	5 or 10 mg/cat/day	56% CR; 39% PR	30 mo if CR; 14 mo if PR	n/a	25
15 mg/m^2 q24h × 4 days every 3 wk	3 mg/kg q24h then 1 to 2 mg/kg if remission	76% CR	19 mo	19 mo if CR; 4 mo if not CR	24
15 mg/m^2 q24h × 4 days every 3 wk	3 mg/kg q24h then 1 to 2 mg/kg if remission	69% CR	16 mo	17 mo overall; 23 mo if CR	48
20 mg/m^2 every 2 wk	Variable	96% CR	26 mo		23

CR, complete response; n/a, no data available; PR, partial response.
Adapted from Gieger T: Alimentary lymphoma in cats and dogs. Vet Clin North Am Small Anim Pract 41:419–432, 2011, with permission.

Table 58-13 Chemotherapy Protocols for Feline Alimentary Lymphoblastic Lymphoma

Drugs	Response Rate	Median Response Duration (Months)	Median Survival Time (Months)	Reference
CHOP	18% CR	n/a	2.7 mo	48
COP	75% CR	8 mo	9 mo	49
COP	32% CR	7 mo if CR	n/a	18
COP or COP then doxorubicin	n/a	3 mo if COP; 9 mo if COP then doxorubicin	n/a	50
CVM	52%	4 mo	n/a	51
CVM-L	62% CR; 20% PR		7 mo if CR	52
Doxorubicin	42%	Median 2 mo		53
Doxorubicin	22%	n/a	n/a	54
CHOP-L-M	47% CR; 33% PR	22 mo if CR; 4 mo if PR	22 mo if CR; 4 mo if PR	55
CHOP-L-M	n/a	5 mo	10 mo	56
CHOP-L-M	74% CR; 14% PR	9 mo if CR	10 mo if CR	57

C, Cyclophosphamide; CR, complete response; H, hydroxydaunorubicin, doxorubicin; L, L-asparaginase; M, methotrexate; n/a, no data available; O, vincristine; P prednisone or prednisolone; PR, partial response; V, vincristine.
Adapted from Gieger T: Alimentary lymphoma in cats and dogs. Vet Clin North Am Small Anim Pract 41:419–432, 2011, with permission.

made to rule out pulmonary metastatic disease. Abdominal ultrasonography is used to rule out abdominal metastatic disease and to guide aspiration and biopsy of enlarged iliac lymph nodes. Proctoscopy and colonoscopy often reveal the local extent of neoplastic disease. It is vital that colonoscopy be continued oral to rectal tumors as additional neoplasms are reported in the colon in a percentage of these cases.[38,39]

Mechanical cleansing is recommended before surgery of the large intestine in human, although preoperative enemas are contraindicated in cases of suspected large intestinal perforation. Perioperative antibiotics are administered to minimize the chance of surgical infection. Randomized, controlled clinical trials of antimicrobial prophylaxis in canine and feline colonic surgery have not been conducted, but based on human trials,[40] antibiotics effective against aerobes, especially the anaerobes that predominate in the large intestine, are administered intravenously once at the beginning of surgery. Antibiotics are not administered again unless either there is contamination at surgery or the procedure takes longer than 2 hours. In the latter case a second intravenous dose of antibiotics is administered. Antibiotics are continued postoperatively in cases with preoperative or surgical contamination based on the results of operative culture and sensitivity testing.

Operative Considerations

In animals requiring surgery for cecal or colonic disease, a ventral midline laparotomy is performed. After conducting a thorough abdominal exploration for concurrent or metastatic disease, the affected area of the large intestine is packed off with moistened laparotomy sponges. Resection of the cecum can be performed with or without preservation of the ileocolic junction, depending on the extent of the local disease. In most cases of cecal neoplasia a complete resection and jejuno- or ileocolonic anastomosis is performed to ensure adequate tumor resection.

Various techniques and surgical approaches have been described for removal of rectal tumors.[39] The approach and technique vary with the extent and location of the mass(es). Tumors in the proximal rectum may be accessed by a ventral midline laparotomy combined with a pelvic osteotomy. Healing of the distal colon and/or proximal rectum is complicated by the poor blood supply to this area of the large intestine.[41] A dorsal approach has been described for tumors involving the middle third of the rectum[39,42]; however, many tumors in this area are also amenable to resection via a rectal pull-through.[39,43] The plexus of pelvic nerves at the peritoneal reflection is vital to postoperative fecal continence. In an experimental study on healthy dogs, both transection alone and resection of 4 cm of rectum via a dorsal approach resulted in fecally continent dogs. Resection of 6 cm of the rectum, including the peritoneal reflection, caused fecal incontinence.[42] This limitation on resection is problematic in animals with larger rectal tumors, as a 2-cm gross margin is recommended on both sides of the tumor.[39,44,45]

Postoperative Considerations

Postoperative treatment depends largely on the underlying reason for cecal, colonic, or rectal surgery. Pre- or postoperative epidural anesthesia using a combination of local anesthetic and narcotic provides effective pain relief. Animals receiving epidural anesthesia may not be able to urinate normally for 12 to 24 hours, hence bladder size must be evaluated frequently and the bladder gently expressed or catheterized if needed. Narcotics, narcotic agonists/antagonists, partial μ-agonists, and COX-2 inhibitory class nonsteroidal antiinflammatory drugs are alternatives for pain management in dogs. Narcotic agonists/antagonists are effective in cats.

Adequate nutrition is vital for dogs and cats recovering from large intestinal surgery. Early feeding increases anastomosis strength and promotes enteric epithelial proliferation and function.[46,47] Ideally, the diet should provide a source of soluble fiber which, when hydrolyzed to short-chain fatty acids, stimulates colonic mucosal proliferation.[46] In animals with fecal continence difficulties after extensive rectal resection, a low-residue diet is fed twice daily. The animal is then walked for 20 to 30 minutes after eating. In many cases, the gastrocolic reflex will result in defecation and near complete emptying of the colon during this time, minimizing subsequent fecal soiling in the house.

Prognosis

The prognosis for adenomatous polyps, leiomyomas, and fibromas is generally favorable. Adenocarcinomas, lymphosarcomas, and plasmacytomas tend to recur and/or metastasize to distant sites. Dogs with annular colorectal adenocarcinomas have a particularly poor prognosis with a mean survival time of only 1.6 months.[1,32] The prognosis for most malignant tumors is generally guarded. Surgical resection alone results in 22 month (dogs) and 15 month (cats) average survival times in dogs and cats.[1,16] It should be noted that cats undergoing subtotal colectomy for colonic adenocarcinoma had a longer survival time than those receiving mass resection only (median survival time of 138 days versus 68 days).[16] Not surprisingly, cats with metastatic lesions had much shorter survival times, 49 days versus 259 days.[16]

ULCER

David E. Holt and Robert J. Washabau

Ulcer Associated with Intervertebral Disk Disease and Steroid Treatment

Etiology

Colonic ulcers may develop following glucocorticoid therapy and neurosurgery in dogs with spinal cord injury. Gastric ulcers are of greater prevalence in this circumstance, but colonic ulcers may be equally devastating.[1-4] Affected dogs were most often Dachshunds with thoracolumbar disk disease treated with decompressive surgery and dexamethasone at doses of 0.25 to 4.4 mg/kg/day. Colonic ulcer is not a frequent complication of either intervertebral disk disease or corticosteroid therapy. In the initial report of the condition, colonic perforation was described in two dogs out of "several thousand."[1] Ten additional cases were subsequently reported until 1986,[2-4] and since then no additional reports have been published. This may represent increased awareness of the condition, reluctance to publish on a previously described condition, or perhaps a shift away from the use of dexamethasone in dogs with intervertebral disk disease. Colonic perforation is infrequent in humans treated with corticosteroids for neurologic disease[5] but may occur more commonly when dexamethasone is used.[6] In nonneurologic conditions, the frequency of perforation is influenced by the underlying disease and the presence of a diverticulum in the sigmoid colon.[7] Why this lesion develops in some dogs but not others is not readily explained.

Pathophysiology

There are many factors that probably interact to cause colonic perforation in this cohort of dogs. Spinal cord injury and sympathetic nerve stimulation associated with pain likely slow colonic transit and increase fecal retention. It is also likely that immobility and pain associated with abdominal muscle contraction inhibit voluntary defecation in dogs with intervertebral disk disease. This leads to fecal retention and colonic distention. In humans, it is postulated that prolonged increases in colonic intraluminal pressure lead to mucosal ischemia resulting in progressive necrosis, ulceration, and perforation.[6]

The effects of corticosteroids have not been extensively studied in the colon and are largely extrapolated from information gained in gastric studies.[8] Corticosteroids are presumed to decrease colonic mucus production, alter the composition of colonic mucus, and decrease mucosal repair in the colon, leading to perturbations in the colonic mucosal barrier.[3] These effects are thought to be secondary to depletion of local prostaglandin production. In addition, glucocorticoids inhibit the expression of inducible nitric oxide synthase in vascular endothelial cells,[9] perhaps further affecting colonic blood supply.[10] Together, these factors coalesce to induce erosion of the colonic mucosa, colonic perforation, and peritonitis.[3] The relationship between intervertebral disk disease, corticosteroid treatment, and colonic perforation is highlighted by a report describing 29 dogs with gastrointestinal perforation associated with administration of a COX-2 inhibitor. None of the latter dogs were treated for intervertebral disk disease, and none of the perforations were in the colon.[11]

The left colic flexure or proximal portion of the descending colon appears to be at greatest risk for colonic ulceration and perforation; two-thirds of the published cases were reported at this site.[3,4] Nonambulatory neurosurgical patients treated with dexamethasone are at greatest risk for development of colonic perforation. Colonic perforation is often preceded by variable nonspecific signs, most frequently depression, anorexia, and emesis. Perforation appears to be associated with 100% mortality, emphasizing the importance of prevention and early clinical recognition.

Clinical Examination

Middle aged, male dogs are most often affected, usually within 5 to 7 days of surgery. Depression, anorexia, emesis, abdominal pain, constipation, melena, and fever are the most important clinical signs. Many of these signs are subtle and easily missed by some pet owners. The immunosuppressive properties of glucocorticoids may mask the initial signs of peritonitis associated with colonic perforation.

Diagnosis

If suspected, patients at risk should be carefully evaluated for perforation and peritonitis. Imaging studies (radiography and ultrasonography), abdominocentesis, peritoneal lavage, and exploratory surgery, if indicated, should be considered in patients at risk. A diagnosis of peritonitis is made from cytologic evaluation of peritoneal fluid or measurements comparing glucose, pH, and lactate concentrations in peripheral blood and peritoneal fluid.[12] The perforations most often occur on the antimesenteric surface of the proximal descending colon.[3]

Treatment

Treatment involves rapid circulatory resuscitation with crystalloids and colloids, administering broad-spectrum bactericidal antibiotics, and emergency laparotomy. The perforation of the colon is identified, the affected area of bowel is resected, and the remaining colon is anastomosed. The abdominal cavity is thoroughly lavaged with warm balanced electrolyte solution. All of the lavage fluid and associated peritoneal contaminants are aspirated. Depending on the degree of residual peritoneal contamination, the abdomen is either closed, closed after placement of closed suction drains, or left open to facilitate drainage and covered with a sterile bandage.

Prognosis

Colonic ulcer and perforation is generally associated with a poor prognosis. A preventive approach to this complication appears to be warranted in high-risk patients: (a) use of less-potent glucocorticoids (e.g., prednisone or prednisolone) instead of dexamethasone, and (b) limited or no use of glucocorticoids.

Histiocytic Ulcerative Colitis (Granulomatous Colitis of Boxer Dogs)

Etiology

HUC was first reported by Van Kruiningen in a kennel of Boxer dogs in 1965.[13] A number of other cases have been reported since then, and a similar disease process has been reported in the French Bulldog. The pathognomonic lesion of this disease is a mucosal infiltration with large numbers of macrophages staining positively with PAS, and accompanied by mucosal ulceration and loss of goblet cells.[14] Although the term *histiocytic ulcerative colitis* describes many features of the disease, it understates the mixed lymphocytic plasmacytic component of the inflammation, and the term *granulomatous colitis* has been adopted to more completely characterize the histopathology. For the most part, the disease is localized to the large intestine and regional lymph nodes; however, in some instances PAS-positive macrophages may be found in lymph nodes remote from the intestine, suggesting that there is limited systemic distribution of the disease. Historically, an infectious etiology had been speculated but never proved. At least two independent lines of investigation now point to an adherent and invasive *E. coli* as the underlying etiology of granulomatous colitis.[14,15] The pathophysiology, clinical examination, diagnosis, and therapy of granulomatous colitis of Boxer dogs and other breeds are discussed in the "Inflammation" section.

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CHAPTER 59

Anorectum

STRUCTURE AND FUNCTION

Debra L. Zoran

The structures that make up the anorectum are responsible for the distal storage and voluntary evacuation of feces, and maintenance of fecal continence. These functions are controlled by a complex interaction of the intrinsic and extrinsic nervous system, and include coordination of the muscles, nerves, and supporting tissues that make up the anorectum. Fecal continence is one of the most important functions of the anorectum, and is defined as the ability to retain fecal content, to perceive that the rectum is full, and to determine appropriate conditions for defecation.[1] Diseases or disorders of the anorectum may cause fecal incontinence or constipation when there is a loss of coordination of the activities of the smooth and striated muscles of the anorectum. Conversely, disorders of the mucosa lining the anorectum result in signs of inflammatory disease, also known as proctitis, which are observed clinically as tenesmus, hematochezia, or frequent defecation. Because of the important social impact associated with anorectal disorders, and particularly in diseases resulting in fecal incontinence, they are an important cause of euthanasia in pet animals when the problem cannot be corrected or improved.

Anatomy of the Rectum and Perineum

The anorectum consists of the rectum, anal canal, internal and external anal sphincters, muscles of the pelvic canal, and the skin and subcutaneous structures of the perineum (Figure 59-1).[1] Although the rectum and anus are confluent, they have separate embryologic origins that account for many differences in blood supply, innervation, and structure.[2] The rectum is a short segment of the distal GI tract that begins at the pelvic inlet as a continuation of the distal colon, and extends approximately 5 cm in length to end at the anal canal.[3] The majority of the rectum lies within the peritoneal cavity and the serosal surface serves as the visceral peritoneum. The cranial portion of the rectum is suspended by the short mesorectum, a tissue which is continuous with the mesocolon and helps to form the pararectal fossa.[3] The rectum is primarily distinguished from the anal canal by the columnar epithelium that lines the mucosal surface.[2] The rectum is surrounded by the perineum, which comprises the tissues that make up the boundary of the pelvic outlet. Internally, the perineum is delineated by the ischial arch ventrally, the third coccygeal vertebra dorsally, and laterally (in the dog only) by the sacrotuberous ligament.[4] In cats, the lateral margin of the perineum is less-well defined because of the lack of a sacrotuberous ligament.[3] Nevertheless, the perineum surrounds the anal and urogenital canals and provides the external structural support for these tissues. The rectum is bounded by the right and left ventral sacrococcygeal muscles dorsally, and the levator ani muscle laterally. The levator ani and coccygeal muscles make up the pelvic diaphragm—the division between the pelvic canal and the ischiorectal fossa. These muscles are crucial in supporting the rectum, and are important not only as a physical partition, but are essential in acting as a counterbalance to the effects of increased intraabdominal pressure. When these muscles fail, as in perineal hernia, abdominal viscera may herniate through the pelvic canal. There are two ischiorectal fossae, each found above the pelvis and lateral to the root of the tail (see Figure 59-1). This fat-filled space contains the arteries, veins, and nerves that supply the distal GI and urogenital tracts—namely the internal pudendal artery and vein, and the pudendal nerve.[3] Lymphatic drainage for the perineum also courses through the fossa draining to the medial iliac nodes.

As an extension of the colon, the rectum contains the same tunics (layers) that exist in the colon: the mucosa, submucosa, muscularis, and serosa. The submucosa and serosal layers are essentially the same as in other regions of the alimentary tract. However, there are two main differences in the mucosa of the rectum compared to the colonic mucosa: the presence of a large number of solitary lymph nodules and the presence of non-effacing folds in the anal canal, which may be longitudinal or circular, depending on their location. The rectal mucosa also contains columnar epithelium, as in the distal colon, which is rich in goblet cells that secrete mucous. The lymph nodules can be visualized endoscopically in the normal rectal mucosa as either raised or punctate depressions in the rectal mucosa, the so-called rectal pits. Secretion of mucous from the goblet cells is regulated by a submucosal neural plexus in the rectal mucosa. Inflammation of the mucosa results in stimulation of this neural plexus, and this is responsible for the clinical signs often observed in anorectal disease: increased mucus on feces, hematochezia, or tenesmus. At the junction of the rectum and anus, the mucosal epithelium is replaced by a squamous epithelium. This transition point defines the junction of the rectum and internal anal sphincter (or beginning of the anal canal). Embryologically, this transition point marks the site of the cloacal membrane that separates the endoderm from the ectoderm in the embryo.[2] Abnormal development of these structures leads to the development of atresia ani and other congenital disorders of anorectal structure such as fistula and clefts.[5] The serosal surface of the rectum is continuous with the serosa of the colon; however, the serosa of the anal canal and most caudal portion of the rectum become retroperitoneal as part of the

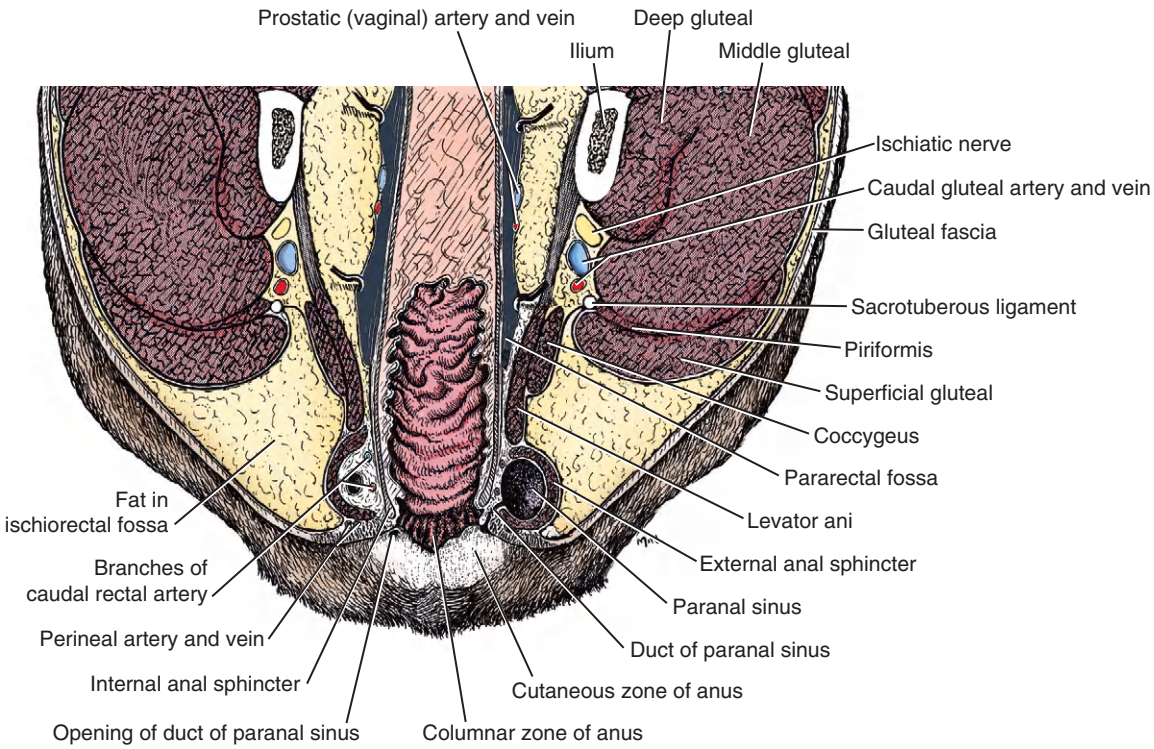

Figure 59-1 Cross-sectional anatomy of the anorectum. (Reprinted and modified with permission from Evans HE, de Lahunta A. *Guide to the Dissection of the Dog*, ed 7, St. Louis, 2010, Saunders, p 696.)

pararectal fossa.[3] The muscularis layer of the rectum includes the longitudinal muscles, which are continuous with the longitudinal muscle layer of the colon. The longitudinal and inner circular muscle layers provide tone and structural support to the mucosa and submucosa. In the distal rectum, the fibers of the longitudinal layer sweep dorsocaudally from the sides of the rectum to form the rectococcygeus muscle.[3] This muscle passes dorsal to the external anal sphincter and attaches to the bodies of the fifth and sixth coccygeal vertebrae. Anchoring the rectococcygeus muscle on the tail serves not only a means of supporting the anal canal, but also permits movement of the tail during defecation. In the distal rectum the circular muscle layer eventually forms the internal anal sphincter. The internal anal sphincter is composed of smooth (involuntary) muscle, is much smaller than the external anal sphincter, and has questionable significance in maintaining fecal continence.[2] Innervation of the rectum is via autonomic nerves from the pelvic plexus, and its blood supply is provided by the caudal rectal arteries.[3]

Anatomy of the Anal Canal

The terminal portion of the alimentary tract is the anal canal: a short (e.g., 1 cm), highly specialized segment that extends from the rectum to the anal opening. The involuntary smooth muscle of the internal anal sphincter, and voluntary striated muscle of the external anal sphincter are the most important muscles controlling the anal canal. Of these, the external anal sphincter is the most important structural determinant of fecal continence. The external anal sphincter is largely a circular band (approximately 1 to 1.5 cm in width in the dog) of striated muscle that serves as the chief guardian of anal control. The muscle attaches dorsally to the coccygeal fascia and ventrally it blends into the muscles of the external genitalia. Laterally, the sphincter is united by fascia to the levator ani muscles. The mucosa of the anal canal is divided into three zones: columnar, intermediate, and cutaneous.[3] The columnar zone connects the rectum to the anus, and is composed of longitudinal ridges of columnar mucosa. The columns formed in this zone encircle the anal canal as an anorectal line. Caudally, these columns loop around to unite as the anal valves, each loop enclosing a tiny pocket called an *anal sinus*. The ring of anal valves and sinuses forms the dentate line that marks the caudal limit of the deepest part of the anus.[2] The intermediate zone (also called the *anorectal line*) is the transition area between the columnar mucosa and the stratified squamous epithelium that makes up the cutaneous zone. Most caudally, the cutaneous zone is subdivided into an internal and external region. The inner most region contains the anal sacs and the termination of the anal sac ducts. The outer most aspect of the cutaneous zone is keratinized and hairless, and peripheral to the anus itself. The anal opening (or anus) is formed by the plane that separates these two regions of the cutaneous zone. The arterial blood supply to the anus is via the caudal rectal artery, a branch of the internal pudendal artery, which is a large vessel that courses through the ischiorectal fossa. However, venous drainage is via cranial rectal and caudal mesenteric veins to the portal system, and via the caudal rectal and perineal veins to the systemic circulation via the caudal vena cava.[3] Lymphatic drainage from the anal canal is also to the medial iliac lymph nodes. Innervation of the anus is supplied by the pudendal nerve.

Anatomy of the Anal Sacs and Glands

In dogs and cats, there are paired anal sacs, which lie ventrolateral (i.e., 4 and 8 o'clock) to the anus in the internal cutaneous zone, lying between the internal and external anal sphincters.[3] Anal sacs were first described as structures lined with keratinized epithelium and wrapped in glandular tissue and a connective tissue stroma that is diffusely infused with lymphoid tissue.[6] These sacs are sometimes termed *paranal sinuses* and are now known to contain coiled,

apocrine, sudoriparous glands, as well as a few sebaceous glands.[3] In cats, there are very few apocrine glands in the anal sacs, with sebaceous glands being found in both the fundus and the ducts of the glands.[7] The ducts emptying the canine anal sac open into the lateral margin of the anus at the intermediate zone; however, the anal sac duct in cats opens on a pyramidal prominence 2 mm lateral to the anus.[5] It has been suggested that either the increased lipid secretion from the increased sebaceous glands in cats, the location of the duct opening lateral to the anus, or possibly both in combination are responsible for the reduced occurrence of anal sac impaction and abscessation in the cat. The composition of secretions from the anal glands in dogs varies from serous to pasty, and accumulates in the anal sacs, along with desquamated epithelium, bacteria, and yeasts.[8,9] The normal canine anal sac secretion is highly variable in its color, consistency, and presence or absence of solid material, even in the anal sacs from the same dog (e.g., right vs. left sacs).[8,9] The typical cytologic composition of canine anal sac material contains mostly corneocytes, Gram-positive cocci, and a large amount of amorphous basophilic debris.[8] It is also not unusual to find a small number of neutrophils, yeasts, or a few rod-shaped bacteria in normal dogs.[9] However, intraepithelial bacteria, undifferentiated epithelial cells, or erythrocytes are not normal components of anal sac secretions and typically indicate the presence of a disease state.[8] Under normal circumstances, the anal sacs are emptied when the animal defecates voluntarily or involuntarily (e.g., fear) contracts the external anal sphincter muscle; however, their primary function in the wild is for territorial scent marking.[3,3a] These sacs are of clinical importance because they may become impacted as a result of anatomic disruption of the ducts caused by increased perineal obesity, anatomic disruption from hernia or neoplasia, or if the secretions become too thick or hardened to allow proper emptying. Impaction of the anal sacs often causes discomfort that is evidenced by scooting or increased licking of the area, and can lead to infection or abscessation. In dogs, anal sac impaction was the third most commonly diagnosed condition in a study of 559 dogs presented for dermatologic assessment.[10] In that study, otitis externa and pyoderma were more commonly reported, but these three conditions were clearly the most common reasons dogs were presented for evaluation of dermatologic conditions in private clinical practice, representing 20% of overall admissions in that study.[10] In addition to the anal sacs, there are two other types of glands present in the anal area. Circumanal, or hepatoid, glands are nonsecretory, subcutaneous sebaceous glands located in the anal subcutaneous zone. These perianal glands may become clinically important in intact male dogs, as they continue to grow throughout life because of the presence of androgens and may grow to form perianal adenomas late in life.[2] In one study, 85% of intact male dogs developed this tumor, making it the most common anal tumor of the dog.[4] It is rarely reported in the cat, likely a consequence of the fact that most pet cats are neutered and have fewer numbers of these glands. The "true" anal glands are tubuloalveolar sweat glands located craniolateral to the circumanal glands. These glands produce a fatty secretion that drains into the intermediate zone of the anus and whose function is unknown.

Physiology of Defecation and Fecal Continence

The innervation of the distal alimentary tract is complex and vital to the normal functions of storage, continence, and defecation (Figure 59-2).[1] Innervation of the rectum is similar to the colon, in that there is a well-defined enteric nervous system consisting of a myenteric and a submucosal plexus.[3] These segments of the autonomic nervous system control the many sensory, integrative and motor neurons that characterize the functions of the rectum, and more specifically control and integrate movements that ensure appropriate storage and transport of feces. The secretions of the goblet cells are also controlled by these systems. The innervation of the anus is more complex (Figure 59-2). The pelvic plexus, specifically the sacral nerve branches of the pelvic nerve, provides parasympathetic fibers which are excitatory to the rectum and inhibitory to the internal anal sphincter. Conversely, sympathetic fibers arise from the hypogastric nerves of the caudal mesenteric ganglion are inhibitory to the rectum (e.g., causing relaxation) and excitatory to the internal anal sphincter (e.g., causing contraction), thus allowing appropriate storage of feces. Relaxation of the internal and external anal sphincters in conjunction with rectal contraction permits defecation. The external anal sphincter is a striated muscle with several muscle bundles that surround the internal sphincter. These muscles are reflexively able to increase anal sphincter pressure, mediated via somatic nerve fibers in the anal branch of the pudendal nerve, while still allowing accommodation of feces within the rectum. The function of the external anal sphincter allows maximal distention (e.g., storage of feces in the rectum) while maintaining anal control. When the pudendal nerve is damaged, the external anal sphincter is incompetent and results in the development of fecal incontinence.

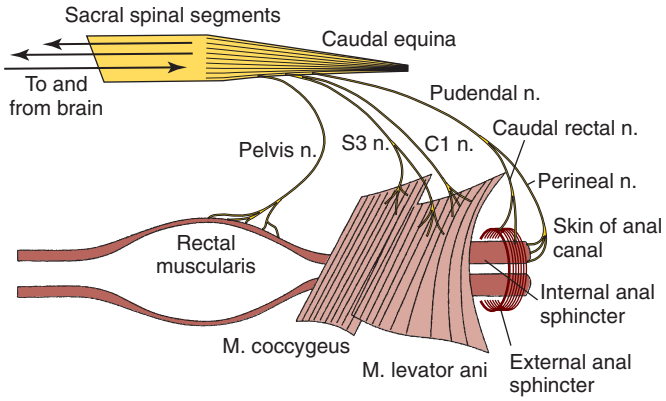

Figure 59-2 Nervous control of defecation. (Reprinted with permission from Guilford WG: *Strombeck's Small Animal Gastroenterology*, ed 3, Philadelphia, Saunders, 1996, p. 507.)

Normal anorectal function and the act of defecation are primarily pressure-based functions that rely heavily on complex interactions between peripheral pressure receptors, myenteric neurons, somatic and autonomic afferent nerve fibers, spinal cord, brainstem, somatic and autonomic efferent nerve fibers, and smooth and striated muscle of the rectum and anal sphincters (see Figure 59-2).[5] When the rectum is empty, intraluminal rectal pressure is low. Increased intraluminal pressure is generated by contraction of the internal anal sphincter, either in response to a sudden increase in intraabdominal pressure (e.g., coughing or sneezing) or an increase in rectal filling, and is the primary component of maintenance of fecal continence.[11] The main stimulus for defecation is increased pressure in the rectum because of distention. The rectoanal inhibition reflex relaxes the internal anal sphincter along with contractions of the external anal sphincter to allow slow, but continuous filling of the rectum.[11,12] As the fecal volume increases in the rectum, conscious awareness of the rectal filling is perceived by sensory signaling of information transmitted via sacral afferent fibers to the cerebral cortex. The rectoanal inhibition reflex allows continued filling of the rectum until defecation is appropriate. If the volume

of feces remains small (i.e., stretch is minimal) or defecation is inappropriate, the internal anal sphincter returns to a state of contraction, resulting in propulsion of feces back into the colon.[13,14] This activity is also stimulated by descending inputs from motoneurons in the sacral spinal cord and pudendal nerve, which mediate voluntary contractions of the external anal sphincter and levator ani. This back-and-forth process is repeated until the volume of feces is sufficient to initiate rectal distention as well as come into contact with the anal mucosa, resulting in a stronger urge to defecate. When defecation is initiated, distention of the rectum activates parasympathetic efferents which control contraction of colonic smooth muscle (resulting in mass movement of the distal colon), and inhibition of the external anal sphincter and pelvic muscles (resulting in relaxation of the sphincters.)[12] Because the rectum itself produces only small contractions that are not propulsive, the main propulsive force to dispel feces out of the body is the contraction of colonic smooth muscles.[12] Thus, the rectum serves primarily as a conduit during the process of defecation and as a storage depot in the periods between this process. Defecation is facilitated by proper posture and generation of increased abdominal pressure (closure of the glottis, fixation of the diaphragm, and contraction of the abdominal wall muscles). Conscious suppression of defecation is facilitated by descending impulses to sacral nerves and the pudendal nerve, which mediate contraction of the levator ani and external anal sphincter, resulting in maintenance of fecal continence.

DIAGNOSTIC EVALUATION

Robert J. Washabau

History and Physical Examination

Because the anorectum is not importantly involved in digestive or absorptive processes, dogs and cats with anorectal disease do not typically manifest signs of maldigestion or malabsorption (e.g., steatorrhea, diarrhea, and weight loss). Instead, dogs and cats affected with anorectal disease manifest signs of inflammation (hematochezia, tenesmus, mucoid feces, or frequent and painful defecations) or abnormal motility (dyschezia, incontinence).

Observation of the animal during the act of defecation should be an important part of the physical examination as many pet owners misinterpret signs of anorectal disease. Pet owners frequently confuse the signs of dyschezia (painful or difficult defecation) and tenesmus (straining to defecate) with constipation. Constipation is best defined as infrequent defecation, excessively hard or dry feces, or diminished fecal volume. The finding of true constipation would be associated with a different set of differential diagnoses.

The perineum is visually inspected for inflammation, tumors, herniation, rectoanal prolapse, and fistulas prior to rectoanal palpation. The anorectum is then digitally palpated for size and texture of the anal sacs, tone of the anal sphincter, integrity of the pelvic diaphragmatic musculature, diameter of the rectal lumen, and texture and regularity of the rectoanal mucosa. Rectoanal palpation may be impossible in some pets because of severe inflammatory disease, in which case palpation may be delayed until the animal is anesthetized for proctoscopy or other procedures. Rectoanal palpation is difficult in the unsedated cat. Abdominal palpation is also important, as anorectal disease may be a manifestation of more diffuse gastrointestinal disease (e.g., proctocolitis or colorectal carcinoma).

Special Examination

Proctoscopy is often performed in conjunction with colonoscopy because the rectum is frequently involved in canine colitis. However, discrete lesions of the anorectum may be evaluated with proctoscopy alone. Proctoscopy is technically less difficult and the instrumentation less costly than with total colonoscopy. A rigid proctoscope, for example, is sufficient for the evaluation of the anorectal structures in most patients. As with colonoscopy, the anorectum is evaluated for color, texture, friability, and bleeding. Mucosal biopsies may be readily obtained with a variety of forceps instruments. Lesions of the terminal rectum and anus can be visualized following gentle prolapse of the rectum and anus using an Allis tissue forceps, or by doing a retroflex endoscopic procedure following intubation of the anorectum and descending colon.

Radiographic examination is not especially useful in the evaluation of inflammatory lesions of the anorectum. However, survey and contrast radiographs may be useful in the evaluation of rectal tumors and rectal stricture. Ultrasonographic studies have assumed increasing importance in the evaluation of lesions of the anorectal canal. Intrarectal ultrasonography, for example, was accurate in assessing depth of rectal tumor penetration as well as the involvement of pararectal lymph nodes in experimentally induced rectal tumors in the dogs.[1]

Manometric evaluation of anorectal function is useful in selected cases of anorectal disease, for example, external anal sphincter incompetence (see Chapter 14) and congenital aganglionic megacolon (see Chapter 58). Animals with external anal sphincter incompetence may be more objectively evaluated for anal sphincter tone.[2]

INFLAMMATION

Debra L. Zoran

Perianal Fistula

Perianal fistula is a chronic, progressive, often debilitating, disease characterized by one or more ulcerated fistulas or draining tracts affecting the perianal skin and associated tissues surrounding the anus (Figure 59-3). *Anal furunculosis* is an alternate term for this

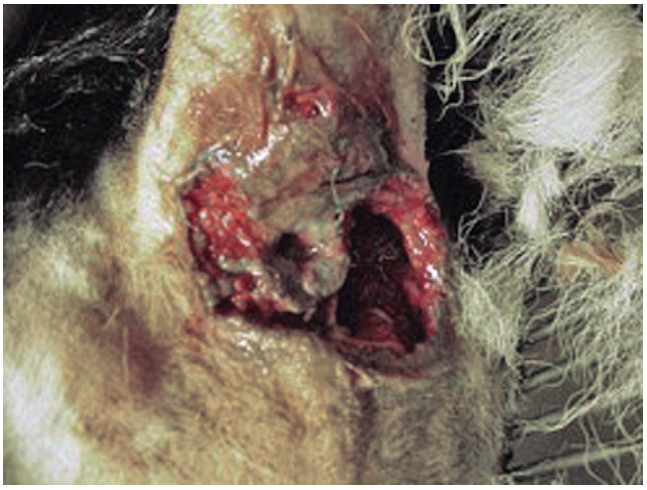

Figure 59-3 Perineal region of a dog with severe ulcerated, draining tracts surrounding the anal orifice.

condition, and may be more appropriate, as true fistulous tracts from the anal canal to the perianal skin are rare. The disease has not been described in cats. The ulcerative lesions are very painful and malodorous because of associated tissue destruction and infection. In most severe and chronic cases, the entire anus is surrounded with open draining tracts that can lead to secondary infection, infestation with ectoparasites, and ultimately to fecal incontinence or rectal stricture if left untreated.

Etiology

Perianal fistula (PF) most commonly affects dogs of the German Shepherd breed or German Shepherd mixed breeds, but Irish Setters, Labrador Retrievers, Old English Sheepdogs, Bulldogs, Spaniels, and Collies are also notably affected.[1-5] In one study, German Shepherds accounted for 84% of the reported cases.[2] PF primarily affects middle-aged to older dogs of either sex, but the disease has been described in dogs of ages ranging from 1 to 14 years.[2,3,6] At this time, the effect of sex hormones on the development or maintenance of PF in dogs is still debated, but it appears that both intact and neutered animals have equal risk of developing PF.[5] The cause of PF remains unknown and only partially defined, but anatomic, bacterial, endocrinologic, and immunologic etiologies have all been proposed. Similarities in clinical appearance between canine PF and human Crohn's disease have caused speculation that these diseases may share a common immunopathogenesis.[2,7-10] This notion has been further supported by clinical improvements reported in dogs treated with cyclosporine and other immunomodulating or immunosuppressive drugs (e.g., tacrolimus, azathioprine, prednisone).[3,4,9-13] Evidence of immune dysregulation has been reported in some studies, including increased plasma cells, CD 3+ T lymphocytes, immunoglobulin (Ig) A- and IgG-secreting B lymphocytes, and macrophages in affected tissue.[14,15] However, immunohistochemical analysis of the number and distribution of B and T lymphocytes has not revealed any simple immunologic defect.[15] An alternative hypothesis has been proposed that IgA deficiency in German Shepherds predisposes this particular breed to anal furunculosis.[15] This hypothesis is further supported by the findings of House et al. who showed that dogs with PF have increased expression of messenger RNA for interleukin (IL)-1β, IL-6, tumor necrosis factor-α, IL8, IL-10, and transforming growth factor-β.[15] Matrix metalloproteinases (MMPs) may contribute to this tissue pathology. MMPs 2, 9, and 13 were found to be significantly increased in tissue biopsies of dogs with PF.[16] MMP-9 and MMP-13 are primarily produced by macrophages, and tissue ulceration may occur as a result of the aberrant activation of macrophages in affected dogs.[16] It has been suggested that pathologic macrophage activity could result from T-cell secretion of interferon-γ, which might explain why lesions resolve following cyclosporine therapy.[16]

Pathophysiology

The pathologic changes that occur in dogs with PF are well described and are typical of chronic inflammation.[2] In particular, anal furunculosis is characterized by mononuclear infiltration of the fistulous or sinus tracts. Dense aggregates of lymphocytes trigger granulation tissue formation in areas adjacent to the sinus tracts. The inflammatory process can affect the anal sac and its associated duct, the circumanal glands, and the muscles of the external anal sphincter. Sinus tracts form in areas of degenerative squamous epithelium and produce obliteration and ulceration of perineal tissue.[2] Erosions and ulcerations typical of PF are believed to result from cell-mediated inflammatory responses and MMP enzyme expression.[16] MMPs are enzymes in the family of zinc-dependent endopeptidases, are produced by macrophages, and are involved in the degradation of extracellular matrix. There are several different families of MMPs: collagenases, gelatinases, stromelysins, and membrane-type MMPs. These enzymes play important physiologic roles in the detachment and migration of cells as well as in tissue remodeling for repair and angiogenesis. MMPs can also play a pathologic role in ulcerogenic diseases such as Crohn's disease, rheumatoid arthritis, periodontitis, and tumor cell invasion and metastasis.[17-19] In a pathologic role, MMPs cause tissue destruction instead of extracellular matrix remodeling.[16] In ulcerative diseases such as inflammatory bowel disease and Crohn's disease, significant elevations in MMP-9 and MMP-13 have been documented,[20,21] and increased MMP-9 expression is specifically associated with fistulous lesions in Crohn's disease.[22] The finding of MMPs in PF tissues adds further credence to the suggestion that tissue destruction, ulceration, and fistulation are a result of an aberrant cell-mediated inflammatory response.

Clinical Examination

Perianal fistulas are most commonly reported in middle-aged to older, large-breed dogs with a broad-based, lower tail carriage that may provide an environment conducive to worsening inflammation and infection once the disease starts. It may also contribute to the fact that the disease is often not noticed by the pet owner until obvious lesions are present, or the discharge or odor becomes overpowering. The only abnormality reported by some owners, especially early in the course of development of PF, is persistent licking of the anus. Other clinical signs that may be reported include hematochezia, dyschezia, perianal discharge, constipation, and tenesmus caused by the irritation and discomfort associated with defecation. In severely affected dogs, anorexia, weight loss, and behavioral changes may be reported as a consequence of the discomfort or associated infection surrounding perianal tissues.

Physical examination may be difficult, if not impossible, without sedation because of the pain associated with the condition. It may be necessary to clip hair and cleanse the area to get a full appreciation of the full extent of the disease. In severe cases, visual inspection will reveal multiple, ulcerated, draining tracts extending into the tissues surrounding the anus (see Figure 59-3). Fistulous lesions are often malodorous and may contain ectoparasites, particularly if the patient resides in warmer climates. Rectal strictures, abnormal anal tone, and granulomatous rectal mucosa may be found during digital rectal examination. In some dogs, the anal sacs are involved in the fistulation resulting in anal sac obstruction and abscessation. In dogs with early disease, the lesions will be more subtle and may require more careful inspection or digital palpation to differentiate other causes of perianal swelling, pain or redness (Figure 59-4). Nevertheless, whether there is one small draining tract or multiple, ulcerated areas with deep fistulas, the diagnosis is the same.

Diagnosis

A diagnosis of PF is made on the basis of signalment, history and clinical signs, and relevant physical examination findings. There are several important differentials for this condition that must be considered, including chronic anal sac abscessation with secondary fistulas, aggressive perianal tumors (e.g., adenocarcinoma), caustic

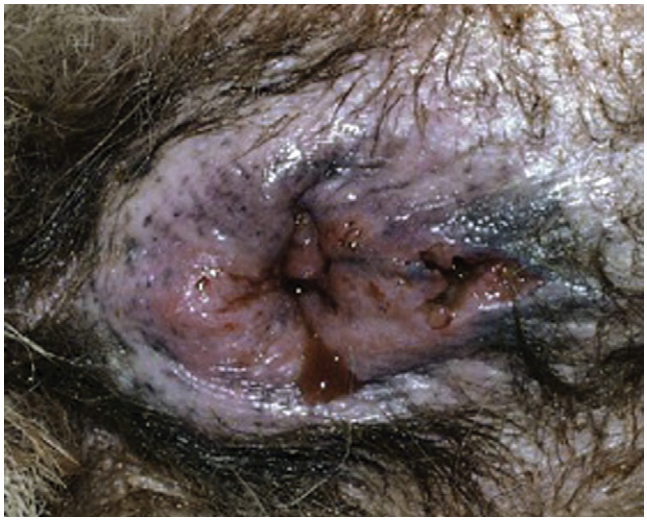

Figure 59-4 A milder version of perianal fistulas with hyperemia, a few draining tracts, and evidence of perianal swelling.

injury, and untreated bite wounds. Although history and physical examination findings are usually sufficient to rule out these other potential causes of perianal disease, a digital rectal examination and probing the extent of the lesions under general anesthesia will confirm the diagnosis. In a recent study of dogs with anal furunculosis, colonoscopy was performed in each case—whether or not the dog had concurrent signs of colitis or colonic disease—and results showed that 50% of the dogs had concurrent colitis.[23] The relationship between colitis in dogs and PF is unknown; also unknown is the effect of therapy of colitis on the outcome of dogs with PF. Nevertheless, the study authors recommended that flexible colonoscopy should be performed to obtain colonic biopsies in all dogs with perianal fistulas.[23]

Treatment

Because of the uncertain etiology of perianal fistulas, a number of medical and surgical treatments have been proposed. Previously, medical therapy included antibiotics, perineal cleansing, antiinflammatory drug therapy (e.g., prednisone), and analgesic drug therapy, all of which were palliative at best.[2-4,24] Surgical excision was frequently cited as the only treatment option in early studies[24-26]; however, remission rates were highly variable (48% to 97%), complication rates were equally variable (3% to 100%), often involving fecal incontinence, rectal strictures, and delayed wound healing, and recurrence rates were generally near 50%.[3,6,24-26] Cryotherapy, Nd-YAG (neodymium:yttrium-aluminum-garnet) laser therapy, and chemical cauterization have been reported with variable success, remission, and recurrence rates.[27,28] Following recent accounts of successful use of cyclosporine therapy with remission rates of 72% to 100%,[3,29] current therapeutic approaches have been aimed at blunting the immune response that appears to be at the core of disease development.

Immunomodulating drug therapies have been used in PF dogs, including high-dose glucocorticoids,[8] cyclosporine,[3,4,9,10,29] tacrolimus,[12] and azathioprine (alone or in combination with antibiotics or prednisone).[11,13,26,29] Low-dose prednisone therapy has been recommended for the initial treatment of the inflammatory component of PF, but as with other earlier medical therapies, low doses of prednisone were found to have mostly a palliative effect.[2] Immunosuppressive doses of prednisone may be more effective, but only 33% of dogs in one study achieved resolution of disease.[8] Topical tacrolimus, a potent immunosuppressive medication, achieves a resolution of lesions in 50% of dogs and improvement in as many as 90% of dogs.[12] Although this approach may provide a viable alternative to other therapies, it is likely to be effective only in dogs with mild to moderate PF, and therefore is not recommended for use in dogs with more severe forms of the disease. Cyclosporine therapy may be the best therapeutic option for this disease. Early studies of cyclosporine showed that upward of 85% of dogs had complete healing with several weeks of therapy.[9] Several other studies of cyclosporine, either alone or in combination with ketoconazole or other therapy (including surgery), confirmed the efficacy of cyclosporine in the treatment of canine PF.[3,4,10,26,30,31] Success rates of 60% to 98% with cyclosporine have been reported, but most studies also revealed that when the drug was discontinued, recurrence rates were very high, confirming the presence of ongoing immune dysfunction. One of the persistent problems with use of cyclosporine in the treatment of this condition in dogs is the very high cost of the drug—both for the medication, and for the drug-level monitoring that is recommended to assure proper dosing. One approach to reduce the cost of cyclosporine therapy is to combine cyclosporine with ketoconazole. Because cyclosporine is transformed by the hepatic cytochrome P450 3, a mixed-function oxidase, addition of ketoconazole to the therapy acts to competitively inhibit this pathway and effectively increase the half-life of cyclosporine in dog.[30] As a result, using this combination of drugs results in an equivalent therapeutic responses, but at a reduction in cost of 50% to 60%.[3,30] In another study, investigators showed that cyclosporine at a dose rate of 5 mg/kg q24h is effective in reducing the surface area and severity of lesions in dogs with PF.[10] However, an important finding in that study is that doses less than 5 mg/kg q24h are ineffective in resolving PF lesions. Thus, in dogs that are intolerant of ketoconazole combined with cyclosporine, single-dose therapy can be used at a slightly lower dose to make the therapy more cost-effective. Finally, because of the high recurrence rate and, in some dogs, incomplete resolution of lesions, studies have investigated using immunosuppressive therapy with concurrent surgical excision of affected tissues as a combination approach.[5] In a recent study, cyclosporine therapy was administered for up to 12 weeks followed by surgical excision of any remaining draining tracts, along with cryptectomy and anal sacculectomy.[26] In that study, all 18 dogs were reported to have resolution of the disease, and only one of the 18 had recurrence of the disease 9 months after completion of the therapy and surgery.[26] This result suggests that there may be significant merit to using the combination of immune suppression and removal of diseased tissue to achieve the best long-term resolution.

Prognosis

The overall prognosis should be considered guarded in dogs with perianal fistulas, even though most methods, whether medical or surgical, have met with some degree of long-term success. The most common complications of surgical approaches are recurrence and fecal incontinence; thus, for most dogs, medical therapy with cyclosporine alone or in combination with ketoconazole should be used as the first-line approach, followed by surgical resection of residual diseased tissue once immune suppression achieves its fullest extent. In this scenario, with less-invasive surgery required, the risk of severe complications, such as fecal incontinence, is reduced, but this also increases the chances of a prolonged remission in affected dogs.

INFECTION

Debra L. Zoran

There are several common diseases affecting the anal sacs, including anal sac impaction, anal sacculitis, and abscessation of the anal sacs. Although each of these may present as different diseases, they likely are variations of the same disease process. These diseases are more common in dogs than in cats, and affect up to 12% of the canine population.[1,2]

Etiology

The initiating events and exact cause of anal sac disease are unknown in many instances. Nevertheless, a variety of contributing factors likely play contributing or causative roles, including fecal consistency, inactivity, diet, body weight, pudendal nerve dysfunction, generalized seborrheic disorders causing increased anal sac secretions, perianal fistulas or intestinal inflammatory disease, and previous perineal surgery resulting in scar tissue that disrupts normal anal sac function.[3-5] In some breeds, such as German Shepherd dogs, the anal sacs lie deeper in the perianal tissues near the rectum, and as a result, may predispose them to an increased risk of impaction or infection within the sac.[5] Small-breed dogs, on the other hand, may have an increased risk of anal sac disease because of anatomically small ducts emptying the sacs that are more likely to become obstructed if anal sac secretions become thicker than normal.[5,6] Finally, any inflammatory disease occurring in the region (proctitis, perianal fistulas, or dermatitis) can result in secondary inflammation of the anal sacs, leading to anal sacculitis or subsequently abscess formation.

Pathogenesis

The most common cause of inflammation or infection of the anal sac is ductal obstruction, which prevents normal secretion and permits proliferation of bacteria and secondary infection. Bacterial species commonly found in the normal canine anal sac include *Streptococcus faecalis*, *Streptococcus faecium*, *Escherichia coli*, *Bacillus* spp., *Clostridium perfringens*, *Staphylococcus intermedius*, and *Proteus* spp.[1,7] In dogs with pyoderma, a significant increase (from 10% to 30%) in the carriage of *S. intermedius* in the anal sacs has been reported.[7] In addition to these bacteria, yeast (e.g., *Malassezia pachydermatis*) are often found in anal sacs, often as opportunistic pathogens.[7] Dogs with atopic dermatitis have also been found to have higher numbers of bacteria and yeasts in their anal sacs, which could predispose them to an increased incidence of infection and anal sacculitis. Anatomic conformation may play an important role in the tendency to develop anal sacculitis or abscessation, such as small ductal anatomy or aberrant duct placement on the anus that decreases effective emptying. Other contributing factors may include secretions that are thicker than usual, development of abnormal anal tone, production of soft feces, and recent estrus in females.[5] Anal sac infection or anal sacculitis can culminate in anal sac abscessation if the secretions and bacteria are retained with ductal obstruction. In dogs with anal sac abscesses, the most common bacteria isolated are *E. coli* and *Proteus* spp.[8] If the duct is completely obstructed, infection will eventually extend beyond the wall of the sac (anal sacculitis) into the surrounding perineal tissues to induce cellulitis and abscess that will eventually rupture through the skin and perineal tissues via draining tracts. The purulent, malodorous, and often bloody discharge will drain once the abscess ruptures, but the surrounding cellulitis may cause significant pain and swelling of the area. In dogs with recurring episodes of anal sacculitis or impaction that are poorly responsive to medical management, surgical correction with anal sacculectomy should be considered.

Clinical Examination

The most commonly reported clinical signs of anal sac disease are associated with anal pruritus or pain: licking or biting at the tail base or anal region, "tail chasing" behavior, scooting or rubbing the anus on the ground, reluctance to sit, and discomfort when sitting.[3,5,8] In more severely affected cases, dyschezia, tenesmus, or reluctance to defecate may result from severe pain. Dogs with long-standing anal sac disease may develop large swellings in the area over the anal sac, and if the abscessed sac ruptures, a draining fistula will be present extending from the affected anal sac.

External or internal digital palpation of the anal sacs may be required in some cases to determine the presence of diseased or impacted anal sacs in some dogs. Normal anal sac secretions are liquid, brown, and foul smelling, but are easily expressed from the sac through ductal openings on the anus. In dogs with anal sac impaction, the material often becomes pasty or even dried, and may be very difficult to express without the animal experiencing severe pain. The material present in infected or abscessed anal sacs is often thicker, may be purulent or bloody, and is frequently very malodorous.

Diagnosis

In most dogs, anal sacculitis is suggested by the history of anal pruritus along with either palpable or visual inspection of a perianal swelling at either the 4 o'clock or 8 o'clock positions lateral to the anus. In the absence of significant external evidence of anal sac enlargement, a digital rectal examination is sufficient to confirm the presence of an enlarged, often painful, anal sac(s). Some dogs, and all cats, will require sedation to safely perform a rectal examination because of the accompanying discomfort. Impaction of the anal sacs is confirmed by expression of thick, pasty anal sac material, or inability to easily empty the sacs with otherwise appropriate technique. If the anal sacs are painful when gently palpated, or the material expressed is bloody or purulent, anal sacculitis should be suspected, but not confirmed until cytologic examination finds the presence of a large number of red blood cells and intracellular bacteria in neutrophils.[7,9] If the anal sac is abscessed or the surrounding tissues severely infected, fever may be present. An unruptured anal sac abscess presents in affected dogs as a painful, perianal swelling in the region of the anal sac that cannot be expressed using appropriate technique. In dogs with long-standing anal sac abscessation, the skin overlying the sac will be thin, edematous, erythematous, and painful to the touch (Figure 59-5). If the abscess is untreated, the infection will erode through the skin leaving a draining tract surrounding the infected tissues (Figure 59-6). The major differentials to consider in dogs with these clinical signs include perianal fistulas, perianal or anal tumors, bite wounds or other trauma (especially in cats), and in the female dog, the possibility of vaginal infection.

Treatment

Treatment of simple anal sac impaction is straightforward, requiring that both of the anal sacs be manually emptied by gentle digital manipulation of the sac during digital rectal examination. If the sacs

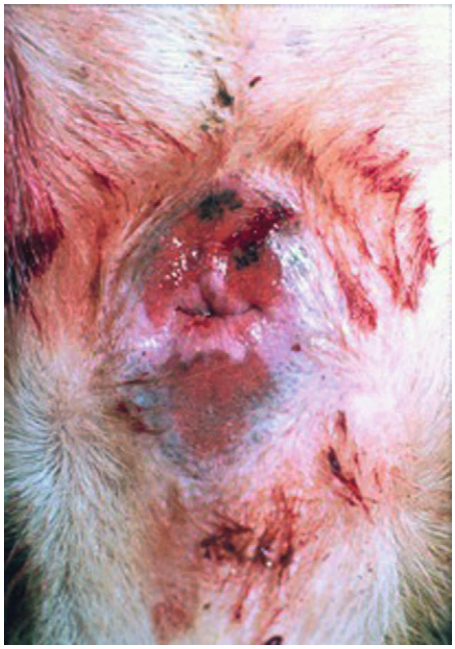

Figure 59-5 Anal sac swelling.

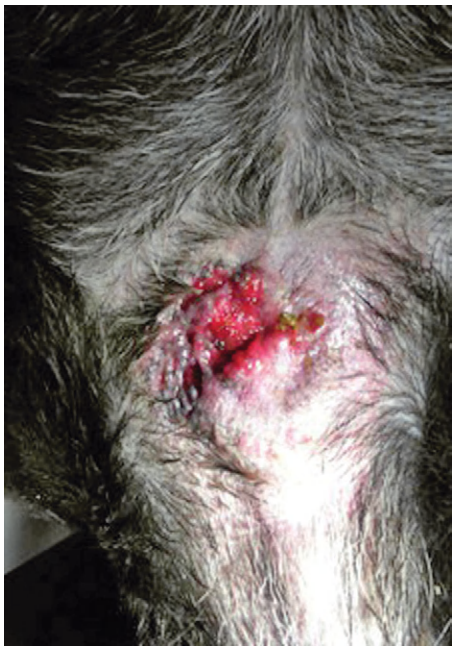

Figure 59-6 Open, draining tract associated with an anal sac abscess that has ruptured.

cannot be easily or completely emptied, the sacs should be gently flushed with warm saline or mineral oil to loosen concretions and pasty material. Once the sacs are emptied, an antibiotic and steroid ointment or solution can be instilled into the sac to reduce local infection and inflammation. If possible, the anal sacs should be emptied by frequent gentle expression for several weeks to prevent recurrence or possible abscessation. In dogs with chronic impactions, pet owners can be shown how to digitally express the anal sacs at home, or the anal sacs can be surgically removed.

Dogs with anal sacculitis or abscessed anal sacs must have expression of the anal sacs, but because of the associated discomfort, sedation or anesthesia is usually required. In dogs with anal sacculitis alone, the sacs should be gently flushed with an antiseptic solution, such as dilute (0.5%) chlorhexidine, and then antibiotic solution instilled into the sacs.[10] Broad-spectrum, oral antibiotic therapy is recommended for 10 to 14 days, along with hot compresses to reduce swelling and pain, and at least weekly emptying of the anal sacs. Antiinflammatory therapy in the form of topical steroids or short-term oral prednisone may be needed to reduce the inflammatory process associated with infection. In the majority of cases managed this way, inflammation and infection resolve and further therapy is not necessary. For dogs with recurring bouts of anal sacculitis, anal sac surgery and removal should probably be considered. Abscessation of the anal sacs is managed as for other abscessed tissue: the abscess must be surgically opened, flushed, and debrided. Even in dogs or cats where the abscess has already opened, the affected area must be flushed and debrided to remove any remaining necrotic and infected tissue. This procedure should be repeated daily for 2 to 4 days to help keep the area open and draining, as well as to help remove any additional material forming in the sacs. Antibiotic therapy should be administered for 10 to 14 days, using a broad-spectrum antibiotic, and preferably based on culture of the contents if the dog has had repeated episodes of anal sac disease requiring antibiotic therapy. Application of hot compresses several times daily for 3 to 5 days will also help reduce the swelling and pain associated with the abscess. As with anal sacculitis, surgical removal of the anal sac is not recommended unless there is recurrence following otherwise appropriate therapy. Surgery should not be performed on the abscessed anal sac until antibiotic therapy has been administered to assure resolution of infection. In general, anal sac removal is recommended only when all other options fail, primarily because of the risk of complications, especially fecal incontinence.

Anal sacculectomy can be performed via either open or closed techniques. Preservation of the caudal rectal artery and pudendal nerve during the surgical procedure is crucial to maintain anal sphincter function. The open technique of anal sac resection is associated with a greater number of complications compared with the closed or modified technique.[11] The closed technique using a Foley catheter to distend the anal sac for visualization during removal appears to facilitate the delineation of the sac and surrounding surrounds, so that the risk of surgical trauma to important vascular and neural structures is greatly reduced.[12]

Prognosis

The prognosis for anal sac impactions and anal sacculitis is generally very good, as they typically respond completely to appropriate medical management. Most dogs or cats with anal sac abscesses also respond well to aggressive medical management, but because they may be more difficult to treat or recur, surgical anal sac removal may be required. The prognosis for animals requiring anal sacculectomy is fair to good when the surgery is performed by an experienced surgeon using techniques designed to reduce the risk of damage to the external sphincter or the associated blood vessels and nerves in the region that control its function. However, even with all due precautions taken, the risk of fecal incontinence cannot be ignored, especially in older dogs who may already have some reduced anal sphincter tone or function, or in dogs that have had significant disease in the area that makes the surgical procedure more difficult.

OBSTRUCTION

Robert J. Washabau

Diseases of the Rectum

Perineal Hernia

Etiology

In dogs, perineal hernia is characterized by disruption of the muscles of the pelvic diaphragm and herniation of the rectum and other pelvic organs (e.g., urinary bladder, prostate) into the ischiorectal fossa.[1] Four types of perineal hernia have been described, but the most common form is the caudoventral perineal hernia, a hernia that develops between the levator ani, external anal sphincter, and internal obturator muscles.[2] Perineal hernia is a condition seen almost exclusively in intact male dogs with a mean age of approximately 8 years; it has been reported in female dogs on rare occasions.[2] Perineal hernia is a rare occurrence in the domestic cat. The pathogenesis of perineal hernia appears to differ between the two species. It is associated with neurogenic atrophy of the levator ani in the dog,[1] whereas in the cat it is often a secondary lesion associated with perineal urethrostomy or idiopathic megacolon.[3]

History and Physical Examination

Dogs with perineal hernia present with one or more of the following complaints: a reducible perineal swelling, tenesmus, dyschezia, constipation, and obstipation. Perineal swelling and tenesmus are reported in 90% to 95% of affected dogs.[2] The perineal swelling is usually ventrolateral to the anus on one side, but severely affected dogs may have bilateral ventral swellings (Figure 59-7). Some dogs have signs of acute urethral obstruction because of retroflexion of the urinary bladder into the perineal hernial space. Tenesmus and constipation are reported in 95% of affected cats; perineal swellings are reported only 22% of the time.[3]

Physical examination findings are usually straightforward. A hernial sac is palpated externally in some cases. Rectal examination reveals a defect in the pelvic diaphragm, confirming the diagnosis. In the dog, perineal hernia contents include, in order of prevalence, retroperitoneal fat, serous fluid, rectum, prostate, urinary bladder, and small intestine.[2] Herniation of peritoneal contents appears to be relatively rare in cats.[3]

Diagnosis

History and physical examination findings are usually sufficient in making a diagnosis of perineal hernia. A hernial defect may be palpated externally, just lateral to the external anal sphincter. Digital palpation of the rectum and anal canal confirms the presence of unilateral or bilateral hernia. Rectal wall abnormalities may also be present (e.g., rectal deviation, sacculation, or diverticulum).

Pathogenesis

The pathogenesis of the disorder is incompletely understood. Anatomic factors, gonadal hormonal imbalance, lesions of the pudendal nerve, and excessive straining because of prostatic or rectal disease have all been cited as factors important in the pathogenesis of the disease. A predisposition in brachycephalic breeds suggests that inherent anatomic defects may contribute to the disease. Boston Terrier, Boxer, Welsh Corgi, and Pekingese breeds are all at apparent increased risk for perineal hernia.[2] As the levator ani is frequently atrophied, it has been suggested that the muscles of the pelvic diaphragm (levator ani, coccygeus) are inherently weakened in these breeds.[2]

Gonadal hormonal imbalance has been proposed as a pathogenesis because greater than 95% of cases are older male dogs, and because of the protective effect of castration reported in some studies.[2] It has been suggested that either excessive production of estrogens or diminished production of androgens by the aging testes results in atrophy and weakening of the muscles of the pelvic diaphragm.[1,2] Evidence in support of this idea comes from studies in female rats showing that testosterone administration prevents involution of the levator ani. However, serum testosterone and 17β-estradiol concentrations in dogs with perineal hernia do not

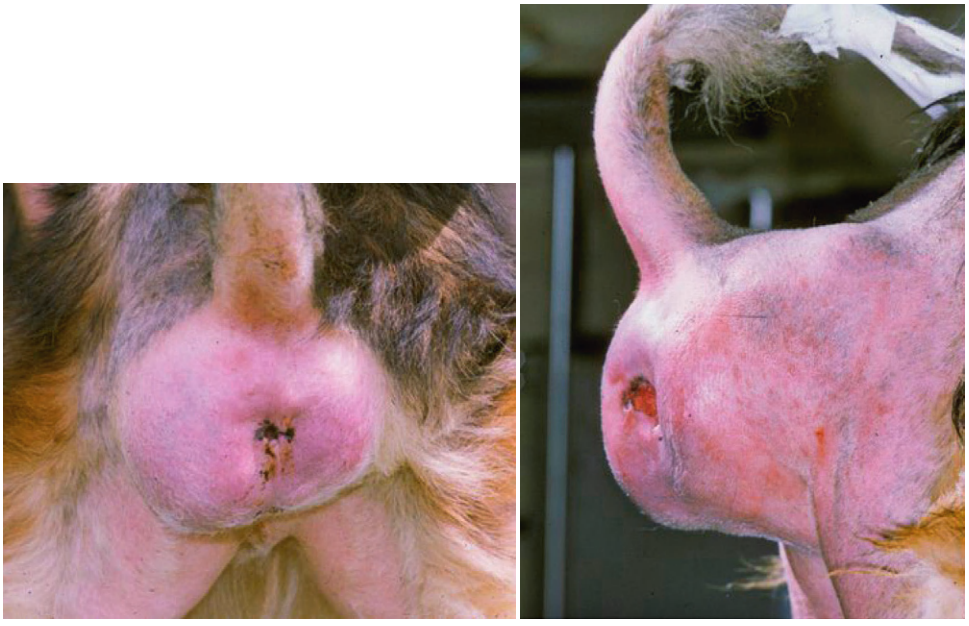

Figure 59-7 Severe bilateral perineal herniation in a dog. (Reprinted with permission from Craven M: Rectoanal disease. In: Ettinger S, Feldman EC, editors: *Textbook of Veterinary Internal Medicine*, ed 7, St. Louis, 2010, Elsevier, p 1598.)

differ from those of normal dogs of the same age and gender.[4] Furthermore, the putative beneficial effects of castration on perineal hernia have not been substantiated in other studies.[2] In a retrospective study of cats affected with perineal hernia, 19 of 20 (95%) cats were either castrated or spayed, suggesting that gonadal hormones are unimportant in this species.[3] It is possible that hormones other than estrogens or androgens are involved. It has been suggested, for example, that the peptide hormone relaxin of prostatic origin may cause weakening of the pelvic diaphragmatic musculature in the dog through a local paracrine effect.[5-7] More recent studies suggest that levator ani dysfunction in canine perineal hernia is associated with increased expression of epidermal growth factor, caspase-3 activation, and decreased expression of transforming growth factor-α, resulting in the further weakening of the levator ani.[8]

Lesions of the pudendal nerve have been suggested as the pathogenesis because of histopathologic evidence of neurogenic atrophy of the levator ani in many dogs affected with perineal hernia.[2] This finding has been substantiated by other histopathologic studies as well as by electrophysiologic evidence (e.g., fibrillation potentials, positive sharp waves, fasciculation potentials, and complex repetitive discharges) of neurogenic atrophy of the levator ani, coccygeus, and anal sphincter muscles.[1] Although it can be concluded that damage to the first, second, and third sacral nerves or to the pudendal nerve or its muscular branches is an important aspect of perineal hernia, it is not known whether nerve damage precedes development of perineal hernia.[1] It is entirely possible that nerve damage follows or occurs as a result of perineal hernia. For example, tenesmus resulting from prostatic disease may cause traction of the nerves of the sacral plexus, and thus prevention or relief of straining could have a role in preventing ·or retarding the progression of development of perineal hernia.[2] It should be noted, however, that dogs with perineal hernia have a rather low incidence of prostatic disease.[9] The exact role of pudendal nerve lesions in the pathogenesis of perineal hernia will require further investigation.

Preexisting rectal disease might be a risk factor for perineal hernia. Rectal sacculation and rectal diverticulum have been reported in the absence of perineal hernia and thus could precede the development of perineal hernia.[2] However, many dogs with perineal hernia do not have such rectal wall abnormalities.[9] Rectal wall abnormalities such as sacculation and diverticula are more frequent in long-standing perineal hernias than in recent perineal hernias, suggesting that rectal disease is a consequence, rather than a cause, of perineal hernia.

Perineal urethrostomy, which causes disruption of the fascial connections between the external anal sphincter and medial coccygeus, and idiopathic megacolon are definite risk factors for the development of perineal hernia in the cat.[3]

Therapy

Medical therapy may be attempted in mild cases of perineal hernia. It has been anecdotally reported that 20% of dogs can be maintained free of signs by the use of fecal softeners and occasional enemas.[10] However, the pet owner should be advised that the signs may become refractory to medical therapy, and that urinary bladder retroflexion can occur at any time.

Herniorrhaphy is indicated for most cases of perineal hernia. In the standard herniorrhaphy technique, the external anal sphincter is approximated to the coccygeus dorsally and laterally, the internal obturator muscle ventrally, and the sacrotuberous ligament laterally.[2] The technical deficiencies of this method are the deformity of the external anal sphincter and the inability to obliterate large ventral hernias. The internal obturator transposition technique overcomes some of these deficiencies by elevating the obturator muscle from the ischium and suturing it to the external anal sphincter medially and to the sacrotuberous ligament laterally. Excellent results have been reported with this technique.[11] Several modifications to this widely accepted technique have been proposed. If the internal obturator is thin or friable, it has been suggested that fascia lata graft be used during primary repair of the hernia.[12] Porcine small intestinal submucosa as a biomaterial has also been used successfully for perineal hernia repair in dogs in which the internal obturator is excessively thin or friable.[13] It should be emphasized that regardless of the technique, improved outcomes may be obtained in some patients in which concomitant lesions (rectal, prostatic, bladder) are first treated in a staged laparotomy approach.[14]

Rectal diverticula should be corrected at the time of surgery. Surgical correction of rectal deviation and sacculation is controversial and may not be warranted. Routine castration of all perineal hernia patients is also controversial. Because there are few contraindications to castration, it may be performed unless it unnecessarily prolongs anesthesia in a high-risk patient.

Cats in which idiopathic megacolon appears to be the primary problem, with secondary development of perineal hernia, probably should be treated with subtotal or total colectomy.[3]

Prognosis

The prognosis for successful repair of long-standing perineal hernias is still guarded. These patients may suffer from rectal wall abnormalities, atrophy of the pelvic diaphragmatic musculature, and large ventral hernias that are not easily repaired by the standard technique. The recurrence rates in these patients have been variably reported to be between 10% and 46%.[9] Patients with perineal hernias of shorter duration have much better prognoses.

Rectal Tumors

Etiology

Primary tumors of the rectum are uncommon in small animals. However, tumors of the colon and rectum represent 36% to 60% of all canine and 10% to 15% of all feline alimentary tract neoplasms.[10,15] The most common tumors of the rectum are benign adenomatous polyps. Polyps of the rectal mucosa are usually focal, pedunculated, or sessile tumors that do not metastasize (Figure 59-8). Occasionally, these rectal polyps invade the lamina propria and submucosa and, although they appear histologically benign, are referred to as carcinoma in situ. These tumors may have a greater propensity for metastasis. Colorectal adenocarcinomas tend to spread beyond the rectal wall to regional lymph nodes, liver, and lung. It has been suggested that, as in humans, the rectal polyp may represent a precancerous lesion.[10,15] Colorectal adenocarcinoma would represent the endpoint in this polyp-cancer sequential hypothesis. However, circumstantial evidence for such a sequence of events has been documented in only a few cases,[10] thus polyps and adenocarcinomas may have entirely different pathogeneses in dogs and cats.

Other tumors that have been reported in the rectum include leiomyoma and leiomyosarcoma, lymphosarcoma, plasmacytoma, and fibrosarcoma.[15,16] Colonic and rectal lymphosarcomas are the most common colorectal tumor of the cat. Most of these tumors occur in the ileocecal sphincter of the cat.[10] Colorectal lymphosarcoma is less common in the dog, but most of these occur in the rectum. Extramedullary plasmacytomas are an uncommon tumor of the gastrointestinal tract, but many of these also occur in the large intestine and rectum.[17] All of the aforementioned tumors are associated with signs of inflammation and obstruction (e.g., hematochezia, tenesmus, and dyschezia). Carcinoids (rare 5-hydroxytryptamine

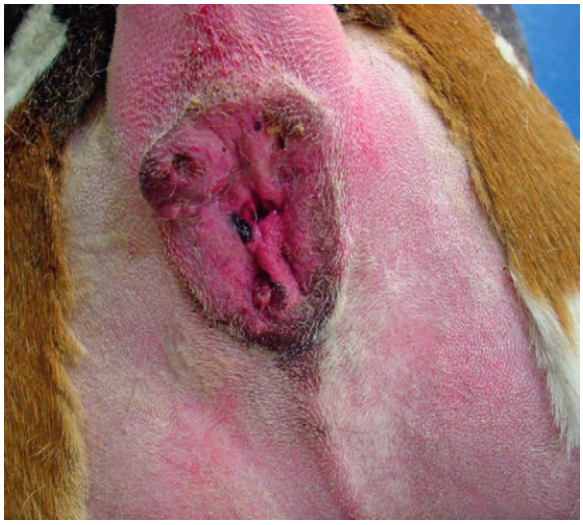

Figure 59-8 Perianal adenoma in a male dog. (Reprinted with permission from Craven M: Rectoanal disease. In: Ettinger S, Feldman EC, editors: *Textbook of Veterinary Internal Medicine*, ed 7, St. Louis, 2010, Elsevier, p 1606.)

[5-HT]-secreting tumors) are occasionally associated with diarrhea because of the effects of 5-HT on secretion and motility (see Chapter 58).

History and Physical Examination

Most affected animals have signs of hematochezia, mucoid feces, tenesmus, and dyschezia of varying severity. Other signs depend on the tumor type and location. Malabsorption and cachexia, for example, may be observed when tumors (e.g., lymphosarcoma) concurrently involve the proximal gastrointestinal tract.

Digital rectal examination typically reveals a prominent mass involving the rectal mucosa or submucosa, narrowing of the rectal lumen, pain on palpation, and blood or mucous. An annular stenotic lesion ("napkin-ring lesion") is often suggestive of a colorectal adenocarcinoma. Colonic distention might be detected on abdominal palpation in such animals owing to partial to complete obstruction of the rectal lumen. These animals may develop rectal prolapse as a consequence of severe tenesmus.

Diagnosis

A rectal mass can usually be palpated on digital rectal examination. Survey and contrast radiography may do little more than confirm the physical examination findings. Intrarectal ultrasonography is increasingly importance in the evaluation of these lesions. In experimental models of rectal tumors in dogs, for example, intrarectal ultrasonography was accurate in assessing depth of wall penetration of rectal tumors as well as the involvement of pararectal lymph nodes.[18] Proctoscopy and biopsy are required for definitive diagnosis. Mucosal tumors are readily diagnosed by proctoscopic biopsy, but submucosal tumors (e.g., lymphosarcoma) may require pararectal aspiration or incisional biopsy for diagnosis.

Pathogenesis and Therapy

The pathogenesis of rectal tumors is poorly understood. Tumors of the rectum are likely to have a multitude of inciting etiologies.

Tumors of the rectum, excluding lymphosarcoma, are best treated by complete surgical excision. Good to excellent results with few recurrences are generally obtained with resections of rectal polyps or carcinoma in situ. Radical full-thickness resection of adenocarcinomas has been recommended in the past, but wound dehiscence, infection, rectal stricture, and fecal incontinence have been reported with radical excision,[19-21] and for that reason several alternative procedures have been recommended, including cryosurgery,[19] transanal pull-through procedures,[22,23] transanal endoscopic resection,[24] carbon dioxide laser surgery,[25] and photodynamic therapy with motexafin lutetium.[26]

Rectal lymphosarcomas are probably best treated initially with chemotherapy. Local resection could be recommended in an animal's failing chemotherapy.

Prognosis

The prognoses for rectal polyps, carcinoma in situ, leiomyomas, and fibromas are generally favorable. Adenocarcinomas, lymphosarcomas, and plasmacytomas tend to recur. Dogs with annular colorectal adenocarcinomas have a particularly poor prognosis with a mean survival time of only 1.6 months.[19]

Rectal Foreign Bodies

Ingested sticks, bones, and metal may traverse the entire alimentary tract with only minor pathology before lodging in the rectum and causing painful obstruction. Rectal foreign bodies are usually diagnosed and removed during digital examination, although general anesthesia may be required because of extreme pain. Foreign bodies in the rectum are probably the most important cause of proctitis in the dog.[27] Complications of rectal foreign bodies include rectal fistula and perirectal abscesses if the rectal wall is compromised.[27] Secondary colonic impaction may also develop in animals that suppress defecation.

Rectal Prolapse

Etiology

Rectal prolapse is a protrusion of one or more layers of the rectum through the anal orifice. The prolapse may be partial or complete, depending on which structures are involved. In partial rectal prolapse, only the rectal mucosa protrudes through the anal orifice, whereas in complete prolapse, all layers of the rectum are involved. Occasionally, a portion of the anal canal also prolapses.

History and Physical Examination

Neither breed nor sex predilections have been described, although several authors anecdotally report an increased incidence in younger animals.[10,28] Affected animals often have an antecedent history of dyschezia and tenesmus associated with anorectal or colonic inflammatory disease (e.g., typhlitis, colitis, or proctitis). Other cited predisposing factors include tumors of the colon, rectum, and anus; rectal foreign bodies; perineal hernia; cystitis; prostatitis; urethral obstruction; and dystocia.[10,27,28] Relative risks for each of these conditions have not been determined, however. In general, rectal prolapse is uncommon, even in animals with long-standing dyschezia and tenesmus.

On physical examination, an elongated, cylindrical mass is evident with complete prolapse of the rectum. Only the rectal mucosa is evident with partial rectal prolapse.

Diagnosis

The presence of an elongated, cylindrical mass protruding from the anal orifice is usually diagnostic. However, this protrusion must be carefully differentiated from a prolapsed ileocolic intussusception (see Chapter 58). Differentiation may be made by passing a well-lubricated finger between the prolapsed mass and anus. With a

prolapsed ileocolic intussusception, the finger may be easily passed 5 to 7 cm further into the fornix than in rectal prolapse. Contrast radiography usually differentiates these two conditions.

Pathogenesis

Because of the low incidence of rectal prolapse even in animals with long-standing dyschezia and tenesmus, it has been suggested that an individual predisposition must be present to contribute to the development of prolapse.[27] Contributing factors were held to be weakness of the perirectal and perianal connective tissues or musculature, uncoordinated peristaltic contractions, and/or inflammation and edema of the rectal mucosa.[27] None of these putative factors have been rigorously investigated, however.

Therapy

Therapy and prognosis depend on recognition of the underlying etiology, degree of prolapse, time elapsed since the prolapse, tissue viability, and the recurrence rate of previous prolapses.[27,28] Incomplete rectal and anal prolapses are usually easily reduced manually with the aid of saline compresses or lubricants.[27] A purse-string suture may be placed if a tendency toward recurrence seems obvious. Topical corticosteroid creams or lotions are useful in treating concurrent proctitis/anusitis.

Complete rectal prolapses characterized by short duration and good tissue viability are probably best managed by manual reduction and placement of an anal purse-string suture. It has been suggested that colopexy be considered in animals suffering from multiple recurrences, or in cases in which manual reduction is impossible.[10] Prolapses of longer duration, in which there is substantial tissue devitalization, should instead be managed either by mucosal resection or complete resection and anastamosis.[27,28] Because of postoperative stricture formation, complete resections and anastomoses are not recommended in cats. Colopexy is currently recommended for cats suffering from rectal prolapse.[27,28] In any case, postoperative management should consist of high-fiber diets and bulk (psyllium) or emollient laxatives (dioctyl sodium or calcium sulfosuccinate) to soften the feces.

Prognosis

Incomplete prolapses, prolapses of short duration, and first occurrences all carry a good prognosis. Complete prolapses, prolapses of longer duration, and multiple recurrences carry a more guarded prognosis. Prolapses requiring complete rectal resection carry a worse prognosis because of the possibility of rectal stricture formation.[20]

Rectal Stricture

Etiology

Rectal stricture is a narrowing of the rectal lumen that results from fibrosis or cellular proliferation. Fibrosing rectal strictures result from anorectal trauma or surgery, whereas proliferative rectal strictures typically result from cancer.

History and Physical Examination

There are no sex or breed predilections for rectal stricture. Rectal strictures do tend to occur in older animals, however, because of the increased incidence of rectal tumors and other anorectal disease.[10,27,28] Clinical signs vary with the severity of the lesion. Most animals have dyschezia, tenesmus, and passage of a thin ribbon of feces. Animals with inflammatory lesions of the anorectum have signs of hematochezia and diarrhea. The history may also provide evidence of recent anorectal trauma or surgery.

Digital rectal examination typically reveals a firm, circumferential fibrotic band in an animal with fibrosing stricture, or an asymmetric mass in an animal with rectal stricture resulting from cellular proliferation. Occasionally, annular strictures associated with colorectal adenocarcinoma are indistinguishable from fibrosing strictures associated with anorectal trauma or surgery.

Diagnosis

History and physical examination findings are usually sufficient in making a diagnosis of rectal stricture, although contrast radiography may be useful in identifying the proximal extent of rectal stricture. Intrarectal ultrasonography is likely to assume increasing importance in the evaluation of proliferative strictures (see "Rectal Tumors" above).[18] Proctocolonoscopy, while theoretically useful, has some practical limitations. The endoscope cannot be passed more than a few centimeters in some cases, and visualization of these lesions is difficult.[10,29] Furthermore, superficial endoscopic biopsies may not identify a tumor of the underlying submucosa or muscularis. Biopsy and histologic examination are recommended if there is any doubt about the pathogenesis of the lesion.

Pathogenesis

Fibrosing rectal strictures result from one of three possible entities: rectal inflammatory disease (e.g., perianal fistula, rectal foreign body, chronic anal sac disease), anorectal trauma, or anorectal surgery (e.g., perianal fistulectomy, rectal tumor resection). The fibrous tissue response usually involves the circumference of the rectum. Proliferative rectal strictures are most commonly associated with colorectal adenocarcinomas and, to a lesser extent, with invasive prostatic adenocarcinomas.[27] Obstruction, without stricture formation, occasionally occurs with rectal polyps or other mucosal tumors.

Therapy

Mild cases of rectal stricture have shown improvement with bougienage or balloon dilation, although the results may be only temporarily palliative.[27,28] Surgical correction is required in most cases. Surgery involves either myotomy of the rectal muscularis, a complete resection-anastomosis procedure, or a rectal pull-through procedure.[27,28,30]

Prognosis

Fibrosing rectal stricture would seem to have a better prognosis than proliferative rectal stricture based purely on biologic behavior. However, the prognosis is guarded to poor in both because of wound dehiscence, fecal incontinence, and recurrences of stricture that accompany attempts at surgical correction.[20]

Congenital Abnormalities of the Rectum

Rectovaginal Fistula and Imperforate Anus

Rectovaginal fistula is a rare congenital disorder of dogs and cats that may occur with or without imperforate anus.[31] Congenital abnormalities of the anus and/or rectum tend to occur in association with urogenital malformations as a consequence of abnormal embryonic development of the cloacal region.[31] In either case the vagina is contaminated with feces, resulting in vaginitis, vulvitis, and perivulvar and perianal dermatitis. Other physical examination findings may include abdominal distention and bulging of the perineum with concurrent imperforate anus. Diagnosis may be achieved either by vaginography or barium enema.

The treatment of rectovaginal fistula is surgical correction of the malformation. Surgical correction consists of excision of the fistula

with reconstruction of the rectovaginal shelf, and creation of a terminal opening for the intestinal tract.[27,28,32,33] The prognosis for return to normal anorectal function is guarded as animals with imperforate anus have an incomplete anal sphincter. Animals suffer postoperatively from fecal incontinence, wound dehiscence, and constipation.[20,27]

Rectal Vascular Ectasia

Rectal hemorrhage associated with vascular ectasia or angiodysplasia of the rectum has been reported in a young dogs.[34] Affected animals have intermittent and undiagnosed hematochezia for weeks to months. Attempts at resection of the affected segment may be complicated by postoperative fecal incontinence.

Diseases of the Anus

Anal Sac Tumors

Etiology

Although their incidence is low, neoplasms arising from the glandular epithelium of the anal sacs are almost invariably malignant adenocarcinomas. These tumors invade the surrounding soft tissues and frequently metastasize to regional lymph nodes. Anal sac adenocarcinomas have been reported in dogs but not in cats.

History and Physical Examination

Most studies report an older age distribution (>10 years) and a predilection for females, intact or spayed,[10,27] although one study reported an equal sex distribution.[35] No breed predispositions are reported. Dyschezia and a noticeable perineal swelling are the most frequent complaints made by pet owners, although anal sac tumors may occasionally be identified as an incidental finding during rectal examination.[36] This finding emphasizes the importance of rectal palpation as part of a complete physical examination. In some dogs, complaints of polyuria/polydipsia, muscular weakness, vomiting, and constipation may be made. These features are secondary to a paraneoplastic syndrome (humoral hypercalcemia of malignancy) sometimes associated with this tumor.[37,38]

Tumors of the anal sac are usually detected during routine anorectal examination. Most tumors are unilateral, although bilateral tumors have been reported.[36] The small size of some tumors (0.2 to 1.0 cm) belies their metastatic and paraneoplastic potential These tumors have often metastasized at the time of initial examination. The external iliac (sublumbar) lymph nodes are a common site of metastasis. The liver, spleen, and lungs are also occasionally involved. Many animals are systemically ill at the time of initial presentation because of the effects of hypercalcemia on kidney, nerve, and muscle function.

Diagnosis

Complete blood cell count, serum biochemistry, urinalysis, and survey radiographs of the chest and abdomen are warranted in any dog with a palpable anal sac mass. It is estimated that more than 50% of affected dogs have physical or radiographic evidence of metastasis at the time of presentation, and that 25% to 50% of affected animals are hypercalcemic and hypophosphatemic.[36]

Pathogenesis

The molecular events leading to the transformation of glandular epithelial cells to adenocarcinoma cells are poorly understood. The humoral hypercalcemia results from expression of the gene for parathyroid hormone-related protein, a peptide with biologic functions similar to those of parathyroid hormone.[37,38] The hypercalcemia mediated by this peptide may be severe enough to induce renal failure. If detected early enough, hypercalcemia may resolve following adequate resection of tumor mass, only to return with recurrence of metastases.

Therapy

Surgical excision of the primary anal sac mass is the recommended treatment for adenocarcinoma of the anal sac. Surgery is fairly straightforward, but postoperative complications have included wound infection and fecal incontinence in a small number of animals.[20,36] Excision of regional metastases has been advocated in several reports,[10,27,39] although one retrospective study of 32 cases of anal sac adenocarcinoma failed to demonstrate improved survival with excision of regional metastases.[36] The role of chemotherapy in the treatment of this disease remains controversial,[10,27] although responses to platinum chemotherapy have been reported.[40] Radiation therapy and immunotherapy have not proved useful in the treatment of this disorder.

Prognosis

Early, complete surgical excision of the primary tumor and regional lymph nodes is recommended as the treatment affording the best outcome.[41] Four negative prognostic indicators have been reported: lack of therapy, presence of distant metastases, presence of lymph node metastases, and primary tumor size.[39] Although controversial and incompletely studied, an association between hypercalcemia and survival has not been established.[40] Lymph node extirpation is a positive prognostic indicator.[39]

Anal and Perianal Tumors

Tumors of the anus and perianal integument are common in the dog. The perianal gland adenoma is a benign lesion arising from the circumanal glands of older intact male dogs. A number of other benign and malignant tumors also occur in the perianal region.

Perianal Gland Adenomas

Adenomas of the perianal glands (circumanal gland or "hepatoid cell" adenomas) affect all breeds, and breed predispositions have been reported in the Cocker Spaniel, Bulldog, Beagle, and Samoyed breeds.[10,27] Development and growth of these tumors seem to be closely related to plasma androgen levels. Thus, 85% of perianal gland adenomas are found in older intact male dogs.[10,27,28] Most of these tumors occur in the perianal integument, but they may also be found in the prepuce, inguinal area, thighs, and ventral skin of the tail root. The majority are firm, single or multiple nodular masses of variable size, but some may eventually ulcerate, bleed, and necrose. They may cause an intensely pruritic anusitis and eventually interfere with defecation. Aside from these features, perianal adenomas are neither invasive nor metastatic.

These tumors can be effectively treated by surgical excision.[27,28] Radiation therapy and cryosurgery are reported to be as effective as surgery.[27,28] Regardless of the technique employed, affected dogs should be castrated because of the androgen-dependence of the tumor. Castration causes regression of existing tumors and reduces the risk of new tumor growth.[27] Estrogen therapy could be considered if the pet owner is unwilling to accept castration; however the myelosuppressive effects of estrogens make this option much less desirable.

Other Perianal Tumors

With the exception of the perianal gland adenoma, other neoplasms are infrequently seen in the perianal area. Adenocarcinomas of the perianal glands, for example, are rare. Other tumors arise from glandular structures such as sweat glands and sebaceous glands or from any other cell type commonly found in the skin and subcutis. Thus, fibromas, lipomas, trichoepitheliomas, melanomas, and squamous cell carcinomas have all been described in the perianal area.[16,27] Anal squamous cell carcinomas, and melanomas to a lesser extent, are highly invasive and metastatic.[27]

DYSMOTILITY

Robert J. Washabau

Fecal incontinence in dogs and cats is defined as the inability to control defecation and retain feces until voluntary, conscious defecation is initiated. Incontinence of feces may result from *reservoir* or *sphincter* incontinence and either condition may be transient or permanent. Reservoir incontinence occurs when there is a reduction in the reservoir capacity of the colon best typified by total or subtotal colectomy.[1,2] Affected animals defecate more frequently, as fecal storage capacity is diminished. This is not an uncommon finding in cats undergoing subtotal colectomy for the treatment of idiopathic megacolon.[3] Sphincter incontinence, on the other hand, results from denervating lesions of the external anal sphincter (called neurogenic sphincter incontinence) or with primary external anal sphincter injury (called non-neurogenic sphincter incontinence). Affected animals experience unintentional anal dribbling. In general, sphincter incontinence is usually more severe and more permanent than reservoir incontinence; consequently the rest of this discussion is devoted to sphincter incontinence. The reader is referred to Chapter 14 for details of the medical workup of sphincter incontinence.

History and Physical Examination

Animals with sphincter incontinence have uncontrolled flatus, accumulate fecal material at the anal opening between defecations, involuntarily eliminate feces with excitement, and have constant anal dribbling. Some animals may be concurrently affected with urinary incontinence. Concurrent urinary incontinence would implicate a neural lesion since micturition and defecation share common neural pathways and regulation.[4-6]

Digital rectal palpation usually reveals a subjective sense of decreased tone of the anal sphincter and rectum in most cases of neurogenic and nonneurogenic sphincter incontinence. Injuries to the external anal sphincter (e.g., perineal surgery, trauma) may be evident in some dogs with nonneurogenic sphincter incontinence. Dogs with neurogenic sphincter incontinence may evidence other neurologic deficits (e.g., hind limb paresthesia or hyperesthesia, gait abnormalities, lumbosacral pain, large atonic bladder, and depressed myotatic reflexes).[7,8] The anal and pudendoanal reflexes should be assessed to determine the integrity of the reflex arcs involving the perineal afferent fibers, sacral spinal segments, pudendal efferent fibers, and external anal sphincter. The anal reflex may be evaluated by pinching the perianal skin and observing contraction of the external anal sphincter. The pudendoanal reflex in a male dog may be evaluated by applying digital pressure to the penis and observing similar contractions of the anal sphincter. These reflexes may be diminished or absent in animals with neurogenic sphincter incontinence. Figure 59-9 outlines the differentiation of neurogenic and nonneurogenic sphincter incontinence.

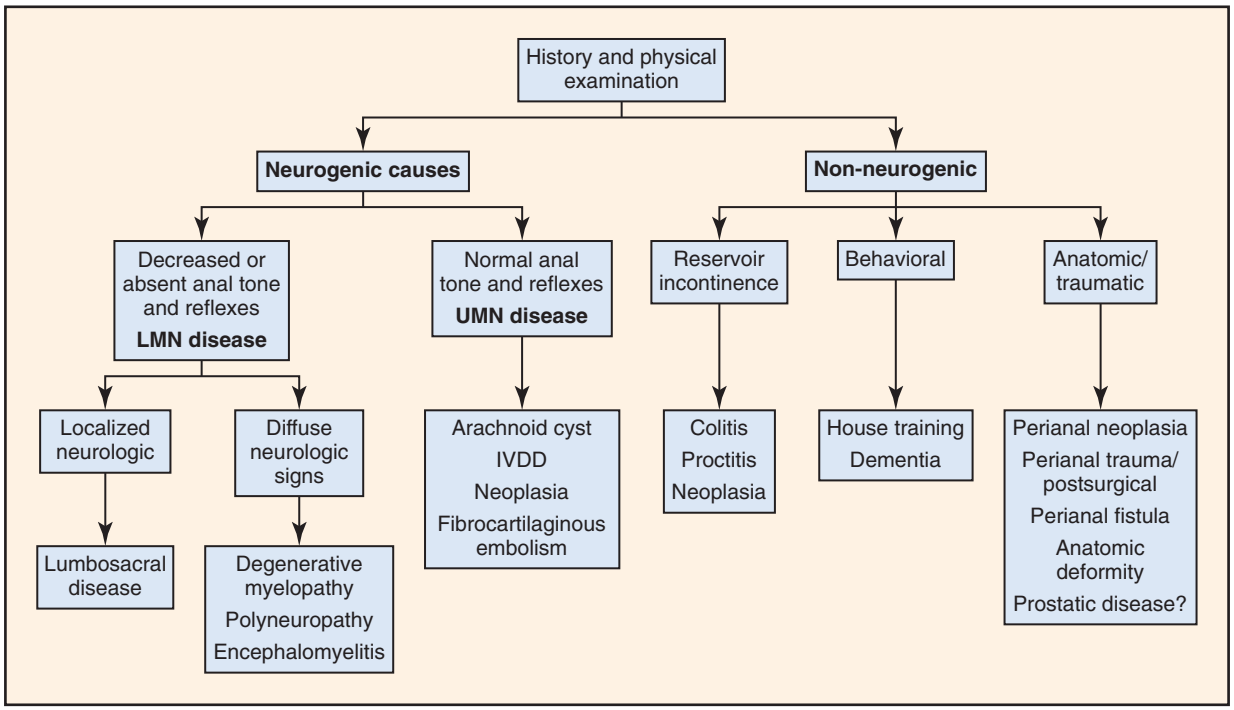

Figure 59-9 Algorithm for the investigation of fecal incontinence.

Table 59-1 Nonneurogenic and Neurogenic Causes of Fecal Incontinence

Disease	Causes
Nonneurogenic Causes	
Colorectal disease	Inflammatory bowel disease
	Colorectal neoplasia
	Idiopathic constipation
	Spinal arachnoid cyst
Anorectal disease	Anorectal trauma
	Anal/perianal surgery
	Anorectal neoplasia
	Perianal fistula
Miscellaneous causes	Secretory diarrheal disorder
	Irritable bowel syndrome
	Cognitive dysfunction
Neurogenic Causes	
Sacral spinal cord disease	Sacral vertebral fracture
	Lumbosacral instability
	Diskospondylitis
	Degenerative myelopathy
	Sacral spinal cord neoplasia
	Vertebral malformations
	Meningomyelitis
	Sacrococcygeal subluxation
	Meningomyelocele
Peripheral nerve disease	Traumatic nerve injury
	Iatrogenic–perineal herniorrhaphy
	Iatrogenic–perineal urethrostomy
	Dysautonomia
	Endocrinopathy–hypothyroidism, diabetes mellitus
	Penetrating wounds

Diagnosis

A diagnosis of sphincter incontinence is usually apparent from history and physical examination findings. Complete neurologic examination generally discriminates neurogenic from nonneurogenic causes of sphincter incontinence. Confirmation of sphincter incontinence may be obtained by direct anal sphincter electromyography[9] or anorectal manometry,[10] although these techniques may require referral to a specialty hospital. Survey spinal radiography, myelography, and magnetic resonance imaging may be indicated in the further evaluation of suspected spinal cord or cauda equina lesions (e.g., lumbosacral dislocations, severe spondylosis). Epidurography and computer-assisted tomography may also be useful in documenting such cases.[7,8] Table 59-1 outlines the causes of neurogenic and non-neurogenic fecal incontinence.

Pathogenesis

Sphincter incontinence may result from spinal cord (e.g., cauda equina syndrome), somatic nerve (e.g., polyneuropathy), autonomic nerve (e.g., dysautonomia), or muscle dysfunction (e.g., anorectal disease).[7,8] In the anorectal disease group, iatrogenic sphincter incontinence is a complication following difficult perianal surgery (e.g., anal sacculectomy, perineal herniorrhaphy, and perianal fistulectomy).[11] Central nervous system disease such as multifocal distemper encephalomyelitis[11] has also been occasionally associated with sphincter incontinence.

Therapy

Neurogenic and nonneurogenic sphincter incontinence are usually permanent and untreatable. It has been suggested that mild cases of incontinence may improve with empirical use of loperamide (Imodium, 0.05 mg/lb [0.1 mg/kg] q8h).[12] Loperamide increases anal canal pressure and attenuates the rectosphincteric relaxation reflex, but is without effect on the external anal sphincter.[6,13] Therefore, most cases of external anal sphincter incompetence are unlikely to be improved by loperamide. Moderate to severe cases of incontinence are refractory to these therapies. A variety of surgical techniques have been employed to replace the muscles of continence with silicone or autogenous muscle grafts, repair the external anal sphincter, and improve the anorectal angulation.[14-17] The success rate with these techniques is still unacceptably low.

NEOPLASIA

Shelby L. Freda and Michael H. Goldschmidt

Anorectal Structure

The rectum, a continuation of the distal colon, is located within the pelvic canal, and in the terminal region is associated with the anal sphincter muscles at the rectoanal junction. The rectum has similar macroscopic and microscopic anatomy to the colon and is covered by a mucosa which consists of elongated glands. These glands are lined primarily by undifferentiated cuboidal epithelial cells at their base and by goblet cells on the luminal surface. The rectal epithelial cells are separated from the lamina propria by a basement membrane. Within the lamina propria are occasional plasma cells and lymphocytes. At the base of the mucosa is the muscularis mucosa, external to which are the submucosa, the inner circular and the outer longitudinal muscle layers, and the serosa. The transition from the mucosa of the rectum to the stratified squamous epithelium of the anus is abrupt. At the rectoanal junction within the subcutis are modified apocrine glands, the anal sacs, which empty directly onto the anal mucosa via long ducts.

Tumors of the Anorectum

Tumors of the GI tract are relatively uncommon in the dog and rare in the cat. Retrospective studies confirm that GI neoplasms most commonly occur in the large intestine of dogs and the small intestine of cats.[1,2] In dogs, adenocarcinoma is the most common malignant intestinal neoplasm, with a reported prevalence of 0.13%, whereas in cats lymphoid tumors and adenocarcinomas arising at the ileocecocolic junction are common. Canine colorectal carcinomas/adenocarcinomas occur more frequently in the rectum than in the colon. Older dogs (mean age: 8.5 years) are more commonly affected, with a higher prevalence in males than females, and purebreds are more often affected. Benign epithelial tumors arising from the rectal mucosa have been referred to as adenomatous polyps, rectal polyps, papillary adenomas, papillotubular adenomas, and villous adenomas, but in the following discussion they are referred to as *rectal adenomas*. These occur most often at or close to the anorectal junction. Malignant mesenchymal tumors, although less common, include leiomyosarcoma and hemangiosarcoma, whereas the most common benign mesenchymal tumor is the leiomyoma. Malignant lymphoma is less common than benign plasmacytoma in

this anatomic location. Up to 50% of primary rectal tumors are reportedly malignant, so rectal neoplasia may be a clinically significant disease. Rectal tumors are uncommon in cats.

Clinical Findings

The most common presenting clinical signs associated with rectal tumors are hematochezia, tenesmus, and dyschezia. Hematochezia is observed because rectal tumors are often well-vascularized, friable, intraluminal masses that readily bleed as feces pass over and abrade the mucosal surface. The masses may also cause irritation of the large bowel or stricture, leading to tenesmus and dyschezia. The duration of clinical signs before a diagnosis is made can vary from 2 weeks to 5 years. Tumors arising in the submucosa or muscular tissue may produce similar clinical signs by impinging on the lumen of the rectum. The duration of clinical signs can be variable with adenomas having the longest duration of signs before treatment. Other clinical complaints associated with rectal tumors include, diarrhea, melena, prolapse of the mass through the anus, abdominal pain, anorexia, anemia, and weakness, the latter a result of anemia.

Histopathology

Adenomas

These are the most common rectal tumors in the archives of the Laboratory of Pathology and Toxicology at the University of Pennsylvania, School of Veterinary Medicine. Affected dogs range in age from 2 to 14 years and there is a 3:2 male-to-female ratio. Boxers, Labrador Retrievers, Rottweilers, and Shetland Sheepdogs have a higher incidence of adenomas.

Most adenomas appear macroscopically as raised, dome shaped, sessile lesions or as pedunculated polyps.[3,4] Microscopically, the neoplastic tissue is sharply demarcated from the adjacent normal rectal mucosa (Figure 59-10). In many lesions the neoplastic tissue occupies the superficial mucosa while the crypts at the base of the neoplastic mass are normal. The branching lamina propria supports the neoplastic epithelium and is often infiltrated by increased numbers of plasma cells and lymphocytes. Ulceration is accompanied by hemorrhage from the vessels in the lamina propria and exocytosis of neutrophils. Neoplastic cells covering the lamina propria are usually columnar with basally located nuclei. They exhibit little pleomorphism, but retain their polarity to the basement membrane and are actively mitotic.

Adenomas do not invade through the basement membrane nor is there invasion through the lamina propria at the base of the crypts. When there is marked nuclear and cellular atypia and atypical mitoses then the neoplasm should be classified as carcinoma in situ (Figure 59-11).

Surgical removal of the entire neoplastic mass allows the pathologist to evaluate margins and ensure that invasion through the basement membrane is not present. The submission of multiple small pieces from polypoid lesions is suboptimal and precludes evaluation of the tissue for evidence of invasion through the basement membrane, primarily at the base of the crypts.

Adenocarcinoma

Adenocarcinomas (carcinomas) are found less frequently in the rectum than adenomas.[5] Affected dogs range in age from 4 to 15 years, but the majority are older than 9 years. There is a 2.5:1.5 male-to-female ratio. Australian Sheepdogs, Great Danes, Shetland Sheepdogs, and West Highland White Terriers have a higher incidence of this tumor.

Most rectal adenocarcinomas appear macroscopically as soft masses or strictures (annular constriction) of the rectum, or there may be a cobblestone appearance to the mucosa. Enlargement of the sublumbar and/or colonic lymph nodes because of metastatic spread may also be evident on clinical examination. Infiltration through the serosa leading to carcinomatosis is infrequent.

Microscopically, all layers of the rectal wall may be infiltrated by neoplastic cells, forming cords, clusters, and acinar structures. The neoplastic cells are large, and exhibit both nuclear and cellular pleomorphism and there is a variable nuclear-to-cytoplasmic ratio. Loss of polarity and invasion through the basement membrane and the lamina propria into the submucosa and deeper tissues is common (Figure 59-12).

Leiomyoma and Leiomyosarcoma

These smooth muscle tumors are less common than their epithelial counterparts. Affected dogs range in age from 4 to 13 years. Leiomyomas occur in older dogs (>10 years) compared with leiomyosarcomas. There is no sex or breed predilection.

Most leiomyomas appear macroscopically as a firm mass in the wall of the rectum that may bulge into the rectal lumen resulting in mucosal ulceration. Although rectal leiomyosarcomas may appear

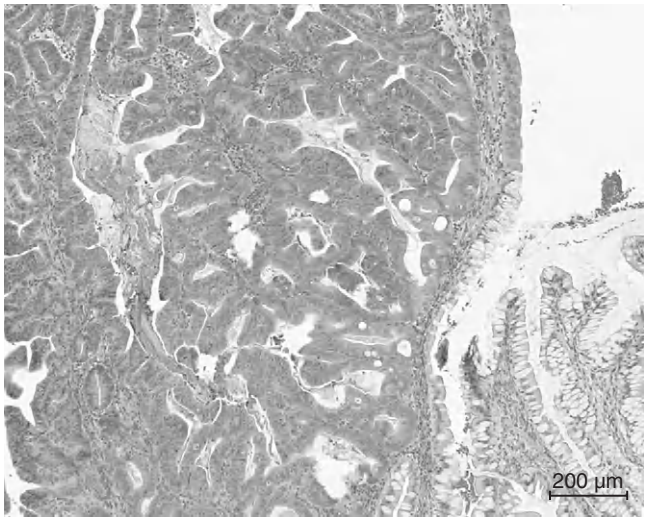

Figure 59-10 Rectal papillary adenoma.

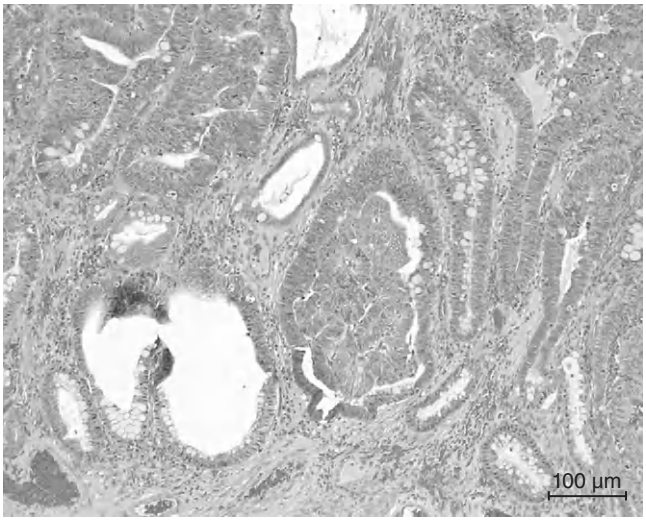

Figure 59-11 Rectal carcinoma in situ.

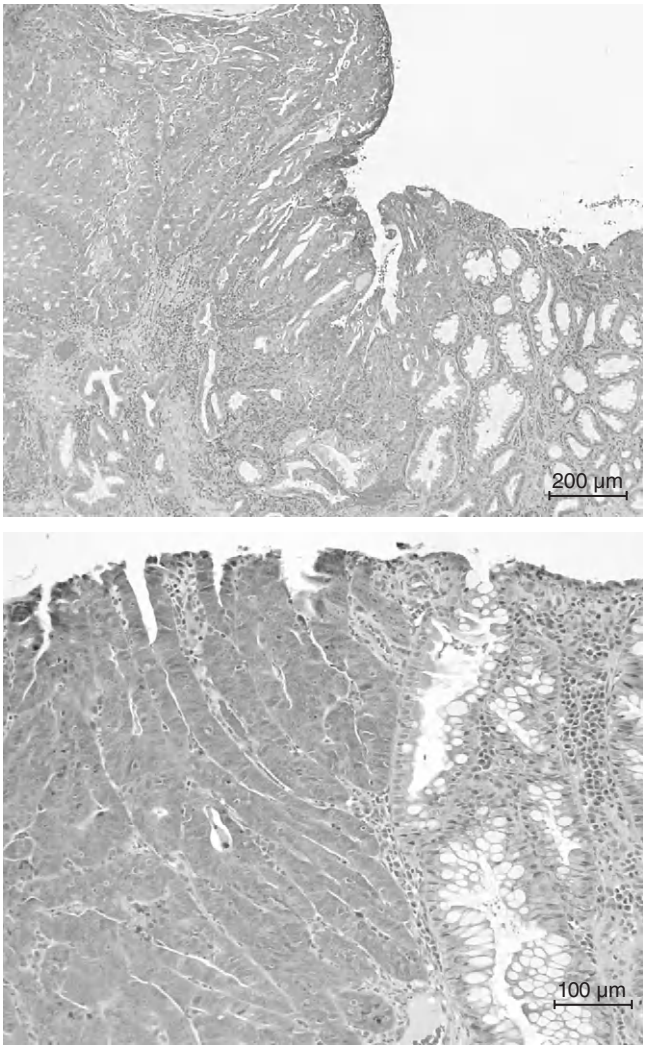

Figure 59-12 Rectal carcinomas.

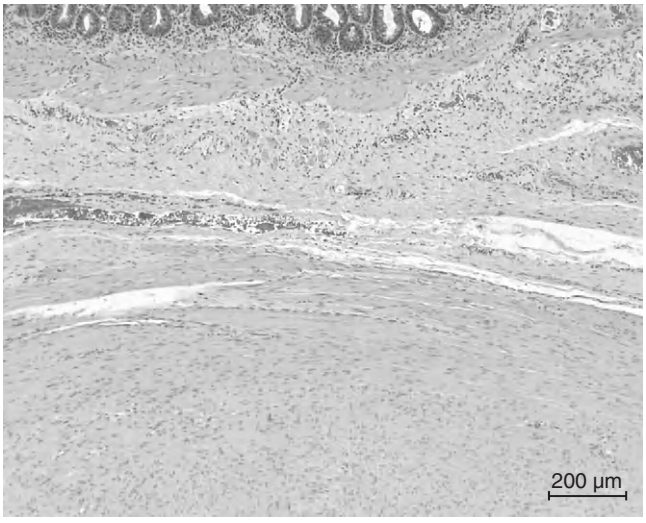

Figure 59-13 Rectal leiomyoma.

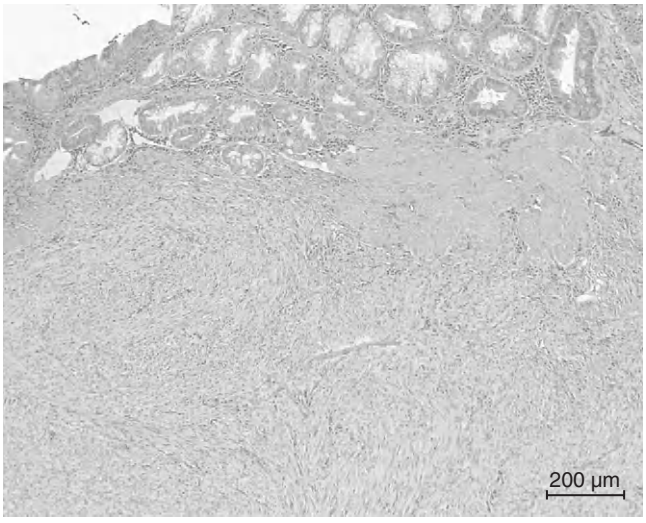

Figure 59-14 Rectal leiomyosarcoma.

similar macroscopically, many feel soft, and in large, rapidly growing tumors there are often areas of hemorrhage and necrosis.

Microscopically in leiomyomas, the mass is present within the submucosa and outer muscle. The overlying mucosa may be ulcerated and covered by hemorrhagic fibrinonecrotic exudate. Neoplastic cells are fusiform with an interwoven pattern. Nuclei are elongated with blunt ends and cells have an extensive eosinophilic cytoplasm (Figure 59-13). Few mitoses are found. Leiomyosarcomas are more cellular and the individual neoplastic cells can be fusiform or round (Figure 59-14). There is usually considerable nuclear and cellular pleomorphism and giant nuclei or multinucleated cells may be present. Metastatic spread is uncommon.

Lymphoma

Lymphoma is uncommon in this anatomic location. Affected dogs range in age from 3 to 17 years. There is no sex or breed predilection. Rectal lymphoma may be found as a solitary, variably sized, soft mass within the wall of the rectum or may be part of a multifocal neoplastic disease with involvement of other areas of the GI tract or other sites. Occasionally the masses have a polypoid appearance and resemble rectal adenomas.

Microscopically, the neoplastic lymphoid cells form sheets. There may be involvement of the lamina propria with extension through the muscularis mucosa (Figure 59-15) and submucosa into the muscle layers. Some cases will show single-cell infiltration of the mucosa or the formation of intraepithelial "microabscesses" of neoplastic lymphoid cells. The majority of cases are lymphoblastic in their cytomorphology, but in some cases there may be plasmacytoid differentiation. Care should be taken to differentiate these cases from rectal plasmacytomas, as their biological behavior is distinct. As noted previously, rectal lymphoma may be part of a multisystemic neoplastic disease or may show metastatic spread from a primary site in the rectum to regional lymph nodes, liver, and spleen.

Plasmacytoma (Rectal Extramedullary Plasma Cell Tumor)

This tumor, although uncommon, is increasing in incidence. Affected dogs range in age from 9 to 15 years. There is no sex predilection, but the Golden Retriever, Briard, and American Pit Bull Terrier have a higher incidence of rectal plasmacytoma.

Rectal plasmacytomas are usually solitary, soft masses that occupy the wall of the rectum, primarily at the rectoanal junction. They are usually quite large before the animal exhibits clinical disease (tenesmus and dyschezia) associated with a space-occupying mass in the

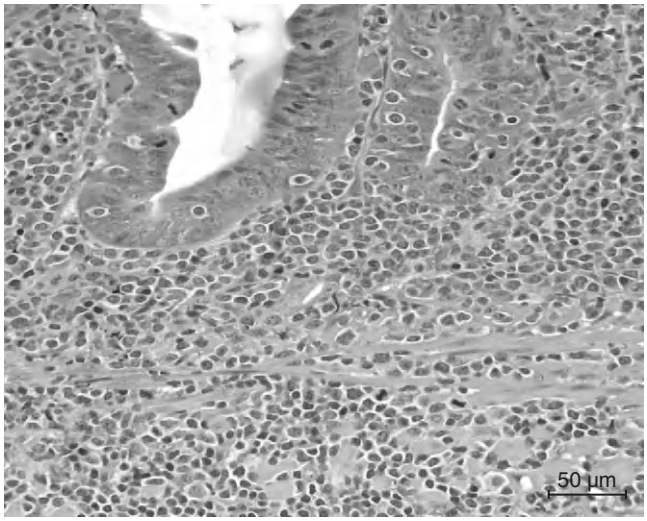

Figure 59-15 Rectal lymphoma.

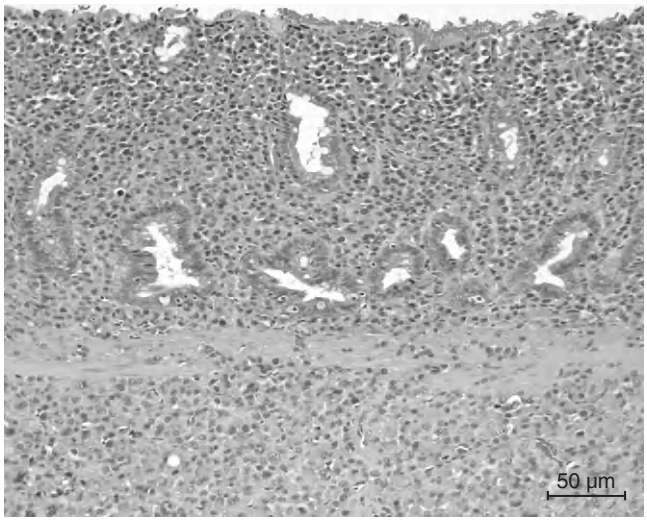

Figure 59-16 Rectal plasmacytoma.

rectal wall. Ulceration of the mucosa is common with hematochezia.

Because these tumors may be large at the time of surgical removal it is often difficult to determine whether they have arisen within the lamina propria with extension into the submucosa and muscular layers or whether involvement of the lamina propria has occurred secondary to invasion of a primary mass in the submucosa (Figure 59-16). Neoplastic cells do not infiltrate into the epithelium as can occur with rectal lymphoma. The neoplastic cells are round and form sheets or nests surrounded by a fine fibrovascular connective tissue stroma. The cells exhibit differentiation to plasma cells, which often have a perinuclear halo (Golgi zone), and plasmablasts. Nuclei are eccentric, and binucleated and multinucleated cells are frequently present. In some tumors amyloid deposition may be evident and these tumors are often less cellular on histopathologic evaluation. Surgical removal of the entire neoplastic mass allows the pathologist to evaluate margins for adequacy of excision. Metastatic spread or involvement of other organs is uncommon and unusual.

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STRUCTURE AND FUNCTION

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CHAPTER 60

Pancreas

STRUCTURE AND FUNCTION

Robert J. Washabau

Structure

Macroscopic Anatomy

The pancreas is a bilobed structure in companion animal species. The right lobe lies in the mesoduodenum in close apposition to the proximal duodenum. The right lobe extends posteriorly from the pylorus to the cecum. The left lobe lies in the greater omentum and lies in close apposition to the transverse colon caudally and the stomach cranially (Figure 60-1). The dog typically has two pancreatic ducts: a ventral or accessory pancreatic duct and a dorsal pancreatic duct. The ventral duct is the larger of the two and drains the right pancreatic lobe, while the dorsal duct drains the left lobe. These ducts usually intercommunicate within the gland. The ventral pancreatic duct is sometimes absent in the cat. In the cat, the dorsal pancreatic duct merges with the common bile duct prior to entry into the proximal duodenum.[1,2]

Microscopic Anatomy

The exocrine pancreas is a tubuloalveolar gland with a division of function between the acinar cells, which secrete the digestive enzymes, and the duct cells, which add water, bicarbonate, chloride, intrinsic factor, and antibacterial proteins. Throughout the pancreatic parenchyma are isolated clusters of cells forming the islets of Langerhans (Figure 60-2). The islets contain four major types of endocrine cells that synthesize and secrete glucagon (A cell), insulin (B cell), somatostatin and gastrin (D cell), and pancreatic polypeptide (PP cell). Although these hormones have other well-known physiologic effects, they also have important endocrine or paracrine effects on the pancreatic acini because of the islet–acinar portal venous system. Insulin appears to have long-term effects on the regulation of the biosynthesis of pancreatic digestive enzymes and short-term effects on the potentiation of pancreatic secretory response to gut hormones and neurotransmitters. Other islet hormones and peptides, including glucagon, somatostatin, and pancreatic polypeptide, probably act as inhibitory regulators of the pancreatic acini.

Blood Supply

The majority of the arterial blood supply of the right lobe of the pancreas arises from the celiac artery via the cranial and caudal pancreaticoduodenal arteries. The pancreatic branch of the splenic artery supplies the left side of the pancreas. Venous drainage of the right lobe of the pancreas is provided by the caudal pancreaticoduodenal vein, whereas the left lobe is drained by two veins that terminate in the splenic vein. Lymphatic drainage is by vessels that course into the duodenal, hepatic, splenic, and mesenteric lymph nodes.

In the dog and cat the exocrine pancreas does not have a direct arterial blood supply. Instead, an islet–acinar portal blood system exists, that is, the acini are perfused by venous blood arising from the islet vasa efferentia. Because some blood courses first to the islets, which secrete hormones into the blood, and then to the acinar cells, which secrete enzymes into the juice in response to stimulation by hormones, the pancreas has the potential to autoregulate part of its own exocrine secretion (see Figure 60-2).

Innervation

The efferent nerve supply to the pancreas is both sympathetic and parasympathetic (see Figure 60-2). Sympathetic postganglionic fibers emanate from the celiac and cranial mesenteric plexuses and accompany the arteries to the organ. Parasympathetic preganglionic fibers are distributed by branches of the vagi coursing down the antroduodenal region. Vagal fibers terminate at either acini and islets or intrinsic cholinergic nerves of the pancreas. In general, the sympathetic nerves inhibit and the parasympathetic nerves stimulate pancreatic exocrine secretion.

Function

Exocrine pancreatic secretions have four major functions: (a) initiate protein, carbohydrate, and lipid digestion through the secretion of digestive enzyme; (b) neutralize the duodenum with bicarbonate, chloride, and water; (c) facilitate cobalamin (vitamin B_{12}) absorption in the distal ileum via secretion of intrinsic factor; and, (d) regulate the small intestinal bacterial flora through secretion of antibacterial proteins.

Duct Cells

Water, anions, and cations are secreted primarily by the pancreatic duct cells. Bicarbonate is necessary to neutralize gastric acid that is emptied into the small intestine during feeding to prevent damage to the intestinal mucosa. Bicarbonate secretion also provides an increase in duodenal pH that is necessary for optimal activity of the secreted enzymes, particularly lipases. A fluid secretion isotonic to plasma and high in bicarbonate concentration is stimulated by the endocrine hormone secretin and the neurotransmitter vasoactive intestinal polypeptide from the duct cells of the exocrine pancreas.

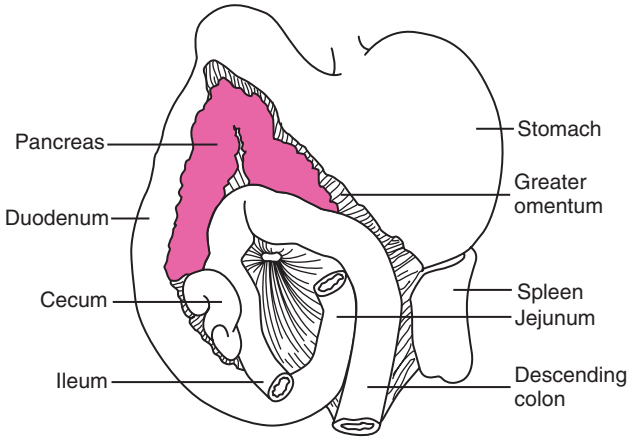

Figure 60-1 Anatomic relationship of the pancreas to other abdominal viscera. (Reprinted with permission from Johnson LR: *Gastrointestinal Physiology*, 2nd ed, Philadelphia, Elsevier, 2007.)

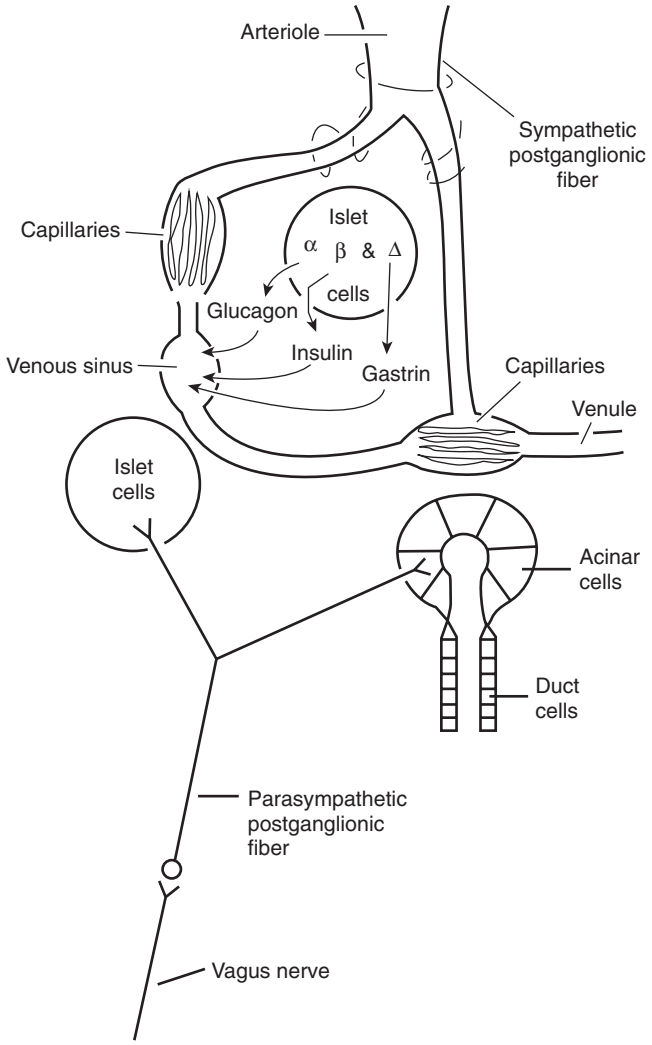

Figure 60-2 The pancreatic acinar and duct cells of the exocrine pancreatic parenchyma with their blood supply and autonomic nervous system innervation. (Reprinted with permission from Johnson LR: *Gastrointestinal Physiology*, 2nd ed, Philadelphia, Elsevier, 2007.)

Box 60-1 Enzymes Secreted from Acinar Cells in the Exocrine Pancreas

Endopeptidases: hydrolyze interior peptide bonds of polypeptides and proteins.
- Trypsin—attacks peptide bonds involving basic amino acids.
- Chymotrypsin—attacks peptide bonds involving aromatic amino acids, leucine, and glutamine.
- Elastase—attacks peptide bonds involving neutral and aliphatic amino acids.

Exopeptidases: hydrolyze external peptide bonds.
- Carboxypeptidase A—active against peptides with aromatic and aliphatic amino acids at the C-terminus.
- Carboxypeptidase B—active against peptides with basic amino acids at the C-terminus.
- Amylase—hydrolyzes dietary starch into the disaccharide maltose and α-limit dextrins.
- Lipase—hydrolyzes triglycerides into free fatty acids, 2-monoglycerides, and glycerol.
- Phospholipase—hydrolyzes phospholipids to 1-lysophospholipids and free fatty acids.
- Ribonuclease—releases pyrimidine nucleotides from polyribonucleotides.

The bicarbonate concentration increases with increasing flow rate, up to 150 mEq/L, while the chloride concentration correspondingly decreases, so that the sum of the anions remains constant. The cation concentrations are plasma-like and do not change with flow rate (Figure 60-3).

Most mammals have developed a complex process for vitamin B_{12} (cobalamin) absorption involving secretion of a gastric intrinsic factor, binding of gastric intrinsic factor to cobalamin, and subsequent attachment of this intrinsic factor–cobalamin complex to specific receptors on ileal enterocytes. The dog and cat appear to have diverged from this pattern and instead rely mostly (dog) or exclusively (cat) on pancreatic intrinsic factor synthesis and secretion. Canine and feline pancreatic duct cells secrete a pancreatic intrinsic factor that is the primary mechanism for binding and receptor-mediated endocytosis of cobalamin in the gut.[3,4]

Duct cells secrete several types of antibacterial proteins that act to regulate the endogenous microbial flora. With exocrine pancreatic insufficiency (EPI), affected animals develop predictable and severe nutrient maldigestion, acid injury to the duodenal mucosa, cobalamin and fat-soluble vitamin malabsorption, and bacterial proliferation in the gut.

Acinar Cells

The pancreatic acinar cell secretes its proteolytic enzymes in precursor form (zymogens). Other enzymes (amylase, lipase, ribonuclease) are secreted in an active form. The enzymes in pancreatic fluid have the ability to hydrolyze dietary starch (amylase), fats (lipase), proteins (trypsin, chymotrypsin, carboxypeptidase, elastase), and nucleic acids (ribonuclease, deoxyribonuclease; Box 60-1). The action of enterokinase, an enzyme secreted by the duodenal mucosa, activates trypsinogen into proteolytically active trypsin. Trypsin then acts autocatalytically to activate trypsinogen and other proteolytic zymogens (Figure 60-4).

Pancreatic acinar cells protect themselves from intraacinar activation of zymogen and acinar cell necrosis through several mechanisms: (a) potentially harmful digestive enzymes are synthesized in the form of inactive precursors or zymogens in the rough

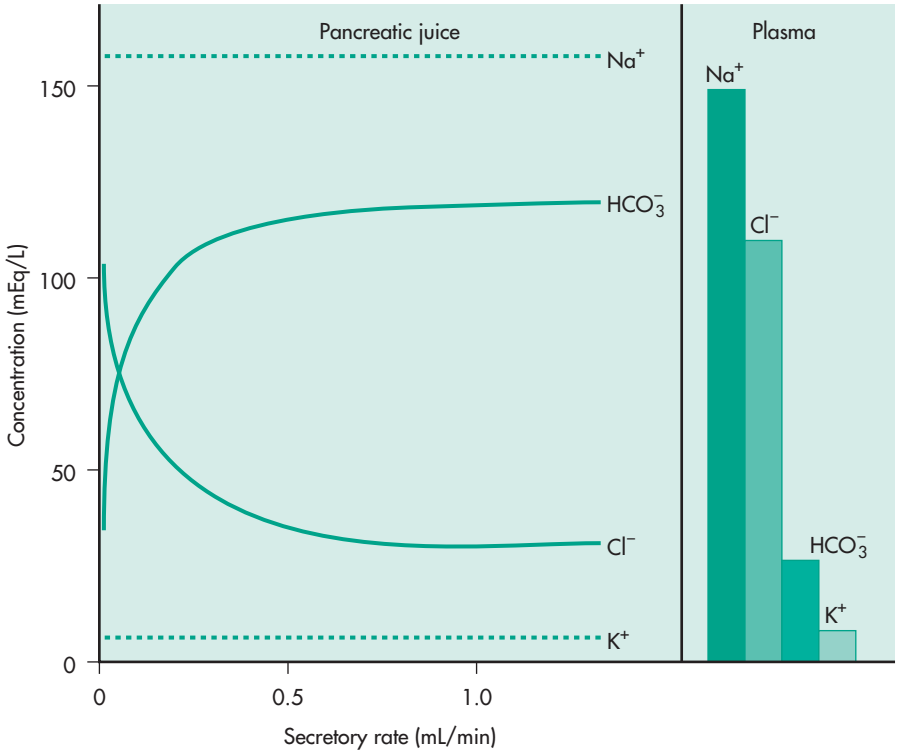

Figure 60-3 Chloride and bicarbonate secretion at low and high secretory flow rates from the canine pancreas. (Reprinted with permission from Johnson LR: *Gastrointestinal Physiology,* 2nd ed, Philadelphia, Elsevier, 2007.)

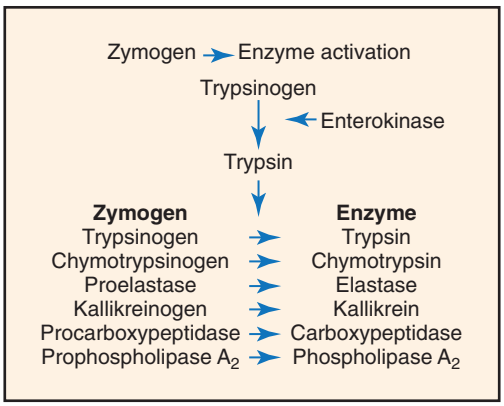

Figure 60-4 Exocrine pancreatic enzyme secretions are initiated by enterokinase activation of active trypsin from inactive trypsinogen.

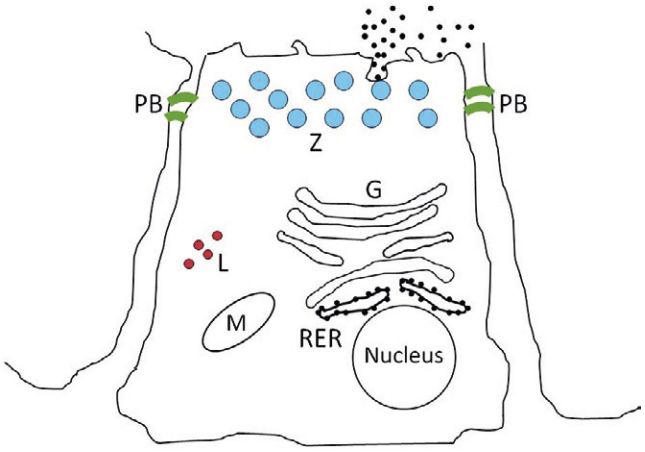

Figure 60-5 Normal pancreatic acinar cell. Zymogen granules are found in the apical region of the cell and their contents are excreted exclusively through the apical surface. Lysosomes are packaged and stored separately from zymogen granules and the paracellular barriers are intact. G, Golgi apparatus; L, lysosome; M, mitochondrion; PB, paracellular barrier; RER, rough endoplasmic reticulum; Z, zymogen granule. (Courtesy of Drs. Panagiotis Xenoulis and Joerg Steiner, Texas A & M University, College Station, Texas.)

endoplasmic reticulum; (b) zymogens are then transported to the Golgi complex where they undergo selective glycosylation. Lysosomal hydrolases that are eventually packaged in lysosomes are separated from zymogens bound for export as they pass through the Golgi complex. Lysosomal hydrolases are first phosphorylated at the six position of mannose residues, bound to receptors specific for 6-phosphoryl mannose, and then transported to lysosomes where the acid pH favors their dissociation from the receptors. Digestive enzymes lack the 6-phosphoryl mannose label, and are instead transported vectorially into a different secretory fraction; (c) packaging of zymogens into maturing zymogen granules sequesters them from contact with other subcellular fractions; (d) pancreatic secretory trypsin inhibitor (PSTI) is incorporated into the maturing zymogen granules. PSTI inactivates trypsin should there be any intraacinar activation of trypsinogen; (e) following stimulation (e.g., feeding and cholecystokinin secretion), mature zymogen granules and their contents are released from the cell into the ductal lumen in a process of membrane fusion and exocytosis; and (f) finally, zymogens are activated physiologically only after they enter the duodenum, where the brush-border enzyme enteropeptidase activates trypsinogen, and trypsin then activates other pancreatic zymogens (Figure 60-5).

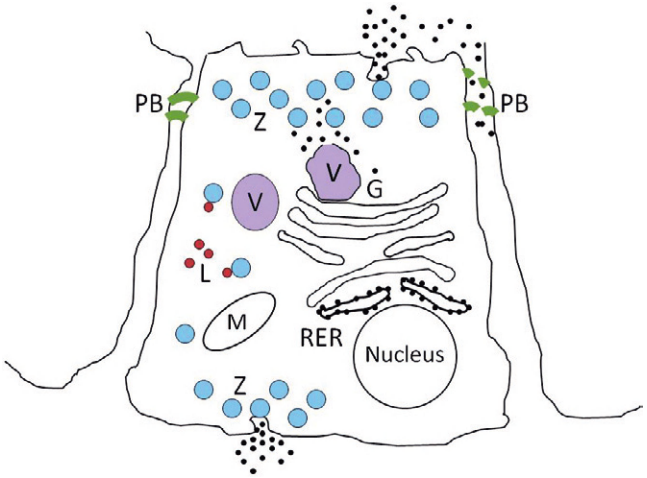

Figure 60-6 Acute pancreatitis. Secretion of the zymogen granules is redirected from the apical pole to the basolateral region of the acinar cell and into the interstitial space. Retention of zymogen granules is followed by co-localization with lysosomes and the formation of large vacuoles and premature intracellular activation of pancreatic enzymes. There is also disruption of the paracellular barrier in the pancreatic duct that allows its contents to leak into the paracellular space. G, Golgi apparatus; L, lysosome; M, mitochondrion; PB, paracellular barrier; RER, rough endoplasmic reticulum; V, vacuole; Z, zymogen granule. (Courtesy of Drs. Panagiotis Xenoulis and Joerg Steiner, Texas A & M University, College Station, Texas.)

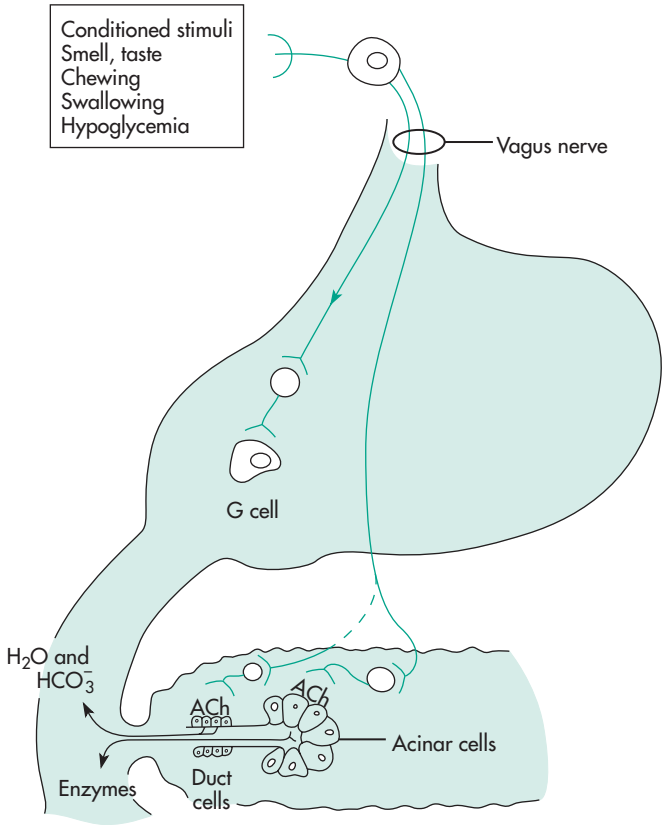

Figure 60-7 The cephalic phase of exocrine pancreatic secretion. (Reprinted with permission from Johnson LR: *Gastrointestinal Physiology*, 2nd ed, Philadelphia, Elsevier, 2007.)

A large body of experimental, and some clinical, evidence suggests that the initiating event of acute pancreatitis is the premature activation of digestive zymogens within the acinar cell.[5-8] Premature activation of digestive zymogen results in acinar cell necrosis and pancreatic autodigestion. In acute pancreatic necrosis, protein synthesis and intracellular transport to the Golgi complex appear to be normal, but digestive zymogens then become colocalized along with lysosomal hydrolases in large vacuoles. Cell biology studies reveal that lysosomal and zymogen granule fractions become colocalized through a process known as *crinophagy*, a process used by many cells to degrade accumulated secretory products when the need for secretion is no longer present. Although this process takes place in other cells without adverse consequences, it can be lethal in pancreatic acinar cells because of the peculiarity of their secretion products (digestive zymogens). Lysosomal hydrolases, such as cathepsin B and *N*-acetyl glucosaminidase, activate trypsinogen to the active trypsin form, and the enhanced fragility of these large vacuoles permits release of active enzyme into the cell cytoplasm (Figure 60-6). Trypsin acts autocatalytically to activate other trypsinogen molecules and other zymogens, each inducing a unique chemical pathology in pancreatic and extrapancreatic cells. A variety of inflammatory mediators and cytokines, interleukins, nitric oxide, and free radicals are involved in the further evolution of pancreatic acinar cell necrosis and inflammation, and often determine the outcome.[9] Thus, a bout of pancreatitis begins with an initiating event (e.g., ischemia, inflammation, or ductal obstruction) followed by acinar events (e.g., colocalization, enzyme activation, and cell injury), the outcome of which is influenced by severity determinants (e.g., inflammatory cytokines, reactive oxygen species, altered oxidation-reduction state, and apoptosis).[9] The further evolution of acute pancreatic necrosis to a systemic inflammatory response syndrome (SIRS) and multiple organ dysfunction syndrome is determined by the balance of proinflammatory and antiinflammatory cytokines.[9]

Regulation of Secretion

Exocrine pancreatic secretions are regulated by hormonal, neural, and paracrine input during the cephalic, gastric, and intestinal phases of secretion. In the cephalic phase of exocrine pancreatic secretion, acetylcholine released by vagal postganglionic neurons stimulates H^+ ion secretion by parietal cells (Figure 60-7). Gastric acid evokes duodenal secretin release, which then stimulates pancreatic fluid and bicarbonate secretion. Vagal stimulation also releases gastrin from antral G cells. In the dog, gastrin is equipotent with cholecystokinin (CCK) in stimulating pancreatic enzyme secretion. Gastrin stimulates the parietal cells to secrete H^+.

In the gastric phase of exocrine pancreatic secretion, the same essential mechanisms are involved as those in the cephalic phase of pancreatic secretion (Figure 60-8). Protein digestion products in the stomach release gastrin, resulting in the stimulation of pancreatic enzyme secretion and gastric acid secretion. Gastric distention stimulates gastric mechanoreceptors, which in turn stimulate parietal cells through vagal reflexes. H^+ stimulates duodenal secretin release.

The intestinal phase of exocrine pancreatic secretion is the major phase of secretion (see Figure 60-8). The stimulus for the alkaline component from the duct cells is the hormone secretin. The only potent releaser of secretin is hydrogen ion. CCK is the principal humoral stimulant of enzyme secretion from the pancreatic acinar cells and is released physiologically in response to amino acids and fatty acids in the small intestine.

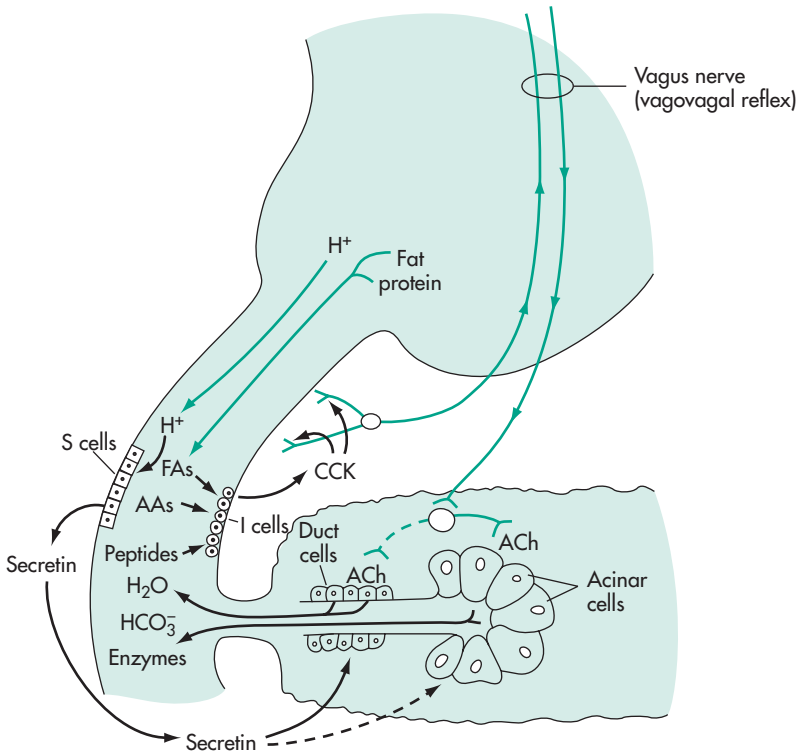

Figure 60-8 The gastric and intestinal phases of exocrine pancreatic secretion. (Reprinted with permission from Johnson LR: *Gastrointestinal Physiology*, 2nd ed, Philadelphia, Elsevier, 2007.)

DIAGNOSTIC EVALUATION OF THE PANCREAS

Panagiotis G. Xenoulis, Jörg M. Steiner

Exocrine pancreatic disorders are common in clinical practice and pancreatitis is by far the most common disorder of the exocrine pancreas in both dogs and cats. Clinical diagnosis of pancreatitis can be challenging and it has been suggested that most cases of canine and feline pancreatitis remain undiagnosed. This is supported by necropsy studies in both dogs and cats that report that histopathologic evidence of pancreatic inflammation is common in both species, even in patients that are not clinical.[1-3] Pancreatitis may be accompanied by relatively uncommon pancreatic complications such as pancreatic abscesses and pancreatic pseudocysts.

Exocrine pancreatic insufficiency (EPI) is the next most common disease of the exocrine pancreas in small animals. It is more common in dogs than in cats. It should be noted that in the past few years EPI has been diagnosed with increasing frequency in the feline population, likely as a result of increased awareness of this condition in cats and the availability of better tests for its diagnosis. In contrast to pancreatitis, the diagnosis of EPI is usually uncomplicated when appropriate tests are utilized.

Uncommon diseases of the exocrine pancreas include pancreatic neoplasia (metastatic or less commonly primary neoplasia), pancreatolithiasis, and pancreatic parasites. Nodular hyperplasia of the pancreas is a very common histopathologic finding, especially in older dogs and cats. However, its clinical relevance is unknown and it is believed that this condition is rarely if ever associated with clinical disease. However, it can potentially interfere with the diagnostic evaluation of the pancreas and display findings that are usually associated with other pancreatic diseases (e.g., pancreatitis, neoplasia).

Although the diagnostic evaluation of any patient, including those with exocrine pancreatic disease, should always take into consideration the clinical presentation and general clinicopathologic findings, this chapter mainly focuses on the diagnostic evaluation of the pancreas using diagnostic modalities that are believed to specifically assess pancreatic structure, function, and/or pathology. Table 60-1 summarizes the clinical performance of commonly used diagnostic modalities with regards to the diagnosis of pancreatitis in dogs and cats.

Pancreatitis

Signalment, History, and Risk Factors

Although dogs of any age, breed, or sex can develop pancreatitis, certain groups might be predisposed. Most dogs presented with pancreatitis are middle-aged or older (usually more than 5 years old).[4,5] Several breeds have been reported or suspected to be at increased risk (e.g., Miniature Schnauzers, Yorkshire Terriers, Cocker Spaniels, Cavalier King Charles Spaniels, Collies, and Boxers) but none of these predispositions are consistent among studies.[3-6] Also, no clear sex predisposition has been identified.

Several pathologic conditions have been identified as potential risk factors for pancreatitis in dogs and, although a cause-and-effect relationship has not been established for most of them, their presence along with compatible clinical signs may raise the concern for pancreatitis. Many dogs with pancreatitis are overweight or obese.[5] Also, endocrinopathies such as hyperadrenocorticism, hypothyroidism, and diabetes mellitus may be risk factors for pancreatitis.[5] A history of drug administration (e.g., potassium bromide, phenobarbital, azathioprine, L-asparaginase, meglumine antimonite) in

Table 60-1 Biochemical and Imaging Findings in Dogs and Cats Affected with Acute Necrotizing Pancreatitis

PERFORMANCE OF SELECTIVE DIAGNOSTIC TESTS FOR PANCREATITIS			
DOGS			
Pancreatic Enzymes	**Sensitivity (%)**	**Specificity (%)**	**Comment**
Serum amylase	18-69	~50	Somewhat useful for initial evaluation. Both positive and negative results require verification with more sensitive and specific tests.
Serum lipase	14-73	~50	Somewhat useful for initial evaluation. Both positive and negative results require verification with more sensitive and specific tests.
Serum TLI	36-47	Relatively high	Low sensitivity—normal concentrations do not exclude pancreatitis. Renal failure and intestinal disease might give false positive results. High concentrations in the absence of renal or intestinal disease are suggestive of pancreatitis.
Serum PLI	64-93	93	Highly sensitive and specific. Most accurate serum test for pancreatitis currently available.
Serum TAP	53	88	Not adequately evaluated. High cost. Limited availability.
Imaging Methods			
Abdominal radiography	24	Low	Not useful for the diagnosis or exclusion of pancreatitis. Useful for the evaluation of other diseases.
Abdominal ultrasonography	68	Relatively high	Useful for the diagnosis of pancreatitis. It is very operator- and equipment-dependent. Relatively high specificity if stringent criteria are applied. Negative results do not rule out pancreatitis.
Computed tomography	N/A	N/A	Not adequately evaluated. High cost.
Pancreatic Cytology	N/A	High	Minimally invasive. Highly specific, but pancreatic lesions might be missed if they are localized (low sensitivity?).
Pancreatic Histopathology	Can be high	High	The gold standard for confirmation of pancreatitis. It is invasive, it has high cost, and cannot be performed in severely compromised patients. Lesions are often highly localized so multiple biopsies must be evaluated before pancreatitis can be ruled out (potentially low sensitivity if only one biopsy is evaluated).
CATS			
Pancreatic Enzymes			
Serum amylase	Low	Low	Not useful for the diagnosis of pancreatitis.
Serum lipase	Low	Low	Not useful for the diagnosis of pancreatitis.
Serum TLI	28-64	82	Low sensitivity—normal concentrations do not exclude pancreatitis. Renal failure and intestinal disease might give false positive results. High concentrations in the absence of renal or intestinal disease are suggestive of pancreatitis.
Serum PLI	54-100	91	Highly sensitive and specific. Most accurate serum test for pancreatitis currently available.
Serum TAP	100	82	Not adequately evaluated. High cost. Limited availability.
Imaging Methods			
Abdominal radiography	Low	Low	Not useful for the diagnosis or exclusion of pancreatitis. Useful for the evaluation of other diseases.
Abdominal ultrasonography	11-67	Relatively high	Somewhat useful for the diagnosis of pancreatitis. It is very operator- and equipment-dependent. Relatively high specificity if stringent criteria are applied. Negative results do not rule out pancreatitis.
Computed tomography	Low	N/A	Low sensitivity. Not recommended.
Pancreatic Cytology	N/A	High	Minimally invasive. Highly specific, but pancreatic lesions might be missed if they are localized (low sensitivity?).
Pancreatic Histopathology	Can be high	High	The gold standard for confirmation of pancreatitis. It is invasive, it has high cost, and cannot be performed in severely compromised patients. Lesions are often highly localized so multiple biopsies must be evaluated before pancreatitis can be ruled out (potentially low sensitivity if only one biopsy is evaluated).

Table 60-1 Biochemical and Imaging Findings in Dogs and Cats Affected with Acute Necrotizing Pancreatitis–cont'd

CLINICAL PERFORMANCE OF SELECTED DIAGNOSTIC MODALITIES FOR THE DIAGNOSIS OF PANCREATITIS

Pancreatic Enzymes	Sensitivity (%)	Specificity (%)	Comment	Usefulness
DOGS				
Serum amylase	18-69	~50	Low sensitivity and specificity. Somewhat useful for initial evaluation. Both positive and negative results require verification with more sensitive and specific tests.	Somewhat useful
Serum lipase	14-73	~50	Low sensitivity and specificity. Somewhat useful for initial evaluation. Both positive and negative results require verification with more sensitive and specific tests.	Somewhat useful
Serum TLI	36-47	Relatively high	Low sensitivity–normal concentrations do not exclude pancreatitis. Renal failure and intestinal disease might give false positive results. High concentrations in the absence of renal or intestinal disease are suggestive of pancreatitis.	Somewhat useful
Serum PLI	64-93	93	Highly sensitive and specific. Most accurate serum test for pancreatitis currently available.	Useful
Imaging Methods				
Abdominal radiography	24	Low	Not useful for the diagnosis or exclusion of pancreatitis. Useful for the evaluation of other diseases.	Not useful
Abdominal ultrasonography	68	Relatively high	Relatively high sensitivity and specificity if stringent criteria are applied. It is very operator- and equipment-dependent. Negative results do not rule out pancreatitis.	Useful
Pancreatic Cytology	N/A	N/A	Minimally invasive. Must be performed under ultrasonographic guidance. Specificity is believed to be high, but pancreatic lesions might be missed if they are localized (low sensitivity?).	Potentially useful
Pancreatic Histopathology	Can be high	High	The gold standard for confirmation of pancreatitis. It is invasive and cannot be performed in severely compromised patients. Lesions are often highly localized so multiple biopsies must be evaluated before pancreatitis can be ruled out (potentially low sensitivity if only one biopsy is evaluated).	Useful
CATS				
Pancreatic Enzymes				
Serum amylase	Low	Low	Not useful for the diagnosis of pancreatitis.	Not useful
Serum lipase	Low	Low	Not useful for the diagnosis of pancreatitis.	Not useful
Serum TLI	28-64	82	Low sensitivity–normal concentrations do not exclude pancreatitis. Renal failure and intestinal disease might give false positive results. High concentrations in the absence of renal or intestinal disease are suggestive of pancreatitis.	Somewhat useful
Serum PLI	54-100	91	Highly sensitive and specific. Most accurate serum test for pancreatitis currently available.	Useful
Imaging Methods				
Abdominal radiography	Low	Low	Not useful for the diagnosis or exclusion of pancreatitis. Useful for the evaluation of other diseases.	Not useful
Abdominal ultrasonography	11-67	Relatively high	Relatively high sensitivity and specificity if stringent criteria are applied. It is very operator- and equipment-dependent. Negative results do not rule out pancreatitis.	Useful
Pancreatic Cytology	N/A	N/A	Minimaly invasive. Must be performed under ultrasonographic guidance. Specificity is believed to be high, but pancreatic lesions might be missed if they are localized (low sensitivity?).	Potentially useful
Pancreatic Histopathology	Can be high	High	The gold standard for confirmation of pancreatitis. It is invasive, it has high cost, and cannot be performed in severely compromised patients. Lesions are often highly localized so multiple biopsies must be evaluated before pancreatitis can be ruled out (potentially low sensitivity if only one biopsy is evaluated).	Useful

conjunction with compatible findings should also raise a concern for pancreatitis.[5,7] Hypertriglyceridemia, when severe (higher than approximately 850 mg/dL), is a risk factor for pancreatitis in Miniature Schnauzers.[8] This might also be true for dogs of other breeds that exhibit severe hypertriglyceridemia, but this has not yet been proven. Dietary factors (e.g., getting into the trash, consuming table scraps, ingestion of "unusual" food) and surgery at any time prior to diagnosis of pancreatitis also have been suggested as risk factors for pancreatitis in dogs.[6]

Similarly to dogs, cats of any age, breed, or sex can develop pancreatitis. Older cats appear to be more likely to develop chronic pancreatitis.[2,9-11] Domestic shorthair and Siamese breeds are reported to be at an increased risk in some studies, but this has not been confirmed by other studies.[2,9-11]

Clinical Signs and Physical Examination Findings

Dogs with pancreatitis can present with a wide variety of clinical signs, which can range from mild partial anorexia with no apparent gastrointestinal signs to cardiovascular shock, disseminated intravascular coagulation (DIC), and death. There is no single clinical sign or combination of clinical signs that is pathognomonic for pancreatitis in dogs. Recent reports suggest that pancreatitis may be subclinical in some cases, or be associated with only mild and nonspecific clinical signs such as anorexia and weakness.[1] In more typical cases, in addition to anorexia and weakness, dogs present with vomiting, diarrhea, and/or abdominal pain.[5,12] The concurrent signs of vomiting and cranial abdominal pain is considered suggestive, but not pathognomonic, of pancreatitis in dogs. Evidence of dehydration, abdominal pain, icterus, fever or hypothermia, icterus, bleeding diathesis, or ascites may be seen on physical examination.[5] Severe systemic complications (e.g., cardiovascular shock, DIC, or multiorgan failure) might occur in patients with severe pancreatitis.[12,13] Other clinical signs may be observed as a consequence of concurrent disease (e.g., polyuria/polydipsia in animals with diabetes mellitus).[5]

The most common clinical signs in cats with pancreatitis do not specifically indicate gastrointestinal disease and include complete or partial anorexia and lethargy.[9-11,14] Vomiting, weight loss, and diarrhea are reported less commonly in the cat.[9-11,14] Abdominal pain may be evident in cats with acute pancreatitis but could be missed during routine physical examination. The most common physical examination findings are dehydration, pallor, and icterus.[9-11,14] Tachypnea and/or dyspnea, hypothermia/fever, tachycardia, signs of abdominal pain, and a palpable abdominal mass may also be noted.[9-11,14] Severe systemic complications (e.g., DIC, pulmonary thromboembolism, cardiovascular shock, and multiorgan failure) occasionally may be seen in cats with severe pancreatitis.

Routine Clinical Pathology[5,9-12,14,15]

Results of complete blood count, serum biochemistry profile, and urinalysis are nonspecific and thus not useful in the definitive diagnosis of pancreatitis in dogs and cats. However, these tests should always be performed in animals with suspected pancreatitis because they are useful for the diagnosis or exclusion of other diseases, and also give important information about the general condition of the patient.

The complete blood cell count, serum biochemistry profile, and urinalysis are often normal in mild cases. Possible hematologic findings in dogs and cats with pancreatitis include anemia or hemoconcentration, leukocytosis or leukopenia, and thrombocytopenia. Coagulopathies and DIC may be seen in more severe cases. Increases in hepatic enzyme activities and hyperbilirubinemia are common in both dogs and cats, and might erroneously direct the clinician to suspect primary liver disease. Azotemia is variably present and is most often associated with dehydration due to vomiting or diarrhea. Other possible findings include hypoalbuminemia, hypertriglyceridemia, hypercholesterolemia, and hyperglycemia. Electrolyte abnormalities are commonly present, most importantly, hypokalemia, hypochloremia, and hyponatremia. Hypocalcemia is much more commonly seen in cats than in dogs, and is one of the most clinically important electrolyte disturbances in this species. Some cats with pancreatitis have hypocobalaminemia, which likely may reflect concurrent intestinal disease.

Clinical Enzymology

Serum Pancreatic Lipase Immunoreactivity Concentration. There are multiple circulating lipases of various cellular origins (e.g., pancreatic, hepatic, and gastric) and all of them share the same function (i.e., hydrolysis of triglycerides). Therefore, in assays of lipase activity, many of the different lipases may contribute to the total serum lipase activity. More recently, it was shown that lipases of different cellular origins are encoded by different genes and consequently have differing amino acid sequences. Pancreatic lipase is expressed exclusively by pancreatic acinar cells and is structurally different from other lipases. Thus immunoassays for the specific measurement of pancreatic lipase have been developed and analytically validated for dogs and cats.[16,17] In contrast to the traditional activity assays for lipase, which indiscriminately measure the activity of lipases of any origin, these immunoassays specifically quantify lipases based on their unique structure. Consequently, they are considerably more useful for exocrine pancreatic disease than assays for serum lipase activity. During pancreatitis pancreatic lipase leaks from acinar cells and enters the circulation in larger than normal quantities and can be detected by specific immunoassays for pancreatic lipase.

The originally developed immunoassays for pancreatic lipase were in-house immunoassays that used polyclonal antibodies and had limited availability. Commercial immunoassays (e.g., Spec cPL for dogs and Spec fPL for cats) are now more routinely available.[18,19]

Canine pancreatic lipase is believed to be exclusively of pancreatic origin.[20-22] An immunolocalization study has identified the pancreatic acinar cell as the cell of origin.[20] Dogs with EPI have near total absence of serum canine pancreatic lipase immunoreactivity (cPLI) again suggesting that cPLI is likely of exocrine pancreatic origin.[21] The specificity of Spec cPL was reported to be 96.8% in another study of 31 dogs with normal pancreatic histology.[22] In a recent multicenter study, the specificity of cPLI was estimated to be at least 78% in dogs with a clinical diagnosis of pancreatitis.[23] Experimentally induced chronic renal failure and prednisone administration have not been found to have any clinically significant effect on serum cPLI concentration.[24,25]

Serum cPLI concentration is also sensitive for the diagnosis of pancreatitis in dogs.[18,23,26,27] The reported sensitivity of cPLI for the diagnosis of canine pancreatitis ranges from 64% to 93%, depending on the severity of the disease. This is considerably higher than the sensitivity reported for serum canine trypsin-like immunoreactivity (cTLI) concentration (36.4% to 46.7%), serum amylase activity (18.2% to 73.3%), and serum lipase activity (13.6% to 69%), and is similar to or higher than that of abdominal ultrasound (67% to 68%) performed by a board-certified radiologist.[5,18,23,26-28] In a recent preliminary report of a multicenter study, the sensitivity of this assay was estimated at 93%.[23] Because of its high sensitivity, normal serum cPLI concentrations make a diagnosis of clinically relevant

pancreatitis very unlikely. However, it remains to be determined if, as a consequence of its high sensitivity, cPLI detects pancreatic pathology that is not clinically relevant. Based on the aforementioned studies, serum cPLI concentration is the most sensitive and specific test currently available for pancreatitis in dogs.

Recently, a point-of-care test for the estimation of pancreatic lipase in serum (SNAP cPL) was released. Studies evaluating the performance of this test are currently lacking and comparative studies (e.g., with serum Spec cPL assay) have not yet been reported. The recommended use of this new test is mainly for rapid rule-out diagnosis in dogs suspected of having pancreatitis. A positive test result should always be followed up by laboratory measurement of serum Spec cPL concentration to confirm the diagnosis and to serve as a baseline for monitoring disease progress. A negative test result makes a diagnosis of pancreatitis unlikely.

Studies in cats with both experimental and spontaneous pancreatitis have shown that serum feline pancreatic lipase immunoreactivity (fPLI) concentration is very sensitive for pancreatitis.[29-31] In one of these studies, fPLI was found to be 100% sensitive for moderate to severe spontaneous feline pancreatitis, which was superior to the sensitivities of serum feline trypsin-like immunoreactivity (fTLI) concentration (28%) or abdominal ultrasound (80%).[29] In a recent preliminary report, the sensitivity of serum fPLI concentration was reported at 78%.[31] Considering the overall sensitivities for pancreatitis reported for serum fPLI concentration (67% to 78%), fTLI (28% to 64%), and abdominal ultrasonography (11% to 67%), serum fPLI concentration currently appears to be the most sensitive test for the diagnosis of feline pancreatitis.[29,31-35] The specificity of serum fPLI concentration of 82% to 91%, has been reported to be superior to that of fTLI (82%) or abdominal ultrasound (73%).[15,29,31] Further studies are needed to confirm the reproducibility of these findings, but serum fPLI concentration currently appears to be the most useful test for the diagnosis of feline pancreatitis.

A point-of-care test for the estimation of Spec fPL (SNAP fPL) has not been released at the time of writing of this chapter, but is expected to be available in the near future.

Serum Amylase and Lipase Activities. Serum amylase and lipase activity assays have long been considered markers for pancreatitis in dogs.[36,37] Serum activities of these two enzymes increase during experimental canine pancreatitis, but studies of spontaneous canine pancreatitis have shown poor sensitivity and specificity.[18,36-41] Gastric mucosal and hepatic parenchymal amylases and lipases are routinely detected in activity assays, which has contributed to limitations in sensitivity and specificity. Moreover EPI and pancreatectomized dogs both have significant residual circulating lipase and amylase activity, indicating that tissues other than the pancreas account for a large portion of the serum activity of lipase and amylase.[21,41] Traditional catalytic assays, are not able to differentiate amylases and lipases according to their tissue of origin. This leads to a low specificity of serum amylase and lipase activities for pancreatitis in dogs.[28,36]

Many dogs that have extrapancreatic disease have increased serum lipase and/or amylase activities.[36] The main nonpancreatic conditions associated with increased serum amylase and/or lipase activities include renal, hepatic, intestinal, and neoplastic diseases, as well as corticosteroid administration (only for lipase activity). It has been suggested that only increases of amylase and lipase activities of more than three to five times the upper limit of the reference range should be considered suggestive of pancreatitis in dogs, so as to increase the specificity of these assays.[42,43] However it has been shown that even such increases can result from nonpancreatic disorders.[28,36,43,44] Therefore increased serum amylase and/or lipase activities do not confirm the presence of pancreatitis in any case and more specific tests need to be utilized.

The sensitivity of serum amylase and lipase activities for spontaneous canine pancreatitis varies but is generally low (32% to 73% for lipase activity and 41% to 69% for amylase activity) and it is even lower when a cutoff value of three or five times the upper limit of the respective reference interval is used (14% for lipase activity and 18% for amylase activity in one study that used a cutoff of three times the upper limit of the reference range).[5,18,27] Thus many dogs with pancreatitis may have normal serum activities , and therefore normal serum amylase and/or lipase activities do not rule out pancreatitis.[5,36] The low sensitivity of serum amylase and lipase activity assays is at least partially associated with the broad reference intervals for these assays, which are the result of extrapancreatic amylase and lipase activities. A new lipase assay (using the substrate 1,2-*O*-dilauryl-rac-glycero glutaric acid-[69-methyl resorufin]-ester (DGGR) was recently evaluated and might be more useful for the initial evaluation of dogs suspected of having pancreatitis because of its higher sensitivity (93%) compared with the traditional assays.[45] However, the specificity of this assay was very low (53%), limiting the clinical usefulness of this assay.[45]

Serum lipase activity increases and serum amylase activity decreases in experimentally induced acute pancreatitis in cats.[30,46,47] Although well-designed clinical studies are lacking, both serum lipase and amylase activities do not appear to be of any clinical value in the diagnosis of spontaneous feline pancreatitis.[10,32,48] Therefore these two tests are not recommended for the diagnosis of pancreatitis in cats.[10,48]

Trypsin-Like Immunoreactivity. Trypsin-like immunoreactivity (TLI) assays are species-specific immunoassays that measure trypsinogen and trypsin in serum. Trypsinogen is the inactive preform (or zymogen) of trypsin, a proteolytic enzyme synthesized exclusively in pancreatic acinar cells and normally secreted into the duodenum where it is activated by enterokinases. Only minimal amounts of trypsin are released into the circulation. During pancreatitis, trypsinogen and prematurely activated trypsin enter the circulation in large quantities, and can be measured with the TLI assay.

Serum cTLI concentrations increase after experimental induction of pancreatitis in dogs, but rapidly decrease to reference interval concentrations within 3 days of disease induction.[40] The sensitivity of serum cTLI for the diagnosis of spontaneous pancreatitis is low (36% to 47%), probably as a result of its short half-life.[18,27,28] In addition, although there is strong evidence that trypsinogen is exclusively of pancreatic origin,[41] it is believed that it is cleared by glomerular filtration, and serum cTLI concentration can be increased in dogs with glomerular and other renal diseases.[28,40] This clearly affects the specificity of the test and complicates the interpretation of increased cTLI concentrations in dogs with azotemia.

In cats with experimentally induced pancreatitis, fTLI concentration increases sharply after induction of pancreatitis, but returns below the cutoff value for pancreatitis within 48 hours.[30] fTLI has been evaluated for the diagnosis of spontaneous pancreatitis in cats and several cutoff values have been suggested.[33-35] When cutoff values allowing adequate specificity of the assay are used (i.e., 100 µg/L), the sensitivity of fTLI for the diagnosis of pancreatitis in cats is generally low (28% to 33%), with the highest reported sensitivity for this cutoff value being 64%.[33-35] In addition, the specificity of fTLI has been questioned, because mildly increased serum fTLI concentrations have been reported in cats with no demonstrable pancreatic disease, but other gastrointestinal disorders (e.g.,

inflammatory bowel disease or gastrointestinal lymphoma) and azotemia.[15,33,35]

In the face of availability of better serum markers (cPLI and fPLI), cTLI and fTLI are currently considered to be of limited usefulness for the diagnosis of canine and feline pancreatitis, respectively.

Other Diagnostic Markers. Several other diagnostic markers for pancreatitis have been developed and studied, but none can be recommended for the diagnosis of canine and feline pancreatitis in clinical practice, either because their diagnostic performance has not been sufficiently evaluated clinically, or because they have been shown to have a low sensitivity and/or specificity. In addition, the availability of most of these diagnostic tests is currently limited. Such tests include the determination of serum concentrations of phospholipase A_2, trypsin-α_1-antitrypsin complexes, and α_2-macroglobulin, plasma and urine concentrations of trypsinogen activation peptide, and lipase activity in peritoneal fluid.

Diagnostic Imaging

Abdominal Radiography. Conclusive diagnosis or exclusion of pancreatitis is not possible based on abdominal radiography alone.[5,9-11,34,43] In the majority of cases of canine and feline pancreatitis abdominal radiographs are normal or reveal nonspecific findings. Despite that, radiography remains a logical initial approach for patients suspected of having pancreatitis because it is relatively inexpensive and useful for the diagnosis and/or ruling out of other differential diagnoses.

In a group of 70 dogs with fatal acute pancreatitis the sensitivity of abdominal radiography was very low (24%).[5] Radiographic findings that have been reported for dogs with pancreatitis include an increased soft tissue opacity and decreased serosal detail in the cranial right abdomen, indicating localized peritonitis.[5] Other findings may include displacement of the stomach and/or duodenum from their normal positions and gaseous dilation of bowel loops adjacent to the pancreas.[5] Abdominal effusion or the presence of an abdominal mass might also be detected. Radiographic findings in cats with pancreatitis are similar to those in dogs.[10,11,34,49] In any case, radiography should always be followed by use of more sensitive and specific tests for the definitive diagnosis or exclusion of pancreatitis.

Abdominal Ultrasound. Abdominal ultrasound is considered the imaging method of choice for the diagnosis of pancreatitis in dogs and cats. However, the performance of ultrasonography in the diagnosis of pancreatitis is highly dependent on the experience of the ultrasonographer and the quality of the instrumentation.

Abdominal ultrasound has been reported to have a relatively high sensitivity of approximately 68% for severe acute pancreatitis in dogs,[5] although with increasing equipment quality the sensitivity might have increased since this report.[5] Abdominal ultrasound has mainly been assessed in dogs with fatal acute pancreatitis, in which lesions are usually pronounced, but its sensitivity would be expected to be lower in cases with mild or moderate pancreatitis.[5] It must be emphasized that a normal pancreas on ultrasound examination does not rule out pancreatitis in dogs.

Ultrasonographic findings in dogs with pancreatitis include hypoechoic areas within the pancreas (possibly indicating necrosis or fluid accumulation), increased echogenicity of the surrounding mesentery (because of necrosis of the peripancreatic fat), enlargement and/or irregularity of the pancreas, dilation of the pancreatic or biliary duct, and abdominal effusion (Figure 60-9).[5,50] On occasion,

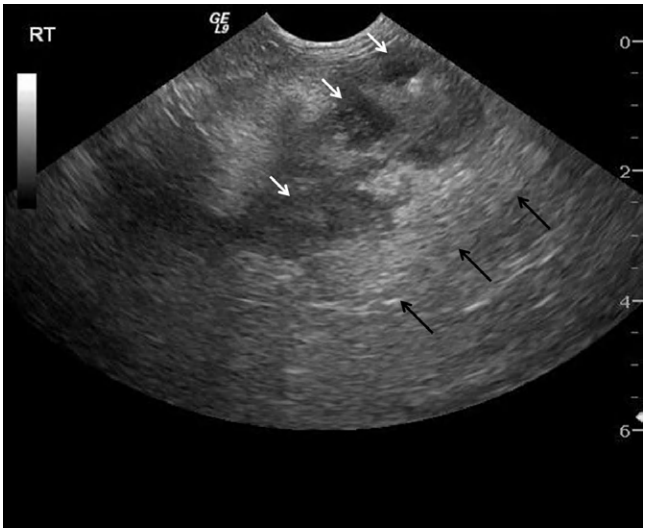

Figure 60-9 Ultrasonographic appearance of the pancreas of a dog with pancreatitis. The pancreas is enlarged and appears heterogenous, with hypoechoic areas (*white arrows*) and hyperechoic surrounding fat (*black arrows*). These findings are highly suggestive of pancreatitis. (Courtesy Dr. B. Young, Texas A&M University.)

hyperechoic areas of the pancreas can be identified, possibly indicating the presence of pancreatic fibrosis. Cavitary lesions, a thickened duodenum, and biliary obstruction might also be noted.[50] If stringent criteria are applied, the specificity of abdominal ultrasonography for canine pancreatitis is considered to be relatively high, although other diseases of the pancreas (e.g., neoplasia, hyperplastic nodules, edema caused by portal hypertension or hypoalbuminemia) may display similar ultrasonographic findings and cannot be differentiated from pancreatitis in many cases.[51,52] In a recent study where ultrasonography was performed in 26 animals (both dogs and cats) with suspected gastrointestinal disease, 6 (23.1%) of the animals had ultrasonographic evidence consistent with pancreatitis, while histopathology revealed either a normal pancreas or pancreatic hyperplasia.[53] In the same study, there was only a 22% agreement between the ultrasound report and pancreatic histopathology in dogs.[53] These data raise concerns regarding the accuracy of ultrasonography in evaluating the canine pancreas and underscore the importance of not overinterpreting ultrasonographic findings.

The reported sensitivity of abdominal ultrasonography for the diagnosis of feline pancreatitis is generally low (11% to 35%), with only one study reporting a sensitivity of 67%.[11,29,33,49] This high range of sensitivity likely reflects differences in the level of suspicion or the skills of the examiner, the equipment used, and the severity of lesions, and highlights the lack of standardized diagnostic criteria.[33,34,49] The low sensitivity of abdominal ultrasonography suggests that many cats with pancreatitis remain undiagnosed if the diagnosis is based solely on ultrasound examination.[11,33,49] The sensitivity of abdominal ultrasonography is believed to have increased since the reports mentioned previously as a result of advances in equipment and an increasing level of awareness of the importance of feline pancreatitis, although this has not yet been confirmed. Abdominal ultrasonography has been thought to be relatively specific for the diagnosis of pancreatitis is cats but, similarly to dogs, other diseases (e.g., pancreatic neoplasia, edema) may be associated with similar findings.[54] In a recent study, there was an overall agreement of only 33% between the ultrasound report and pancreatic histopathology in cats, and some cats that had ultrasonographic evidence of

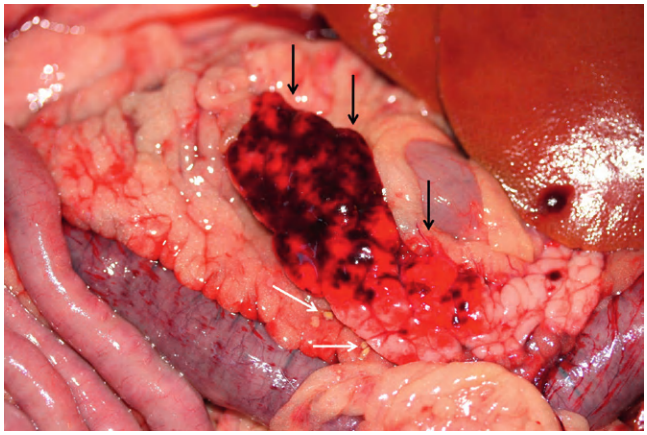

Figure 60-10 Gross Appearance of the pancreas of a dog with acute pancreatitis. The pancreas appears severely hemorrhagic, necrotic, and edematous (*black arrows*). There is also peripancreatic fat necrosis (*white arrows*). Such appearance is highly suggestive of pancreatitis. (Courtesy Dr. D. Ajithdoss, Texas A&M University.)

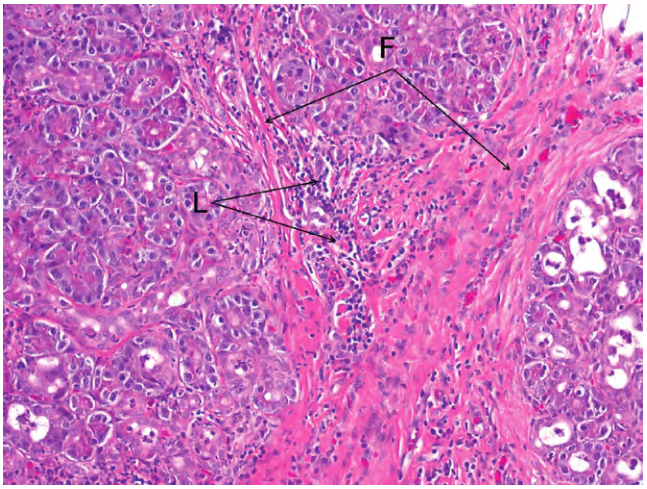

Figure 60-11 Histopathologic appearance of the pancreas of a cat with chronic pancreatitis. There is extensive fibrosis (*F*) and lymphocytic infiltration (*L*). Hematoxylin and eosin; magnification: 200×. (Courtesy Dr. B.F. Porter, Texas A&M University.)

pancreatitis had no evidence of pancreatitis on histopathology.[53] Ultrasonographic findings in cats with pancreatitis are similar to those described in dogs.[11,33,49,50,55] It has been suggested that a dilation of the pancreatic duct is suggestive of pancreatitis in cats, but studies have not confirmed this hypothesis.[56] In general, feline pancreatitis is often difficult to diagnose by abdominal ultrasound examination and it is important to note that a normal ultrasound examination does not rule out feline pancreatitis.[29,33]

Overall, abdominal ultrasonography is very useful for the diagnosis of pancreatitis in dogs and cats, especially when performed by an experienced ultrasonographer. Caution should be taken however not to overinterpret ultrasonographic findings. Abdominal ultrasonography is also helpful in detecting possible concurrent abdominal disease in dogs and cats suspected of having pancreatitis. In addition, ultrasound-guided fine-needle aspiration is a useful tool for the diagnosis of pancreatitis and some of its complications (e.g., pancreatic pseudocyst and pancreatic abscess), as well as the management of noninfectious fluid accumulations (e.g. pancreatic pseudocyst).[55]

Other Imaging Modalities. Although contrast-enhanced computed tomography is an extremely valuable tool for the evaluation of human patients with suspected pancreatitis, initial studies in dogs have not been promising.[57] Also, computed tomography performed in cats with histologically confirmed pancreatitis showed disappointing results and currently cannot be recommended.[29] Other imaging methods (e.g., endoscopic retrograde cholangiopancreatography, endoscopic ultrasonography), have been used in healthy dogs and cats, in dogs with experimentally induced pancreatitis, and in dogs with gastrointestinal diseases, with varying results. Because of the lack of standardized criteria for the diagnosis of pancreatitis, the complexity of these modalities, their limited availability, and the cost of the equipment, they cannot currently be recommended for the diagnosis of canine or feline pancreatitis.

Pathology

Direct visualization of the pancreas is possible during exploratory laparotomy and laparoscopy. Gross pancreatic lesions suggestive of pancreatitis include peripancreatic fat necrosis, pancreatic hemorrhage and congestion, and a dull granular capsular surface (Figure 60-10).[10,18,49] However, gross pathologic lesions may not always be apparent in dogs and cats with pancreatitis.[1,10,49]

At present, a definitive diagnosis of pancreatitis can only be made by histopathologic examination of the pancreas. Histopathology is also the only way to differentiate acute and chronic pancreatitis. Histopathologic scoring systems for the evaluation of severity of pancreatitis have been proposed for both dogs and cats.[1-3,58] However, histopathologic criteria for the classification of pancreatitis have not been universally standardized in veterinary medicine and substantial confusion exists regarding both classification and terminology of canine and feline pancreatitis, underlying the need for a universally accepted multidisciplinary classification system as is available for humans. The presence of permanent histopathologic changes (such as fibrosis and acinar atrophy) is generally considered suggestive of chronic pancreatitis (Figure 60-11).[1,43] Also, the predominant inflammatory cellular infiltrate (neutrophils or lymphocytes) is often used to describe pancreatitis as suppurative or lymphocytic, and some authors consider a suppurative inflammation compatible with acute disease and lymphocytic infiltration compatible with chronic disease (Figure 60-12).[10,11] A significant degree of necrosis is usually used to characterize the pancreatitis as necrotizing. It should be noted that some animals can show histopathologic evidence of both suppurative and lymphocytic pancreatitis.

Several limitations are associated with pancreatic histopathology as a definitive diagnostic tool for pancreatitis. First, determining the clinical significance of histopathologic findings may be challenging. In a recent study, 47 (64%) of 73 dogs that presented for necropsy for various reasons had microscopic evidence pancreatitis.[1] Similarly, histopathologic lesions of pancreatitis were found in 67% of all cats examined, including 45% of healthy cats.[2] Currently, there are no standardized criteria that distinguish microscopic findings leading to clinical disease from those that do not, and it is possible that clinically insignificant pancreatic lesions could lead to a false diagnosis of pancreatitis. At the same time, exclusion of pancreatitis based on histopathology is difficult because inflammatory lesions of the pancreas are often highly localized and can easily be missed.[1,2,10,49] Therefore, multiple sections of the pancreas must be evaluated to increase the likelihood of finding microscopic lesions, although this is not always feasible in clinical practice. The absence of histopathologic findings of pancreatitis must be evaluated with caution, especially when only one section of the pancreas has been examined.[1,2]

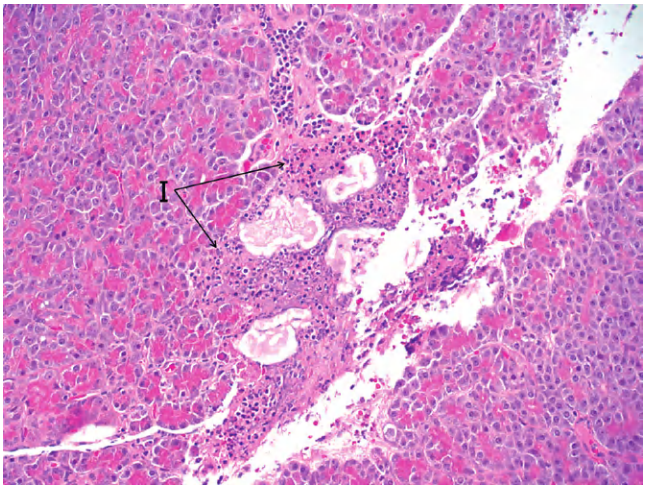

Figure 60-12 Histopathologic appearance of the pancreas of a cat with acute pancreatitis. There are areas of inflammatory infiltration (*I*) but there is no evidence of fibrosis or other permanent histopathologic changes. Hematoxylin and eosin; magnification: 200×. (Courtesy Dr. B.F. Porter, Texas A&M University.)

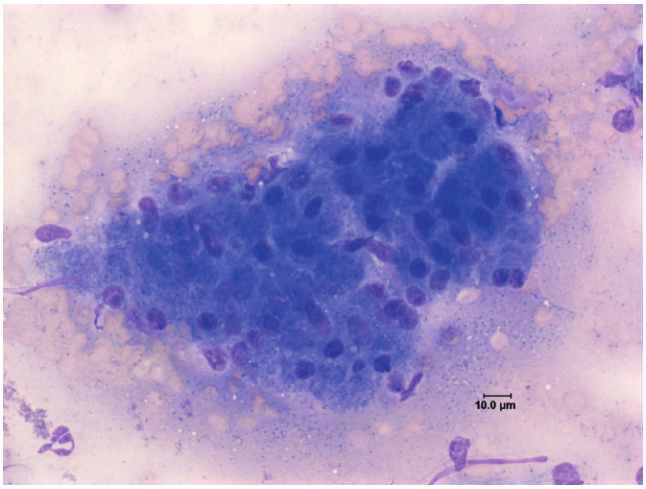

Figure 60-13 Cytologic Appearance of a fine-needle aspirate from a normal canine pancreas. Acinar cells can be seen in the form of a multicellular cluster. Diff-Quik; magnification 500×. (Courtesy Dr. P.J. Armstrong, University of Minnesota.)

Finally, although pancreatic biopsy per se is considered safe, it requires invasive procedures that are expensive and potentially detrimental in patients with pancreatitis that are hemodynamically unstable.[53]

Because concurrent inflammation of the intestines and/or liver appears to be a common problem in cats and may also occur in dogs, intestinal and hepatic biopsies should be considered in patients (especially cats) suspected of having pancreatitis that are undergoing exploratory laparotomy. Likewise, cats with inflammatory bowel disease and/or cholangitis that undergo laparotomy or laparoscopy should be considered for pancreatic biopsy.

Cytology

Fine-needle aspiration of the pancreas and cytologic examination is minimally invasive, relatively safe, and can be used for the diagnosis of pancreatitis in both dogs and cats.[59] To date no study has evaluated the sensitivity and specificity of this modality for the diagnosis of canine or feline pancreatitis, but the finding of inflammatory cells is considered specific for pancreatitis. Pancreatic acinar cells constitute the majority of the cells found in fine-needle aspiration smears from a normal pancreas (Figure 60-13).[59] In patients with acute pancreatitis the cytologic picture is mainly characterized by hypercellularity and the presence of intact and degenerated neutrophils and degenerated pancreatic acinar cells (Figure 60-14). In patients with chronic pancreatitis, small numbers of lymphocytes and neutrophils are usually present, and the specimen is often characterized by low cellularity, possibly as a result of replacement of the normal pancreatic tissue by fibrotic tissue.[59]

Fine-needle aspiration cytology should be performed either under ultrasonographic guidance or during laparotomy.[59] It should be noted that, as for histopathology, highly localized lesions might be missed. Thus negative results are not sufficient to rule out pancreatitis. Fine-needle aspiration cytology might also be useful in differentiating other conditions of the pancreas.

Assessment and Prediction of the Severity of Pancreatitis

Assessment of the severity of human acute pancreatitis is based on the application of standardized severity scores.[60] Prediction of the severity of pancreatitis constitutes a very important component of

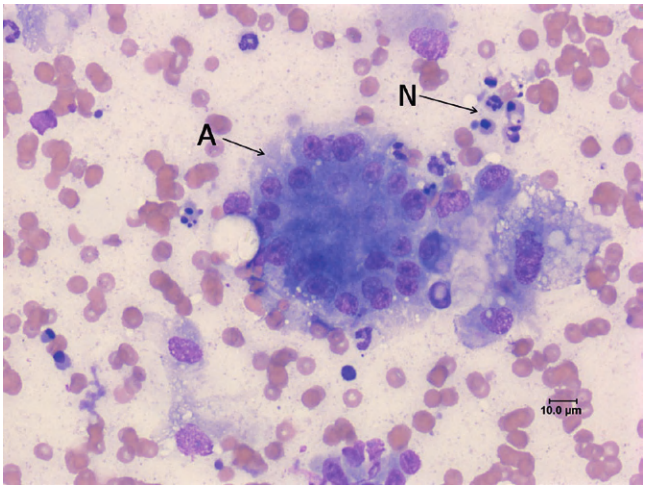

Figure 60-14 Cytologic appearance of a fine-needle aspirate from a canine pancreas with suspected pancreatitis. There is mild to moderate neutrophilic inflammation (*N*) with neutrophilic degeneration. A cluster of normal acinar cells (*A*) can also be seen. Diff-Quik; magnification 500×. (Courtesy of Dr. P.J. Armstrong, University of Minnesota.)

the diagnosis of pancreatitis, because it allows prediction of the likelihood of complications and morbidity, and helps determine the optimal therapeutic plan before the patient enters a critical stage. It is based on a theory that states that the severity of a pancreatitis episode is determined by events that occur within the first 24 to 48 hours of the episode.[61] These events are reflected through clinical, clinicopathologic, and imaging findings that can be used to predict the severity of the pancreatitis.[61]

In veterinary medicine, no well-established and universally accepted severity scores for pancreatitis have been described. Serum PLI and TLI concentrations lack prognostic significance because they correlate poorly with histopathologic severity.[18] Currently, severity of canine and feline pancreatitis is determined based on the clinician's clinical judgment, and typically a diagnosis of severe pancreatitis is made after the animal has entered a critical stage. In

general, evidence of systemic complications (e.g., oliguria, azotemia, icterus, severely increased hepatic enzyme activities, hypocalcemia, hypoglycemia, severe hyperglycemia, leukocytosis, shock, or DIC) are considered as indicators of severe disease and a poor prognosis.[62-64] However, prediction of the severity of pancreatitis has not been sufficiently studied in dogs and cats. Markers that might prove useful in predicting the severity and/or outcome of a pancreatitis episode are serum C-reactive protein concentrations, serum interleukin-6 concentrations, and plasma and urine trypsinogen activation peptide concentration as well as urine trypsinogen activation peptide-to-creatinine ratio.

Concluding Remarks

No single diagnostic modality is 100% reliable for the diagnosis of canine or feline pancreatitis. A careful evaluation of the animal's history, physical examination, and routine clinical pathology findings, as well as the use of highly specific and sensitive tests (serum cPLI and fPLI concentration, abdominal ultrasonography, cytology, and/or histopathology), are crucial for an accurate diagnosis of pancreatitis. In clinical practice, a combination of serum cPLI or fPLI concentration, abdominal ultrasound, and in some cases fine-needle aspiration of the pancreas, currently constitutes the most practical and accurate approach for the diagnosis of both canine and feline pancreatitis.

Exocrine Pancreatic Insufficiency

Clinical Features

The classical and most common presentation of dogs with EPI involves a chronic history of weight loss, a normal or increased appetite, and loose stools, which is usually characterized by passage of large volumes of semiformed feces. However, it is not uncommon for some dogs with EPI to present with a clinical picture that deviates from the classical picture. In those cases, periods of anorexia, absence of loose stools, occasionally watery diarrhea, or vomiting might be seen. Other possible clinical signs include coprophagia, borborygmus, flatulence, abdominal discomfort, and a poor hair coat. In some cases, EPI may be subclinical and those cases can only be diagnosed with appropriate laboratory testing (see "Trypsin-Like Immunoreactivity" section that follows). Cats with EPI have a similar presentation to that of dogs. In cases where chronic pancreatitis is the cause of EPI, polyuria and polydipsia may be seen as a result of concurrent diabetes mellitus.

Trypsin-Like Immunoreactivity

Serum cTLI is the test of choice for the diagnosis of EPI in dogs. This test is highly sensitive and specific for the diagnosis of EPI, and a positive test (usually defined as <2.5 µg/L) in a dog with compatible clinical signs is sufficient to make a diagnosis of EPI.[65] A cTLI result that is well within the reference range is sufficient for excluding EPI, and a normal cTLI result should direct clinicians toward the investigation of other disorders as the cause of the clinical signs observed.[65] Single cTLI results within the equivocal range (usually between 2.5 and 5.7 µg/L) in dogs with clinical signs of gastrointestinal disease need to be interpreted with caution.[66] In these patients, subsequent retesting of serum cTLI concentration shows either a normal concentration or progression to EPI.[66] Therefore, patients with cTLI results in the equivocal range should be investigated for chronic intestinal disease, while reevaluating the cTLI a few weeks later. Some dogs with no clinical signs characteristic of EPI have repeatedly subnormal (<5.7 µg/L) cTLI concentrations.[66,67] These dogs have been shown to have subclinical EPI and some are expected to develop clinical EPI in the future.[66,67] The time of progression from the subclinical to the clinical stage varies greatly and might be from a few months to years.[67] Thus these patients should be closely monitored for the development of clinical signs of EPI and cTLI testing should be repeated every 3 to 6 months.[66,67] Finally, because renal disease might increase serum cTLI concentrations and obscure a diagnosis of EPI, reevaluation of nondiagnostic serum cTLI concentrations in azotemic dogs suspected of having EPI is recommended. Similarly, concurrent inflammation might falsely increase the serum cTLI concentration.

Because EPI appears to be less common in cats than in dogs, diagnosis of this disease has been less-well investigated. Similar to dogs, the fTLI test appears to be the most reliable test for the diagnosis of EPI in cats, having a specificity of at least 85%.[68] The sensitivity of this assay for the diagnosis of feline EPI has not been evaluated to date. Although there are currently two assays that measure fTLI in serum (one radioimmunoassay that is available in the United States and one enzyme-linked immunosorbent assay that is available in Europe), the analytical validation has only been published for the radioimmunoassay, which is available through the Gastrointestinal Laboratory at Texas A&M University. Similar to dogs, it can be recommended that equivocal serum fTLI concentrations in azotemic cats suspected of having EPI be reevaluated, because renal disease might falsely increase serum fTLI concentrations. The same is true for cats with concurrently increased serum fPLI concentrations indicating residual pancreatic inflammation.

Pancreatic Fecal Elastase

An enzyme-linked immunosorbent assay for the measurement of pancreatic elastase in feces is commercially available and is marketed in Europe (Shebo Biotech, Germany) for the diagnosis of canine EPI.[69,70] A recent study reported false-positive results in 23.1% of cases[71] and its sensitivity has not been sufficiently evaluated. The fact that this test is easy and quick to perform might make it a reasonable initial approach for dogs with suspected EPI, but as a consequence of its poor positive predictive value a positive test result must be verified by measurement of serum cTLI concentration. This test might also be useful for EPI cases that are a result of pancreatic duct obstruction. However, to date such a case has only been anecdotally reported in the veterinary literature.

Other Tests

Serum amylase and lipase activities have been shown to have no value in the diagnosis of EPI in either dogs or cats.[21,41,72] Canine PLI concentrations are low or undetectable in most dogs with EPI, but some overlap between healthy dogs and dogs with EPI does exist, making this test inferior to cTLI for the diagnosis of EPI.[21] However, cPLI might be used to diagnose isolated pancreatic lipase deficiency, a rare form of EPI, where serum cTLI and other pancreatic zymogen concentrations are expected to be normal.[73] Commercial assays for the measurement of serum PLI concentration (Spec cPL and Spec fPL) are not useful for the diagnosis of EPI in dogs and cats, respectively, because they have been optimized to detect changes in the higher ranges of their respective working ranges.

Measurement of the fecal proteolytic activity has been used in the past for the diagnosis of EPI in dogs and cats, but are now only used for species for which a TLI assay is not available.[74,75] A plethora of other tests, including microscopic examination of feces and the bentiromide absorption (benzoyl-tyrosyl-paraaminobenzoic acid [BT-PABA]) test, have also been described for the diagnosis of EPI in the past. However, these tests often give false-positive and/or

false-negative results and many of them are impractical, expensive, or of limited availability. Thus none of these tests are recommended for the diagnosis of canine or feline EPI.

Histopathology

Because EPI is a functional and not a histopathologic diagnosis, histopathology is not indicated for the diagnosis of EPI. Given that it has been estimated that more than 90% of the pancreatic parenchyma needs to be destroyed before clinical signs of EPI develop, it is almost impossible to accurately grossly or histopathologically determine the extent of pancreatic atrophy. The only usefulness of histopathology is limited to the determination of the underlying cause of EPI (pancreatic acinar atrophy or pancreatitis). However, in dog breeds that have been shown to be predisposed to EPI because of acinar atrophy (i.e., German Shepherds, Rough-Coated Collies, and Eurasians), histopathology is redundant.[76] Therefore histopathology should only be used in atypical cases where the cause of EPI needs to be definitively determined.

NECROSIS AND INFLAMMATION: CANINE

Panagiotis G. Xenoulis and Jörg M. Steiner

Strictly speaking, *pancreatitis* refers to inflammation (i.e., infiltration with inflammatory cells) of the exocrine pancreas. However, the term pancreatitis is commonly expanded to also include diseases of the exocrine pancreas characterized mainly by necrosis that may have a minimal inflammatory component (often referred to as acute pancreatic necrosis or necrotizing pancreatitis).[1] It is widely believed that pancreatic necrosis is associated with a severe and often fatal course of disease, whereas pancreatitis without necrosis (e.g., edematous interstitial pancreatitis) is usually mild. However, no convincing scientific evidence currently exists to support this assumption in clinical cases of canine pancreatitis.

Pancreatitis is generally divided into acute pancreatitis (which typically includes acute pancreatic necrosis) and chronic pancreatitis (characterized by the permanent histopathologic changes of fibrosis and atrophy). The term *recurrent acute pancreatitis* is sometimes used to describe recurrent episodes of pancreatitis that are not associated with permanent histopathologic changes. A plethora of other clinical (e.g., mild or severe, fatal or nonfatal) and histopathologic (e.g., edematous, interstitial, necrotizing, neutrophilic, lymphocytic) terms have been used to further classify pancreatitis in dogs. However, no universally standardized terminology and definitions exist for pancreatitis in animals, and different authors classify pancreatitis is different ways. It is not clear at this time whether the different forms of pancreatitis (e.g., acute edematous pancreatitis, acute pancreatic necrosis, chronic pancreatitis) represent different phenotypes of the same disease or distinct disease entities, whether they share the same etiologic and pathogenic mechanisms, or which factors determine the development of each form.

Prevalence

Pancreatitis in dogs is common and is associated with significant morbidity and mortality. The prevalence of pancreatitis in dogs varies widely based on the methods used to diagnose the disease. Clinically, its overall prevalence has been estimated at approximately 0.8% in dogs, although certain canine breeds seem to have a higher prevalence.[2] Histopathologic evidence of canine pancreatitis is considerably more common, even in dogs that died from unrelated causes, and has been reported to be as high as 65% when multiple sections of the pancreas are examined.[3] It remains to be determined, however, which degree and/or forms of histopathologic pancreatitis are clinically significant. The mortality for dogs with pancreatitis also varies widely; most dogs with mild pancreatitis recover within a few days and have a very good prognosis, whereas mortality rates in patients with more severe forms of acute pancreatitis have been reported to be 20% to 42%.[4-7]

Pathogenesis and Pathophysiology

Most of our understanding regarding the pathogenesis of pancreatitis is based on animal models and some clinical studies in human patients. There is mounting evidence that genetic and possibly also environmental factors may sensitize the pancreas to injury induced by one or more etiologic factors.[8,9] Regardless of the actual etiology, there appears to be a common pathogenic mechanism in most cases of acute pancreatitis. The initiating events that lead to pancreatitis take place in the acinar cell. Two early intracellular events that precede the development of acute pancreatitis are retention and intracellular activation of zymogens.[8,9] Zymogens are pancreatic enzyme precursors stored in zymogen granules that are normally secreted into the pancreatic duct through the apical membrane of the acinar cell. The factors that lead to retention of zymogen granules and premature intracellular activation of the zymogens are not fully elucidated. One of the most popular theories is the colocalization theory,[8,9] which suggests that zymogen granules accumulate in the acinar cell and colocalize with lysosomes. Lysosomal enzymes, such as cathepsin B, are thought to activate trypsinogen into trypsin, which subsequently activates other zymogens. The cytosolic concentration of free ionized calcium also plays an important role in the intracellular activation of zymogens.[10-12] In addition to decreased secretion and intracellular activation of pancreatic enzymes, there is evidence of disruption of the paracellular barrier in the pancreatic duct that allows its contents to leak into the paracellular space, and also redirection of secretion of zymogen granules from the apical pole to the basolateral region of the acinar cell and into the interstitial space (Figure 60-15).[9]

Once intracellular activation of pancreatic enzymes has taken place, autodigestion of the acinar cell follows and activated enzymes escape into the pancreatic tissue (leading to local effects) and then into the peritoneal cavity and the systemic circulation (potentially contributing to systemic effects). Local effects vary and can range from mild interstitial edema to severe acinar cell necrosis, hemorrhage, and peripancreatic fat necrosis. The extent and severity of local effects determine to a large degree the systemic response. Acinar cell injury leads to recruitment and activation of inflammatory cells (mostly neutrophils and macrophages), which release proinflammatory cytokines and other inflammatory mediators (e.g., IL-1, IL-2, IL-6, IL-18, tumor necrosis factor-α, substance P, platelet-activating factor) that play a crucial role in modulating systemic manifestations.[8,13] Such manifestations include cardiovascular shock, disseminated intravascular coagulation (DIC), SIRS, and multiple organ failure, and are seen in cases of severe acute pancreatitis.[8,13]

Etiology and Risk Factors

In contrast to human patients, in whom an etiology of pancreatitis can be identified in the majority of cases, the etiology of canine

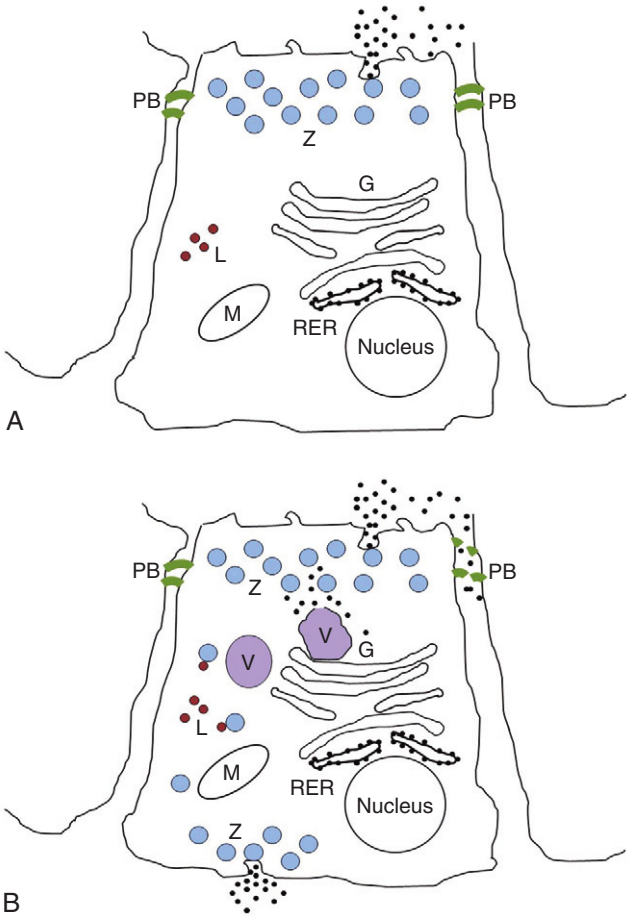

Figure 60-15 Proposed pathogenesis of acute pancreatitis. A, Normal acinar cell. Zymogen granules are found in the apical region of the cell and their contents are excreted exclusively through the apical surface. Lysosomes are packaged and stored separately from zymogen granules and the paracellular barriers are intact. **B,** Acute pancreatitis. Secretion of the zymogen granules is redirected from the apical pole to the basolateral region of the acinar cell and into the interstitial space. Retention of zymogen granules is followed by colocalization with lysosomes and the formation of large vacuoles (*V*) and premature intracellular activation of pancreatic enzymes. There is also disruption of the paracellular barrier in the pancreatic duct that allows its contents to leak into the paracellular space. G, Golgi apparatus; *L*, lysosome; M, mitochondrion; *PB*, paracellular barrier; *RER*, rough endoplasmic reticulum; Z, zymogen granule; *V*, vacuole.

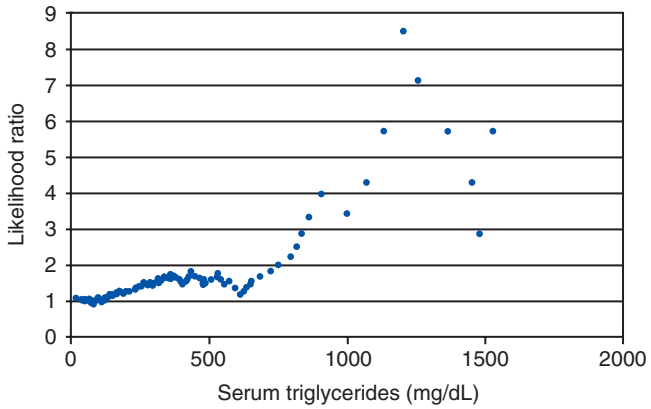

Figure 60-16 Likelihood ratios for different serum triglyceride concentrations for serum cPLI concentrations consistent with pancreatitis (≥200 µg/L; values measured with the original cPLI-ELISA). The likelihood ratio remained between 1 and 2 for serum triglyceride concentrations below approximately 800 mg/dL, and increased sharply for serum triglyceride concentrations of more than 800 mg/dL. (From Xenoulis PG, Suchodolski JS, Ruaux CG, Steiner JM: Association between serum triglyceride and canine pancreatic lipase immunoreactivity concentrations in Miniature Schnauzers. *J Am Anim Hosp Assoc* 46:229, 2010 with permission.)

pancreatitis usually remains unknown (idiopathic pancreatitis).[2,14] It is expected that recognition of new causes of canine pancreatitis will allow etiologic classification in a larger proportion of cases in the future. Several risk factors for canine pancreatitis are described, but the majority of these have been implicated by association, so few definitive causes of pancreatitis have been reported.[2] The main causes of human pancreatitis (i.e., biliary obstruction and alcoholism) do not represent common problems in small animals.[8,14] Other well-defined causes of human pancreatitis (e.g., autoimmune pancreatitis) currently have not been proven in dogs.

Hypertriglyceridemia

Hypertriglyceridemia has been suspected to be a risk factor for pancreatitis in dogs, but convincing evidence was lacking until recently.[15-17] A definitive etiologic association between hypertriglyceridemia and pancreatitis has been difficult to prove, as hypertriglyceridemia might be the result of pancreatitis rather than the cause. Two recent studies suggest that hypertriglyceridemia, which is a known risk factor for human pancreatitis, is also a risk factor for pancreatitis in Miniature Schnauzers.[18,19] Miniature Schnauzers have a high prevalence of idiopathic hypertriglyceridemia, which is often relatively severe.[20] As in humans, the severity of hypertriglyceridemia appears to be important and only Miniature Schnauzers with serum triglyceride concentrations above 862 mg/dL were found to be at increased risk for pancreatitis (Figure 60-16).[8,14,18,19] Interestingly, hypertriglyceridemia appears to be present before the development of pancreatitis and persists after the resolution of the disease, unless a low-fat diet is fed.[19] This supports the hypothesis that, at least in Miniature Schnauzers, severe hypertriglyceridemia is likely a preexisting condition and risk factor for pancreatitis, rather than an epiphenomenon. The exact role of hypertriglyceridemia in the development of pancreatitis, as well as the interaction between hypertriglyceridemia and other risk factors, remains to be determined as not all Miniature Schnauzers with severe hypertriglyceridemia develop clinical pancreatitis. It is not known whether an association between hypertriglyceridemia and pancreatitis also exists in other breeds. Further studies are also needed to determine whether secondary hypertriglyceridemia associated with diseases such as diabetes mellitus, hyperadrenocorticism, and obesity, represents a risk factor for canine pancreatitis.

Hereditary Pancreatitis

A combination of three variants in the serine protease inhibitor Kazal type 1 (*SPINK1*) gene has been identified in Miniature Schnauzers, and an association of these variants with pancreatitis is reported.[21] Mutations in the *SPINK1* gene, although different from those described in Miniature Schnauzers, have also been described and associated with pancreatitis in humans.[22] The product of the *SPINK1* gene, PSTI, is found in acinar cells and acts as one of the defense mechanisms against prematurely activated trypsin. It is possible that the mutant protein lacks this function, therefore leaving

the acinar cell more susceptible to injury, although this has not been shown convincingly. The exact role of the *SPINK1* gene in the development of pancreatitis in Miniature Schnauzers remains to be determined. It is hypothesized that mutations in this gene may not actually cause pancreatitis, but they might sensitize the pancreas to injury through other factors. Genetic causes of pancreatitis have also been suspected in other breeds (e.g., Yorkshire Terriers).[16]

Breed

Several breeds are reported to be at increased risk for pancreatitis, although different studies are not always in agreement with each other. Breed predisposition most likely reflects either genetic causes of pancreatitis or a predisposition to other diseases or conditions that are risk factors for pancreatitis (e.g., hypertriglyceridemia in Miniature Schnauzers). Differences in breed predispositions probably exist in different geographical regions, as blood lines might be different, especially where a breed was introduced to a region decades ago. Miniature Schnauzers, Yorkshire Terriers, and Terriers in general are consistently shown to have a higher risk of developing pancreatitis.[4,16,17,23] Boxers, Cavalier King Charles Spaniels, Cocker Spaniels, and Collies have also been suggested to be overrepresented.[24]

Diet

The role of diet, and more specifically the fat content of the diet, in the development of canine pancreatitis remains unclear. Based on anecdotal clinical observations, high-fat foods increase the risk for pancreatitis. Older experimental studies suggested that diets with a very high fat content may induce pancreatitis and may increase the severity of experimentally induced pancreatitis in dogs.[15,25] The mechanism by which high-fat diets increase the risk for pancreatitis is not known, but it is possible that they may predispose to pancreatitis through hypertriglyceridemia. In a recent retrospective case-control study in dogs, several factors, such as access to trash, consuming table scraps, and ingestion of "unusual" food, were found to be associated with an increased risk of pancreatitis.[23] However, no specific foods were identified that were associated with an increased risk for pancreatitis.

Drugs

As in humans, drug-induced pancreatitis has been reported in the dog, but a cause-and-effect relationship has not been established for most cases.[26] Nevertheless, a history of drug administration in conjunction with compatible findings should raise a concern for drug-induced pancreatitis. Based on the remarkably large number of drugs prescribed in both human and veterinary medicine, and the fact that drug-induced pancreatitis appears to be quite rare, drugs are thought to cause pancreatitis in an idiosyncratic fashion and theoretically, any drug can potentially cause pancreatitis. However, pancreatitis in dogs seems to be more commonly associated with the use of potassium bromide, phenobarbital, L-asparaginase, azathioprine, and meglumine antimonate.[27-29]

Endocrine Disease

In one study, hyperadrenocorticism, hypothyroidism, and diabetes mellitus were reported to be more commonly present in dogs with pancreatitis than in controls.[17] In another study 29 (13%) of 221dogs with diabetes mellitus were reported to have pancreatitis.[30] However, evidence is far from convincing that these endocrine diseases represent risk factors for canine pancreatitis. It has been hypothesized that hypertriglyceridemia associated with these endocrine diseases might be a more significant risk factor for pancreatitis in this species than the conditions themselves.

Obesity

A relationship between obesity and pancreatitis has been suggested for dogs. Studies show that dogs diagnosed with pancreatitis are more frequently obese than are dogs that do not have pancreatitis.[16,17,23] However, a pathogenic link between obesity and pancreatitis has not been convincingly shown to date.

Other Factors

Age is often listed as a risk factor for pancreatitis as most dogs with pancreatitis are middle-aged or older. No clear sex predisposition has been identified. Hypotension (e.g., during anesthesia or after severe blood loss), hypercalcemia (both iatrogenic and as a result of diseases such as neoplasia and hyperparathyroidism), abdominal trauma, extensive surgical manipulation of the pancreas, certain infections (e.g., with certain *Babesia* spp.), and obstruction of the pancreatic duct (e.g., as a consequence of neoplasia) are also suspected risk factors for canine pancreatitis, but evidence is weak or lacking.[2,31] Chronic gastrointestinal (GI) disease might also be a risk factor for pancreatitis in dogs.[32] Primary or metastatic neoplasia of the pancreatic parenchyma is often associated with secondary inflammation of the exocrine pancreas. Previous surgery and epilepsy have also been reported as potential risk factors.[17,23]

Signalment

Dogs of any age, breed, or sex can develop pancreatitis. Most animals are middle-aged to old.[4,17] Miniature Schnauzers and Yorkshire Terriers appear to be at increased risk, while predisposition of other breeds is less clear.[2,16,17,23] In one study some other breeds (e.g., Boxers, Cavalier King Charles Spaniels, Cocker Spaniels, and Collies) were suggested to be predisposed, but this has not been confirmed by other studies.[24] No clear sex predisposition has been identified.

Clinical Signs and Physical Examination Findings

Dogs with pancreatitis can have subclinical disease or present with a variety of clinical signs, ranging from mild partial anorexia with no apparent GI signs to severe systemic signs with cardiovascular shock and DIC. There is no single clinical sign or combination of clinical signs that is pathognomonic for canine pancreatitis. Clinical signs of severe acute pancreatitis may include anorexia (91%), vomiting (with or without blood; 90%), weakness (79%), polyuria and polydipsia (50%), and diarrhea (with or without blood; 33%).[16] Many of the clinical signs are likely to be the result of complicating or concurrent diseases rather than pancreatitis per se (e.g., polyuria and polydipsia are more likely to be the result of concurrent diabetes mellitus). The most common physical examination findings in dogs with severe acute pancreatitis include dehydration (97%), abdominal pain (58%), fever (32%), and icterus (26%).[16] The combination of vomiting and abdominal pain, although suggestive of pancreatitis, is also seen with other diseases (e.g., GI foreign bodies, peritonitis). Other possible findings include shock, hypothermia, cardiac murmur, tachycardia, bleeding diathesis, ascites, a palpable abdominal mass, and harsh lung sounds.[16] Patients with less severe or chronic pancreatitis are typically presented with less-profound clinical signs (e.g., anorexia and depression), or might even be subclinical.

Clinical Pathology[7,16]

Results of the complete blood cell count (CBC), serum biochemistry profile, and urinalysis are nonspecific and thus of limited

usefulness for the diagnosis of pancreatitis in dogs. However, these tests should always be performed in animals with suspected pancreatitis because they are useful for ruling out other differential diagnoses and provide important information about the general condition of the animal.

Often, especially in mild cases, the CBC, serum biochemistry profile, and urinalysis are normal. Possible hematologic findings in dogs with pancreatitis include anemia or hemoconcentration, leukocytosis or leukopenia, and thrombocytopenia. Evidence of coagulopathy, such as prolonged activated clotting time and prothrombin (PT) and partial thromboplastin times, are seen in some cases, and may or may not be associated with spontaneous bleeding. In other cases, there might be evidence suggestive of DIC, such as thrombocytopenia, prolongation of clotting times (activated clotting time, PT, partial thromboplastin time), and a positive D-dimer test. Different combinations of increases in liver enzyme activities and hyperbilirubinemia are common, and might erroneously direct the clinician to suspect primary liver disease. Increases in serum creatinine and blood urea nitrogen (BUN) concentrations are variably present and most often associated with dehydration as a consequence of vomiting, diarrhea, and/or decreased water intake. In severe cases, azotemia might be the result of secondary renal failure. Other possible findings include hypoalbuminemia, hypertriglyceridemia, hypercholesterolemia, and hyperglycemia or hypoglycemia. Electrolyte abnormalities are commonly present and variable, with hypokalemia, hypochloremia, and hyponatremia being the most common.

Clinical Enzymology

Serum Pancreatic Lipase Immunoreactivity

The only cell type known to synthesize pancreatic lipase is the pancreatic acinar cell. An immunoassay for the measurement of canine pancreatic lipase has been developed and analytically validated.[33] In contrast to the traditional activity assays for lipase, which indiscriminately measure the activity of lipases of any origin, this immunoassay specifically quantifies the pancreatic lipase based on its unique antigenic structure. The originally developed in-house immunoassay for canine pancreatic lipase has been replaced by a widely available commercial immunoassay (Spec cPL).[34,35]

Clinical studies suggest that serum cPLI (or Spec cPL) has a high specificity for canine pancreatitis. In one study of 31 dogs with a normal pancreas on histopathology, the specificity of Spec cPL was very high (96.8%).[36] In a recent multicenter study of dogs with clinical evidence of pancreatitis, the specificity of this assay was reported at 78%.[37] Experimentally induced chronic renal failure and prednisone administration do not significantly affect serum cPLI concentration.[38,39] The association between gastritis and serum cPLI concentration requires further evaluation as gastritis was shown to be associated with increased serum cPLI in one study.[40] However, no pancreatic biopsies were examined in that study to exclude pancreatic pathology. The specificity of cPLI also requires further investigation in dogs with various GI diseases but not pancreatitis. It also remains to be determined whether serum cPLI concentration can be increased in patients with histopathologically mild pancreatitis that might be of minor clinical importance and does not contribute to the development of clinical signs. Compared with other serum tests currently available, serum cPLI is considered to have the highest specificity for pancreatitis.[36-39,41-43] However, false-positive results cannot be excluded.

The serum cPLI concentration is also sensitive for the diagnosis of pancreatitis in dogs,[34,37,44,45] ranging from 64% to 93%, possibly depending on the severity of the disease in the patients studied. The sensitivity of serum cPLI is higher than for any other serum test currently available.[34,37,44,45] However, false-negative results are likely to occur, especially in mild cases.

Overall, serum cPLI concentration appears to be a sensitive and specific marker of canine pancreatitis, and is currently considered to be the serum test of choice for the diagnosis of pancreatitis in this species.

Based on clinical observations and the results of studies available to date,[34] serum cPLI concentrations do not appear to correlate with the severity of pancreatitis. Therefore individual measurement of cPLI concentrations cannot be used to determine the severity of pancreatitis. No studies have examined the significance of changes in serum Spec cPL concentrations over time in individual patients.

A point-of-care test for the estimation of pancreatic lipase in serum (SNAP cPL) is available. Published studies evaluating the performance of this test are currently lacking, but it is suggested that it shows the same clinical performance as the serum Spec cPL assay. The recommended use of this test is to rule out pancreatitis in dogs suspected of having the disease. Because of the high sensitivity of Spec cPL, a negative result makes a diagnosis of pancreatitis unlikely. However, false-negative results might occur in some cases. A positive test result should be followed by laboratory measurement of serum Spec cPL concentration.

Serum Amylase and Lipase Activities

Serum amylase and lipase activities have long been considered markers for canine pancreatitis, but several studies show that they have low sensitivity and specificity.[41,46] In one study, approximately 50% of dogs with increased activity of either serum amylase or lipase activity had no histopathologic evidence of pancreatitis.[41] This means that a large proportion of dogs that have diseases other than pancreatitis (e.g., certain renal, hepatic, intestinal, and neoplastic diseases) have increased serum lipase and/or amylase activities.[41] Significant increases of amylase and lipase activities can result from nonpancreatic disorders, and identification of elevated concentrations of these enzymes should always be followed up by the use of more specific and sensitive tests.[15,41,42,47] In addition, the sensitivity of serum amylase and lipase activities for spontaneous canine pancreatitis is generally low (14% to 73% for lipase and 18% to 69% for amylase).[16,34,45] Therefore pancreatitis cannot be confidently diagnosed or ruled out based on serum amylase and/or lipase activities alone.[16,41]

Serum Trypsin-like Immunoreactivity

TLI assays are species-specific immunoassays that measure trypsinogen and trypsin in serum. Trypsinogen is the inactive precursor of trypsin and is synthesized exclusively in the pancreatic acinar cells. The sensitivity of serum cTLI for the diagnosis of canine pancreatitis is low (36% to 47%), probably because of its short half-life.[34,42,45] In addition, although there is strong evidence that trypsinogen is exclusively of pancreatic origin,[48] it is believed that it is cleared by glomerular filtration in dogs, and serum cTLI concentration can be increased in dogs with renal failure.[42,43] In the face of availability of a better serum marker (cPLI), cTLI is currently considered to be of limited value for the diagnosis of canine pancreatitis. If the Spec cPL assay is not available, cTLI might be used to rule in pancreatitis if renal disease has been ruled out. However, a normal cTLI concentration cannot rule out pancreatitis.

Other Diagnostic Tests

Several other tests have been developed and evaluated for the diagnosis of canine pancreatitis. However none can be recommended for

clinical use, either because their clinical value has not been determined accurately or because they have a low specificity and/or sensitivity. In addition, most of these tests have limited availability.

TAP is a small peptide that is released when trypsinogen is activated to trypsin.[42] Under physiologic conditions, trypsinogen is activated mainly in the intestinal lumen, and thus serum TAP concentrations are low or undetectable.[42] During pancreatitis, trypsinogen is prematurely activated in the pancreas and TAP is released into the circulation.[42,49] Plasma and urinary TAP concentrations have been evaluated in healthy dogs, dogs with histopathologically confirmed pancreatitis, and dogs with other systemic diseases.[42] In that study, plasma TAP concentration had good specificity (87.9%), but low sensitivity (53.3%), for the detection of pancreatitis. Urine TAP concentrations did not show any advantage over serum TAP concentrations in diagnosing pancreatitis. Both tests show increases in dogs with severe pancreatitis, but were normal or low in cases of mild pancreatitis. However, this study suggested that, as in humans, serum and urine TAP concentrations might be more useful as a prognostic indicator in dogs with pancreatitis.[42]

Measurement of lipase activity in peritoneal fluid and comparison with serum lipase activity has been evaluated as a tool for the diagnosis of acute pancreatitis in dogs.[50] However, further studies are needed before this method can be recommended for clinical use. Other tests that have been evaluated for the diagnosis of canine pancreatitis include trypsin-α_1-proteinase inhibitor complex concentrations in serum and α_2-macroglobulin concentrations in serum.[51-54]

Diagnostic Imaging

Abdominal Radiography

Conclusive diagnosis or exclusion of pancreatitis is not possible based on abdominal radiography alone.[16] In the majority of cases of pancreatitis, abdominal radiographs are normal or only show nonspecific changes.[16] Despite that, abdominal radiography remains a logical initial approach for patients suspected of having pancreatitis, because it is useful to rule out other differential diagnoses.

Possible radiographic findings in dogs with pancreatitis include increased soft-tissue opacity and decreased serosal detail in the cranial right abdomen, displacement of the stomach and/or duodenum, dilation of bowel loops adjacent to the pancreas, abdominal effusion, and the presence of a cranial abdominal mass.[16]

Abdominal Ultrasound

Abdominal ultrasound is the imaging modality of choice for the diagnosis of pancreatitis in dogs. However, abdominal ultrasonography is also associated with disadvantages, and its performance in the diagnosis of pancreatitis is highly dependent on the experience of the ultrasonographer and the quality of the equipment used. It has been reported to have a relatively high sensitivity of approximately 68% for severe acute pancreatitis in dogs.[16] In a recent study where ultrasonography was performed in 26 animals (both dogs and cats) with suspected GI disease, six (23.1%) of the animals had ultrasonographic evidence consistent with pancreatitis, while histopathology revealed either a normal pancreas or pancreatic hyperplasia.[55] In the same study, there was only a 22% agreement between the ultrasonographic and the histopathologic diagnoses.[55] Although not free of limitations, this study highlights that ultrasonographic findings in animals with suspected pancreatitis should be interpreted with caution. A normal pancreas on ultrasound examination does not rule out pancreatitis.[16,56] If stringent criteria are applied, the specificity of abdominal ultrasonography for pancreatitis is considered to be relatively high, although other diseases of the pancreas (e.g., neoplasia, hyperplastic nodules, pancreatic edema as a consequence of portal hypertension or hypoalbuminemia) may display similar ultrasonographic findings and sometimes cannot be differentiated from pancreatitis.[57,58]

The most important ultrasonographic findings suggestive of pancreatitis in dogs include hypoechoic areas within the pancreas, increased echogenicity of the surrounding mesentery (because of necrosis of the peripancreatic fat), and enlargement and/or irregularity of the pancreas.[16,56,59] Differentiation between necrotizing and edematous pancreatitis might be possible based on ultrasonographic examination (Figures 60-17 and 60-18), although this has not been

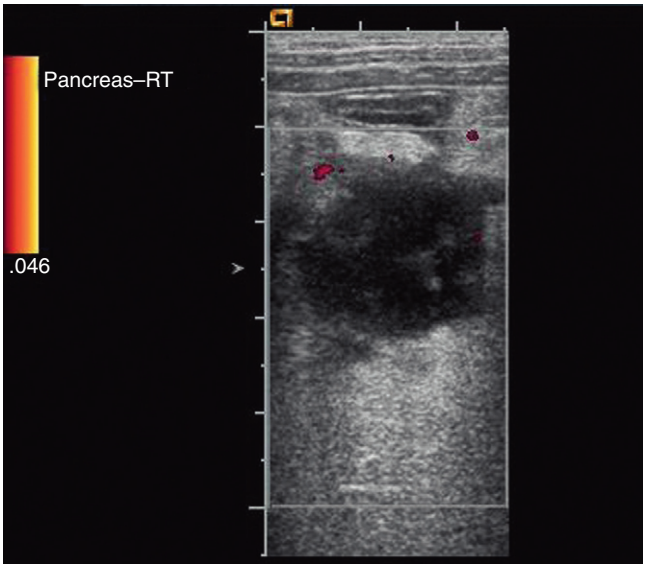

Figure 60-17 Ultrasonographic appearance of the pancreas of a dog with acute necrotizing pancreatitis. The pancreatic lobe is diffusely hypoechoic with a focal anechoic region. No blood flow is present in the necrotic portion, as shown with power Doppler interrogation. (Courtesy of Dr. B. Young, Texas A&M University, College Station, TX.)

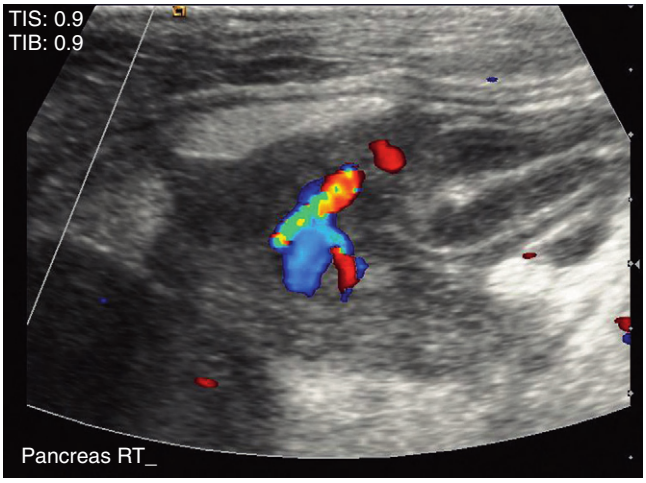

Figure 60-18 Ultrasonographic appearance of the pancreas of a dog with acute edematous pancreatitis. The affected lobe is enlarged, irregularly marginated, and hypoechoic. Note the preservation of blood flow within the pancreas on color flow Doppler interrogation. (Courtesy of Dr. B. Young, Texas A&M University, College Station, TX.)

confirmed in clinical studies. On occasion, hyperechoic areas of the pancreas possibly indicating the presence of pancreatic fibrosis may be present. Less-specific findings may include a dilation of the pancreatic or biliary duct and abdominal effusion. Abdominal ultrasonography is also very useful for the diagnosis of local complications of pancreatitis such as pancreatic abscesses, pancreatic pseudocysts, and biliary obstruction.[59] In addition, ultrasound-guided fine-needle aspiration is a useful tool for the management of noninfectious fluid accumulations of the pancreas (e.g., pancreatic pseudocyst) and for obtaining pancreatic specimens for cytologic evaluation.[60]

Other Imaging Modalities

Several other imaging modalities are routinely used to diagnose or evaluate pancreatitis in human patients. Contrast-enhanced CT is a valuable tool for the evaluation of people with suspected pancreatitis and might also prove to be useful in dogs, but it has not yet been evaluated in an adequate number of canine cases.[61] Other imaging modalities (e.g., endoscopic retrograde cholangiopancreatography, endoscopic ultrasonography) have been studied in healthy dogs and in dogs with GI diseases with varying results.[62,63] However, because of the lack of standardized criteria for the diagnosis of pancreatitis, the complexity of these modalities, their limited availability, and the cost of the equipment, they cannot be currently recommended for the diagnosis of canine pancreatitis.

Pathology

Certain macroscopic lesions identified during surgery, laparoscopy, or necropsy are highly suggestive of pancreatitis and are preferred sites for biopsy collection.[34] Lesions suggestive of pancreatitis may include peripancreatic fat necrosis, pancreatic hemorrhage and congestion, and a dull granular capsular surface (Figure 60-19).[34] However, gross lesions may not always be apparent and in some cases they might be difficult to differentiate from nodular hyperplasia.[3]

A definitive diagnosis of pancreatitis can only be made by histopathologic examination of the pancreas and this is also the only way to differentiate acute and chronic pancreatitis, and in some cases, pancreatitis from pancreatic neoplasia. The presence of permanent histopathologic changes (e.g., fibrosis and acinar atrophy) is considered suggestive of chronic pancreatitis.[3,15] Acute pancreatitis is characterized by absence of permanent histopathologic changes.

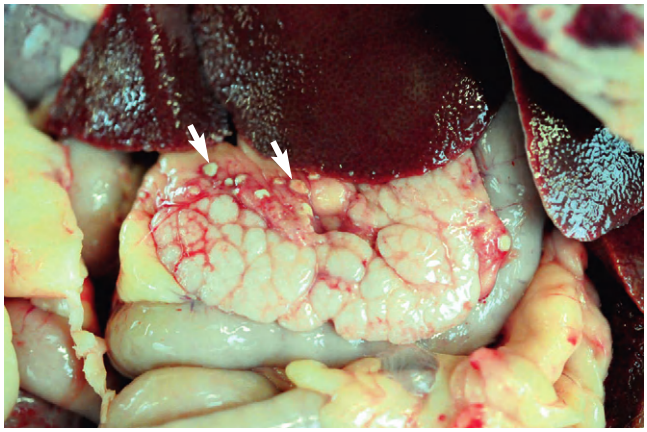

Figure 60-19 Gross appearance of the pancreas of a dog with acute pancreatitis. The pancreas appears edematous and hemorrhagic. Several areas of pancreatic fat necrosis can be seen (*arrows*). Such appearance is highly suggestive of acute pancreatitis. (Courtesy of Dr. John Edwards, Texas A&M University, College Station, TX.)

The predominant inflammatory infiltrate (i.e., neutrophils or lymphocytes) is often used to describe pancreatitis as suppurative or lymphocytic, respectively, and a significant degree of necrosis is usually used to characterize the pancreatitis as necrotizing.

Several limitations are associated with pancreatic histopathology as a definitive diagnostic tool for pancreatitis. First, determining the clinical significance of histopathologic findings may be challenging. At the same time, exclusion of pancreatitis based on histopathology is difficult because inflammatory lesions of the pancreas are often highly localized and can easily be missed.[3] Therefore, multiple sections of the pancreas must be evaluated in order to increase the likelihood of finding microscopic lesions, although this is not always feasible in clinical cases.[3] Finally, although pancreatic biopsy per se is considered safe, it requires invasive procedures that are expensive and potentially detrimental in patients that are hemodynamically unstable.[55]

Cytology

Fine-needle aspiration of the pancreas with cytologic examination was recently introduced as a diagnostic tool for pancreatitis in small animals. It should be performed either under ultrasound guidance or during laparotomy.[64] To date, no studies have evaluated the sensitivity and specificity of this modality for the diagnosis of canine pancreatitis, but the finding of acinar and inflammatory cells in the aspirate is considered specific for pancreatitis. Pancreatic acinar cells constitute the majority of the cells found in fine-needle aspirations from a normal pancreas.[64] In patients with acute pancreatitis there is hypercellularity with intact and degenerate neutrophils and degenerate pancreatic acinar cells. As for histopathology, highly localized lesions might be missed so negative results do not rule out pancreatitis. Cytology might also be useful in differentiating other conditions of the pancreas (e.g., neoplasia) from pancreatitis.

Concluding Remarks on the Diagnosis of Pancreatitis

There is currently no test that is 100% sensitive and specific for the diagnosis of pancreatitis, so false-positive and false-negative results can occur with all tests. The use of careful assessment of the clinical history, physical examination findings, results of routine clinical pathology, diagnostic imaging studies, measurement of cPLI concentration, and when appropriate cytologic and/or histopathologic findings is crucial for a correct diagnosis or exclusion of pancreatitis.

Treatment

Treatment of the Cause

The etiology of pancreatitis remains unknown in the majority of cases, and therefore, treatment of pancreatitis remains almost exclusively supportive. Future recognition of specific causes of canine pancreatitis may lead to the development of more specific treatments for different forms of pancreatitis that are now classified as idiopathic. Until then, the presence of possible risk or etiologic factors should always be investigated. If any of these factors are present, they should be managed where possible. Thus, dogs with pancreatitis should be investigated for the presence of hypertriglyceridemia, hypercalcemia, endocrine diseases, obesity, certain toxicities (e.g., zinc), certain infectious diseases, and inflammatory diseases of the intestine and liver. Important information from the history of the animal include drugs administered (especially potassium

bromide, phenobarbital, and azathioprine), diet offered (especially high-fat diets), and recent surgery or trauma.

Nutrition

Nutritional approaches in people and animals with acute pancreatitis usually include one of the following: (a) enteral nutrition, (b) parenteral nutrition (total or partial), and (c) no nutritional support.[65] In the past, the main concept of nutritional approach during acute pancreatitis was to "rest the pancreas" as it was believed that feeding induced the stimulation of exocrine pancreatic secretion, which might lead to exacerbation of pancreatitis.[15,66] This was based on physiologic observations in normal people and experimental animals, which showed that CCK release during feeding led to stimulation of the exocrine pancreas.[67] Therefore, the standard approach to patients with acute pancreatitis included complete avoidance of any form of enteral nutrition, which was achieved either by providing no supplementary nutrition or by parenteral nutrition.[66] However, subsequent studies showed a decreased exocrine pancreatic secretion in response to CCK in experimentally induced pancreatitis.[67] It is now recognized that both parenteral and enteral routes of alimentation are superior to providing no nutritional support, and thus providing early and adequate nutritional support has become a priority in the treatment of human patients with acute pancreatitis.[66] In addition, several human studies show that enteral nutrition is superior to parenteral nutrition, and enteral nutrition is now the preferred method of alimentation for patients with acute pancreatitis.[65,66] Regarding the location of food delivery through enteral feeding, jejunal feeding is considered by many to be the method of choice, but studies in humans show that nasojejunal feeding offers no advantages compared with nasogastric feeding.[66,67] Thus, gastric delivery of nutrients is preferred in many cases as it is much simpler than jejunal feeding and is well tolerated by most patients.

Unfortunately, studies in dogs with pancreatitis are limited. Information from clinical experience and preliminary studies suggest that enteral nutrition is generally well tolerated and improves, or at least, does not worsen the course of pancreatitis.[68,69] Using this information and applying the knowledge based on studies in experimental animals and humans to dogs, the following recommendations can be made: (a) dogs with pancreatitis should not be kept without enteral nutritional support for more than 24 hours (including times of anorexia before presentation); (b) dogs with acute pancreatitis that are not vomiting should generally be fed by mouth. If they are anorectic, a feeding tube should be used (esophagostomy, nasoesophageal, gastrostomy, nasogastric, or jejunostomy tube) until the animal is eating again. Esophagostomy and nasoesophageal or nasogastric tubes are usually preferred because their placement is less invasive and is associated with few complications[70]; and (c) if the animal is vomiting, antiemetics should be used to control vomiting and enteral nutrition should be given as soon as possible. Jejunostomy tubes should be considered in animals with refractory vomiting or animals that undergo exploratory or therapeutic laparotomy. Their use is relatively safe with severe complications (e.g., breakdown of the surgical site) being reported in 0% to 6% of dogs.[70,71] Endoscopic techniques for percutaneous gastrojejunostomy tube placement might prove helpful in the future.[72]

A diet of choice has not been determined in people or dogs with pancreatitis, but a balanced extra-low-fat diet is currently our preferred choice for dogs. Administration of parenteral nutrition has been reported in dogs, but we rarely recommended its use (unless enteral nutrition is contraindicated in a patient), mainly because of data from human studies (see earlier discussion), its unproven efficacy in dogs with pancreatitis, and the potential for serious complications.[73-75]

Fluid Therapy

Dogs with pancreatitis are often presented with variable degrees of dehydration because of decreased water intake, vomiting, diarrhea, and/or third space losses. In these cases, dehydration results most commonly from isotonic fluid loss. The degree of dehydration can be estimated by evaluating physical parameters (e.g., dryness of mucous membranes, reduced skin turgor), or by detailed serial monitoring of body weight.[76,77] Dehydration might also be evident in clinicopathologic testing (e.g., hemoconcentration, increased total protein concentration, high urine specific gravity, prerenal azotemia, and others).[76,77] Replacement isotonic fluid solutions (e.g., lactated Ringer solution, 0.9% NaCl) are the treatment of choice for dehydrated dogs with pancreatitis. Mild dehydration (approximately 5%) may be treated by subcutaneous fluid administration. If the animal is not vomiting, oral rehydration therapy may also be used. Moderate and severe dehydration (>6%) should be treated with intravenous fluid administration. Severely dehydrated animals might be in shock, in which case they require aggressive intravenous fluid therapy (see following discussion).[76]

In dogs with severe acute pancreatitis, rapid and excessive fluid loss as a consequence of vomiting, diarrhea, and/or third space accumulation of fluid, might lead to hypovolemia and compromised perfusion of organs and tissues. Tissue hypoperfusion and especially diminished pancreatic microcirculation is believed to contribute to the development of major local and systemic complications.[78] Hypovolemic patients may or may not be dehydrated, depending mostly on the volume and rapidity of fluid loss.[76] Severe hypovolemia leading to hypovolemic shock is a life-threatening condition and must always be treated as an emergency. In addition to the volume deficit, some animals have a reduced red blood cell volume as a result of GI blood loss, which further decreases tissue perfusion. Clinical findings indicating hypovolemia include hypotension, reduced peripheral pulses, tachycardia, cold extremities, prolonged capillary refill time, and pale mucous membranes.[76,77]

In human patients, aggressive fluid resuscitation using crystalloid solutions is recommended in most cases, while colloids are used only in specific cases (e.g., where there is hypoalbuminemia).[78] Although studies are lacking in dogs, aggressive intravenous fluid therapy (fluid resuscitation) should be initiated as soon as possible when there is hypovolemic shock, before initiating the rehydration phase (if the animal is also dehydrated).[76] Current recommendations for initial fluid therapy of hypovolemic shock include rapid intravenous administration of one or more small boluses (10 to 20 mL/kg in <5 minutes) or a single bolus (90 mL/kg in 15 to 20 minutes) of an isotonic crystalloid solution and close monitoring of physical parameters for evidence of improvement (e.g., slower heart rate, improved pulse quality and capillary refill time).[77,79] Care should be taken not to cause fluid overload in these patients. Based on the response to initial treatment and the severity of hypovolemia, crystalloid fluids can then be administered at rates of 20 to 90 mL/kg/h. Colloids (e.g., dextran 70, hydroxyethyl starch) may also be added to the isotonic crystalloid solutions for more effective volume expansion of the intravascular space, especially when severe hypoalbuminemia (<1.5 g/dL) is present.[76,77,79] Studies of experimental acute pancreatitis in dogs suggest that hypertonic saline-dextran solutions may be more efficacious than crystalloid solutions in restoring tissue perfusion.[80] However, studies of dogs with spontaneous pancreatitis are lacking and current recommendations in humans favor crystalloid use in most cases.[78]

Plasma and Blood Transfusion

The use of fresh-frozen plasma (10 to 15 mg/kg once a day) is recommended by some authors for dogs with severe pancreatitis because it contains several beneficial components, such as proteinase inhibitors (e.g., α_1-proteinase inhibitor, α_2-macroglobulin), albumin, as well as coagulation and anticoagulation factors.[15,81] Proteinase inhibitors may protect from development or worsening of pancreatitis, and depletion of proteinase inhibitors has been reported in dogs with both experimental and spontaneous pancreatitis.[15,54,82] However, in one study, α_2-macroglobulin concentrations did not correlate with severity of pancreatitis in dogs.[54] Studies in humans show no benefit of plasma administration in the clinical outcome of patients with acute pancreatitis, despite the increase in plasma concentrations of proteinase inhibitors.[83] Therefore fresh-frozen plasma is generally only recommended for the treatment of people with pancreatitis when they have coagulopathies. In addition, in a recent retrospective study, dogs with pancreatitis that received fresh-frozen plasma had a worse outcome than dogs that did not receive fresh-frozen plasma.[7] In that study, there was no significant difference in the severity of pancreatitis before treatment, although treatments were not controlled in the two groups and group allocation was not randomized.[7] Thus, the actual value of plasma administration is highly questionable in dogs with pancreatitis. It is possible that, as in humans, its usefulness is limited to cases where coagulopathies are present.[81] Well designed prospective and randomized studies are needed to critically evaluate the usefulness of plasma administration in dogs with pancreatitis. Fresh whole blood (20 to 25 mL/kg once a day) might be used if fresh-frozen plasma is not available or if there is severe blood loss.

Therapy for Electrolyte and Acid–Base Abnormalities

Electrolyte abnormalities are common in dogs with acute pancreatitis. Various combinations and degrees of hypokalemia, hyponatremia, and hypochloremia can be present as a result of diarrhea, vomiting, fluid therapy, and/or anorexia.[16] Hyperkalemia, hypernatremia, and hypocalcemia or hypercalcemia are reported less frequently.[16] Unfortunately, the nature of electrolyte abnormalities in dogs with pancreatitis cannot be accurately predicted and serum potassium, sodium, chloride, and ionized calcium concentrations should always be measured and corrected in these patients. The variability of electrolyte abnormalities in animals with pancreatitis is further complicated by the presence of concurrent diseases such as diabetes mellitus. Hypokalemia may or may not be associated with clinical signs such as muscular weakness and cardiac arrhythmia. Its correction should be achieved by addition of potassium chloride to intravenous fluids, and it should be administered at a rate of 0.15 to 0.5 mEq/kg/h, depending on the severity of depletion and ongoing losses. Hyponatremia is usually asymptomatic and is usually corrected by administration of crystalloid solutions (lactated Ringer solution or 0.9% saline). Although not as common as in cats, hypocalcemia can also be seen in dogs with pancreatitis, but clinical signs attributable to hypocalcemia are rarely noted.[16,84] The value of supplementing calcium has not been evaluated in dogs. Most hypocalcemic patients with pancreatitis have no clinical signs of hypocalcemia, and thus can be treated with 10% calcium gluconate at a dose of 5 to 10 mg/kg/h of elemental calcium given in the crystalloid infusion.

Acid–base disturbances are also common in dogs with pancreatitis and may occur as a result of vomiting, diarrhea, and/or hypoperfusion. The nature of acid–base disorders in dogs with pancreatitis cannot be accurately predicted and blood gas analysis is recommended. Patients with vomiting of gastric fluid typically develop metabolic alkalosis because of loss of chloride and H^+, while patients with diarrhea are more likely to develop metabolic acidosis as a result of loss of HCO_3^-. In patients with both vomiting and diarrhea, or with vomiting that also includes duodenal content, the acid–base status is more difficult to predict. Mild acid–base disorders are corrected through fluid therapy. Treatment of more severe forms of acid–base disorders depends on the specific type of the disorder.

Analgesic Therapy

Pain is believed to accompany virtually all cases of pancreatitis in dogs, even when pain is not clinically obvious.[85] Pain induces several physiologic changes, including decreased appetite, decreased GI tone, decreased regional blood flow to several abdominal organs (including the pancreas), and tachycardia, and it may produce a catabolic state.[86,87] Therefore, analgesic therapy is extremely important and should be used in all dogs with pancreatitis.

Pain in dogs with pancreatitis can range from mild to severe. Opioid administration is mandatory in the management of pain in acute pancreatitis. The intravenous route is usually preferred because it provides fast results. For mild to moderate pain, administration of buprenorphine (0.005 to 0.015 mg/kg, IV, IM, or SC, q6-12h) is usually sufficient. In dogs with severe pain, administration of morphine (0.5 to 1.0 mg/kg, slowly IV or IM q2h; constant-rate infusion [CRI], 0.05 to 0.2 mg/kg/h), hydromorphone (0.1 to 0.2 mg/kg, slowly IV or IM q2h; CRI, 0.0125 to 0.05 mg/kg/h), methadone (0.1 to 0.5 mg/kg IV, IM, or SQ q2-6h), or fentanyl (0.005 to 0.01 mg/kg IV, IM, or SQ q2h; CRI, 0.002 to 0.006 mg/kg/h) is very effective, especially when used as a CRI. Multimodal pain management might be indicated in some cases with severe pain, because it may be more effective and associated with fewer side effects because of lower dosages of the drugs administered. Combinations commonly used in dogs include morphine (0.1 mg/kg/h), lidocaine (2.5 mg/kg/h), and ketamine (0.6 mg/kg/h). Fentanyl patches (patch size is based on patient size, every 3 to 4 days) are safe and practical, but they should be used only after analgesia has been achieved by use of injectable opioids, as it takes longer for transdermal application to achieve analgesia. Analgesic therapy in outpatients can be achieved with fentanyl patches, buprenorphine, or tramadol (4 mg/kg PO q12h).

Antiemetic Therapy

Antiemetic therapy should be initiated in all dogs with pancreatitis that are vomiting or appear nauseated. Maropitant is a neurokinin-1 (NK-1) receptor antagonist, which acts through inhibition of substance P.[88] Although not specifically tested for pancreatitis, several studies have demonstrated the effectiveness of this drug in both preventing and treating vomiting of different etiologies in dogs.[89,90] Maropitant has been shown to be effective in controlling both peripherally and centrally mediated emesis, because NK-1 receptors are located both centrally (emetic center, chemoreceptor trigger zone) and peripherally (mainly vagal nerve terminals).[89,90] Based on recent unpublished data, maropitant may also have analgesic effects, that may be primary or secondary (Dr. D. Twedt, Colorado State University, Fort Collins, CO, personal communication). For the treatment of acute vomiting, the injectable solution is administered at a dose of 1 mg/kg SC q24h for up to 5 consecutive days. If therapy is needed for longer periods, a 48- to 72-hour washout period is recommended.[88] Maropitant is generally well tolerated in dogs.

5-HT_3 antagonists such as dolasetron (0.6 mg/kg IV, SC, or PO q12h) and ondansetron (0.1 to 0.2 mg/kg, slowly IV, q6-12h) can also be used and seem to be effective in many cases. 5-HT_3 antagonists can be used in combination with maropitant in refractory cases

of vomiting, although the safety of this combination is only anecdotal. Dopaminergic antagonists (e.g., metoclopramide 0.2 to 0.5 mg/kg IV, IM, SQ, or PO q6-8h) are considered to be less effective and might negatively affect the course of pancreatitis because dopamine protects against experimentally induced acute pancreatitis in experimental animals.[91,92] CRIs of metoclopramide (0.3 mg/kg/h IV) seem to be more effective than single doses. Finally, α_2-adrenergic antagonists such as chlorpromazine should be avoided because of their potentially serious side effects (mainly hypotension).

Antibiotic Therapy

Prophylactic use of antibiotics is controversial in human patients with pancreatitis. Prophylactic antibiotics have been recommended in people with pancreatic necrosis.[8] The goal of antibiotic prophylaxis in human patients with necrotizing pancreatitis is to prevent bacterial translocation from the intestinal lumen, prevent or decrease pancreatic colonization, and reduce mortality.[93,94] Meta-analysis studies have often arrived at conflicting results.[8,78,93,94] Because multicenter, double-blinded, placebo-controlled, and meta-analysis studies have failed to show a clear advantage of prophylactic antibiotic use in people with severe necrotizing pancreatitis, most authors do not recommend antibiotic prophylaxis in human pancreatitis.[8,78]

Studies on prophylactic antibiotic use in dogs with spontaneous pancreatitis are lacking. Because infectious complications occur much less frequently in dogs compared with people and given that prophylactic antibiotic use is not clearly efficacious in human patients, prophylactic use of antibiotics is believed to be of no benefit in dogs with pancreatitis. In addition, side effects such as anorexia and vomiting might be associated with some antibiotics, while others might be implicated in the initiation of pancreatitis. The use of antibiotics is recommended in cases where infectious complications are identified (e.g., aspiration pneumonia, infected pancreatic necrosis) or are suspected. Antibiotic selection should be based on culture and sensitivity but cefotaxime, ciprofloxacin, metronidazole, clindamycin, and chloramphenicol achieve therapeutic levels in the pancreas in experimental pancreatitis.[95,96]

Surgery

Surgery for Pancreatitis

Surgical management of canine pancreatitis without pancreatic complications is rarely recommended. Some clinicians recommend peritoneal lavage to treat dogs with severe pancreatitis as it was suggested to remove harmful substances, such as trypsin and inflammatory cytokines, from the peritoneal cavity.[97] However, recent well-designed and metaanalysis studies in humans show that use of peritoneal lavage is not associated with any significant improvement in morbidity or mortality.[97]

In an older study of experimental canine pancreatitis, there was a significant improvement in survival with the use of peritoneal dialysis.[98] However, experimental models for pancreatitis do not represent an ideal model of spontaneous pancreatitis, and no studies have evaluated the usefulness of peritoneal lavage in naturally occurring pancreatitis in dogs. Given that peritoneal lavage is invasive, expensive, often associated with severe complications (e.g., peritonitis, anesthesia of compromised patients), and of unproven value, it is generally not recommended for the management of acute pancreatitis in dogs.

Surgery for Pancreatic Complications of Pancreatitis

Several pancreatic complications of pancreatitis have been reported in dogs, and surgical intervention is used in some cases to treat them. Because these complications of pancreatitis have been reported infrequently in the veterinary literature, evidence-based information regarding the treatment of choice is lacking. In addition, the terminology and definition of pancreatic complications of pancreatitis used in dogs has been adapted from the human literature and does not accurately illustrate these complications in dogs. The human classification of pancreatic complications of pancreatitis is currently being updated[99] and will most likely be adapted for dogs as well. In this chapter, and in order to avoid confusion, the terminology used in the previously published reports in dogs is used.

A *pancreatic abscess*[100-105] is the most commonly reported complication of pancreatitis in dogs, and has been described in association with both acute and chronic pancreatitis. Pancreatic abscesses are believed to occur infrequently, with a reported prevalence of 1.4% to 6.5%. In contrast to people, pancreatic abscesses are usually sterile in dogs, with only up to 22% of the reported cases yielding bacterial growth, although many of these dogs had received antibiotics prior to admission. Surgical intervention is almost always recommended when a pancreatic abscess is identified, and several surgical techniques have been described. Mortality in dogs with pancreatic abscesses ranges from 50% to 86%, making the presence of a pancreatic abscess a poor prognostic indicator.

Pancreatic pseudocysts[105-108] are reported as a complication of pancreatitis (both acute and chronic), but appear to be uncommon. Their pathogenesis is unknown and they are usually sterile. Ultrasound-guided fine-needle aspiration of the cystic fluid may be used for the management of small pseudocysts. In other cases, however, clinical signs persist or worsen despite treatment and enlargement of the pseudocyst may occur over time. In these cases surgical intervention is usually recommended, although surgical techniques are poorly described. Internal drainage appears to be the treatment of choice in humans.

Necrotic masses,[101,105] usually arising from necrotizing pancreatitis, have been reported in a small number of dogs. These dogs were treated surgically (debridement and drainage) but died or were euthanized soon after surgery.

Extrahepatic biliary tract obstruction[109] has also been reported as a result of pancreatitis in dogs, and surgery is usually required in cases of complete obstruction of the bile duct or in cases where the obstruction does not subside within 2 to 3 weeks.

Other Treatments

A plethora of other therapeutic agents (e.g., dopamine, H_1- and H_2-histamine receptor antagonists, somatostatin, anticholinergics, protease inhibitors, antioxidants, platelet-activating factor inhibitors, IL-10, selenium, probiotics) have been recommended by some authors in both veterinary and human medicine. Some of these therapeutic agents have shown potential benefit in feline models of experimental pancreatitis (e.g., dopamine, H_1- and H_2-histamine receptor antagonists)[110,111] or in clinical trials in people (e.g., the protease inhibitor gabexate mesylate),[112] and may prove to be beneficial for clinical use in the future. For the majority of the therapeutic agents mentioned previously, however, either appropriate clinical trials are lacking or have shown no benefit in the treatment of acute pancreatitis in humans.[112] There is currently no convincing evidence that any of these agents is beneficial for the treatment of spontaneous pancreatitis in dogs.

There are anecdotal reports that some dogs with chronic pancreatitis respond to corticosteroid (e.g., prednisone) or other immunosuppressive therapy. It is likely that, as in humans, some cases of canine chronic pancreatitis might have an autoimmune component

and these cases might benefit from corticosteroid administration. The safety and effectiveness of corticosteroids or other immunosuppressive agents in dogs with pancreatitis has not been evaluated, and therefore, these agents should be used with caution and only when all other treatments have failed.

Prognosis

The prognosis for dogs with pancreatitis depends on the severity of the disease. Mild cases usually have a good prognosis, and if recurrent episodes of pancreatitis do not occur, these animals live for long periods of time. In contrast, the prognosis for dogs with severe pancreatitis is usually guarded. The mortality associated with severe acute pancreatitis is high and the existence of pancreatic complications (e.g., pancreatic abscess) or concurrent diseases (e.g., diabetes mellitus) further contributes to a poorer outcome. It is unknown if dogs that have a single episode of pancreatitis are at risk for developing chronic or recurrent acute pancreatitis. The prognosis for dogs with chronic or recurrent acute pancreatitis is difficult to predict, and it depends on the severity of each acute exacerbation of the disease. Unfortunately, no accurate method has been reported to date for the prediction of the outcome of dogs with spontaneous pancreatitis, and the prognosis should be evaluated on an individual basis.

NECROSIS AND INFLAMMATION: FELINE

Robert J. Washabau

Several pathologies involving the feline exocrine pancreas have been identified (Figure 60-20).[1-12] Pathologic classification systems have been used to delineate these disorders,[13,14] although it should be emphasized that significant overlap exists between several disease categories particularly with regard to acute and chronic forms of pancreatitis.[8,10]

- ANP: This lesion is characterized by pancreatic acinar cell and peripancreatic fat necrosis (>50% of the pathology), with varying amounts of inflammation, hemorrhage, mineralization, and fibrosis. Inflammation may be present, but necrosis is the predominant feature. Reports of this condition were uncommon prior to the early 1990s, probably related to difficulties in diagnosis as well as lower incidence of disease. ANP is now a well-recognized gastrointestinal disorder of significant morbidity and mortality in the domestic cat.[1-10]
- Acute suppurative pancreatitis: Acute suppurative pancreatitis differs from ANP in that neutrophilic inflammation accounts for >50% of the pancreatic pathology. Necrosis may be present, but neutrophilic inflammation is the predominant feature. Acute suppurative pancreatitis is less common than ANP, appears to affect younger animals, and may have a differing pathogenesis.[2,5,6,10]
- Chronic nonsuppurative pancreatitis: This lesion is characterized by lymphocytic inflammation, fibrosis, and acinar atrophy. Necrosis and suppuration may be present in small amounts, but lymphocyte infiltration is the predominant feature. Antemortem differentiation of chronic nonsuppurative pancreatitis and ANP cannot be made on the basis of clinical, clinicopathologic, or imaging findings[10]; histopathology remains the only dependable method of differentiating these two disorders.[10] Chronic nonsuppurative pancreatitis and ANP may vary in their pathogeneses or they may represent a continuum of disease from necrosis to inflammation and fibrosis.[1,10]
- Pancreatic nodular hyperplasia: Nodules of pancreatic acinar or duct tissue are distributed throughout the pancreatic parenchyma. Fibrosis, inflammation, necrosis, and hemorrhage are not features of this condition. The clinical significance of this lesion is unknown. Pancreatic nodular hyperplasia is often detected at the time of routine abdominal ultrasonography or as an incidental finding at necropsy. Its importance resides in the need to differentiate its ultrasonographic characteristics from those of ANP.
- Pancreatic neoplasia: Neoplastic disorders of the pancreas may be primary (e.g., adenoma, adenocarcinoma) or secondary, and they are classified as benign or malignant. Pancreatic adenocarcinoma is the most common malignancy of the feline exocrine pancreas and is of ductal (primarily) or acinar origin. Neoplastic infiltration may be accompanied by necrosis, inflammation, fibrosis, hemorrhage, or mineralization in some instances.
- Pancreatic pseudocyst: Pancreatic pseudocyst is a common complication of pancreatitis in humans, and a not-so-common complication in cats and dogs.[15] Pancreatic pseudocyst is a nonepithelial lined cavitary structure containing fluid, pancreatic cells, and/or enzyme. It is observed at the time of ultrasound, CT scan, surgery, or necropsy. Its importance resides in the need to differentiate its ultrasonographic characteristics from those of pancreatic abscessation.
- Pancreatic abscess: Pancreatic abscess is a circumscribed collection of purulent material involving the right or left lobe of the pancreas. Like pseudocyst, pancreatic abscessation appears to be a complication of pancreatitis in humans and dogs.[16] The incidence and significance of this lesion in the cat are unknown. Medical and surgical therapies have been used to manage pancreatic abscesses in the dog.
- Pancreatic atrophy: Atrophy may result from degeneration, involution, necrosis, or apoptosis of the exocrine portion of the gland. Most feline cases are believed to represent the end stage of chronic pancreatitis. The endocrine portion of the gland may or may not be involved in the same process. EPI is the clinical syndrome that results from 95% or greater loss of exocrine pancreatic function. Affected animals develop a classic maldigestion syndrome characterized by weight loss, steatorrhea, and diarrhea.[11,17]

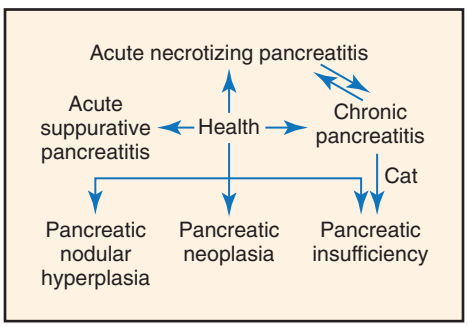

Figure 60-20 Pathogenesis of feline exocrine pancreatic disease.

Etiology

The etiologies of ANP are probably not yet completely recognized. Biliary tract disease, GI tract disease, ischemia, pancreatic ductal obstruction, infection, trauma, organophosphate poisoning, and lipodystrophy all have known associations with the development of ANP in the cat. Hypercalcemia, idiosyncratic drug reactions, and

Box 60-2 Etiologies of Feline Acute Necrotizing Pancreatitis

Known Associations
Biliary tract disease
Ischemia
Infection
Organophosphates
Gastrointestinal disease
Ductal obstruction
Trauma
Lipodystrophy

Suggested Associations
Hypercalcemia
Nutrition
Drug reactions

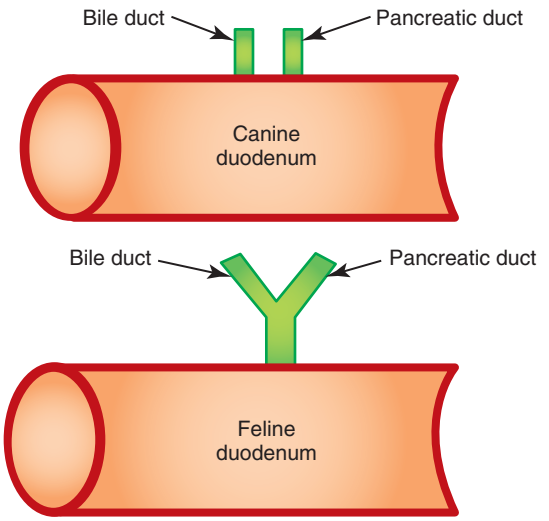

Figure 60-21 Differences in pancreaticobiliary anatomy between cats and dogs. Pancreatic and bile ducts have separate channels of entry in the canine small intestine, whereas these ducts merge prior to their entry in the feline small intestine.

nutritional causes are suggested but poorly documented causes of the disease (Box 60-2).

Concurrent Biliary Tract Disease

Concurrent biliary tract pathology has a known association with ANP in the cat. Cholangitis is the most important type of biliary tract disease for which an association has been made,[18] but other forms of biliary tract pathology (e.g., stricture, neoplasia, and calculus) have known associations.[2,9] Epidemiologic studies[18] show that cats affected with suppurative cholangitis have significantly increased risk for pancreatitis. The pathogenesis underlying this association is not entirely clear but relates partly to the anatomic and functional relationship between the major pancreatic duct and common bile duct in this species.[19,20] Unlike the dog, the feline pancreaticobiliary sphincter is a common physiologic and anatomic channel at the duodenal papilla (Figure 60-21). Mechanical or functional obstruction to this common duct readily permits bile reflux into the pancreatic ductal system.[21-23] Bile salt perfusion (e.g., 1 to 15 mM sodium cholate or glycodeoxycholate) of the major pancreatic duct induces changes in the permeability of the pancreatic duct,[21,22] and sustained elevations in ductal pressure (>40 cm H_2O) and bacterial infection induce pancreatic acinar necrosis.[1,22] Ductal pressures are readily increased by biliary infection, and ductal compression is a predictable consequence of sustained ductal hypertension and pancreatic interstitial edema.[22,23]

Concurrent Gastrointestinal Tract Disease

Like concurrent biliary tract disease, inflammatory bowel disease (IBD) is an important risk factor for the development of ANP in the cat.[18,24] Several factors appear to contribute to this association: (a) High incidence of IBD—IBD is a common disorder in the domestic cat.[24-26] In some veterinary hospitals and specialty referral centers, IBD is the most common GI disorder in cats. (b) Clinical symptomatology of IBD—Vomiting is the most important clinical sign in cats affected with IBD.[24-26] Chronic vomiting raises intraduodenal pressure and increases the likelihood of pancreaticobiliary reflux. (c) Pancreaticobiliary anatomy—The pancreaticobiliary sphincter is a common physiologic and anatomic channel at the duodenal papilla,[19,20] thus reflux of duodenal contents would perfuse pancreatic and biliary ductal systems. (d) Intestinal microflora—Compared with dogs, cats have a much higher concentration of aerobic, anaerobic, and total (10^9 vs. 10^4 organisms/mL) bacteria in the proximal small intestine.[27,28] Bacteria readily proliferate in the feline small intestine because of differences in GI motility and immunology.[29,30] If chronic vomiting with IBD permits pancreaticobiliary reflux, a duodenal fluid containing a mixed population of bacteria, bile salts, and activated pancreatic enzyme would perfuse the pancreatic and biliary ductal systems.[31]

Ischemia

Ischemia (e.g., hypotension, cardiac disease) is a cause or consequence of obstructive pancreatitis in the cat. Inflammation and edema reduce the elasticity and distensibility of the pancreas during secretory stimulation. Sustained inflammation increases pancreatic interstitial and ductal pressure which serves to further reduce pancreatic blood flow, organ pH, and tissue viability.[32-34] Acidic metabolites accumulate within the pancreas because of impaired blood flow.[34-36] Ductal decompression has been shown to restore pancreatic blood flow, tissue pH, and acinar cell function.[35,36]

Pancreatic Ductal Obstruction

Obstruction of the pancreatic duct (e.g., neoplasia, pancreatic flukes, calculi, and duodenal foreign bodies) is associated with the development of ANP in some cases.[9,37] Pancreatic ductal obstruction has marked effects on pancreatic acinar cell function. During ductal obstruction, ductal pressure exceeds exocytosis pressure and causes pancreatic lysosomal hydrolases to colocalize with digestive enzyme zymogens within the acinar cell.[38] Colocalization is the underlying pathogenesis for digestive enzyme activation within the acinar cell because lysosomal enzymes (e.g., cathepsin B) readily activate trypsin.[38]

Infection

Infectious agents (*Toxoplasma gondii*, feline herpesvirus 1, feline infectious peritonitis) have been implicated in the pathogenesis of feline ANP[39-41] although none have been reported as important causes of ANP in any of the recent clinical case series.[1-10,12] The pancreas is readily colonized by *T. gondii* organisms during the acute phase of infection.[39] In one survey of *T. gondii*-infected cats, organisms were found in 84% of the cases, although organ pathology was more severe in other organ systems.[39] *Feline herpesvirus 1*

and feline infectious peritonitis viruses have been implicated as causative agents in several case reports,[40] and feline parvoviral infection is associated with viral inclusion bodies and pancreatic acinar cell necrosis in young kittens.[41] Pancreatic (*Eurytrema procyonis*) and liver fluke (*Amphimerus pseudofelineus*, *Opisthorchis felineus*) infections are known causes of feline ANP in the southeastern United States and Caribbean Basin.[37,42] Recent reports of virulent caliciviral infections have been reported in multiple cat households or research facilities. Affected cats manifest high fever, anorexia, labored respirations, oral ulceration, facial and limb edema, icterus, and severe pancreatitis.[43-45] Caliciviral infection has not been reported in any of the recent clinical case series of feline ANP,[1-10,12] but some cases of active infection could have been overlooked. The importance of calicivirus infection in the pathogenesis of feline acute pancreatic necrosis remains to be determined.

Trauma

Automobile and fall ("high-rise syndrome") injuries are associated with the development of ANP in a small number of cases.[46,47] These tend to be isolated cases that do not show up as important causes in clinical case surveys.

Organophosphate Poisoning

Organophosphate poisoning is a known cause of ANP in humans and dogs,[48] and several cases have been reported in the cat.[2] In one survey, several cats developed ANP following treatment for ectoparasites, and two cats developed ANP following treatment with fenthion.[2] Diminishing organophosphate usage will probably lead to a reduced incidence of this lesion.

Lipodystrophy

Lipodystrophy has been cited as an occasional cause of ANP in the cat,[49] but it has not been reported in any of the large clinical case series.

Hypercalcemia

ANP develops in association with the hypercalcemia of primary hyperparathyroidism and humoral hypercalcemia of malignancy in humans, and a weak association with hypercalcemia has been reported in dogs.[15] Moderate hypercalcemia was found as a preexisting laboratory finding in 10% of the cases of fatal canine acute pancreatitis.[15] Acute experimental hypercalcemia does indeed cause acute pancreatic necrosis and pancreatitis in cats,[50,51] but it is probably not very clinically relevant. Acute hypercalcemia is an uncommon clinical finding in feline practice. Chronic hypercalcemia, a more clinically relevant condition, is not associated with changes in pancreatic morphology or function.[52]

Idiosyncratic Drug Reactions

Therapy with azathioprine, L-asparaginase, potassium bromide, and trimethoprim-sulfa drugs are associated with the development of ANP in the dog.[15,53] Similar associations have not been made in the cat. Glucocorticoid administration has been suggested as a cause of acute pancreatitis in the dog, but a firm association has not been confirmed in either species. Indeed, antiinflammatory doses of glucocorticoids appear to be beneficial in the management of experimental canine acute pancreatic necrosis.[54]

Nutrition

High-fat feedings[55] and obesity[53] are associated with the development of pancreatitis in the dog, but similar associations have not been made in the cat. Most recent surveys associate underweight body condition with the development of feline ANP.[2,6,8,10]

Pathogenesis

The acinar and ductal cells of the exocrine pancreas are interspersed between the islet cells of the endocrine pancreas. Like the endocrine pancreas, the exocrine pancreas is a secretory organ with several physiologic functions. Exocrine pancreatic fluid contains digestive zymogens that initiate protein, carbohydrate, and lipid digestion; bicarbonate and water that serve to neutralize the duodenum; intrinsic factor that facilitates cobalamin (vitamin B_{12}) absorption in the distal ileum; and antibacterial proteins that regulate the small intestinal bacterial flora. Digestive zymogens and antibacterial proteins are secreted primarily by acinar cells, while bicarbonate, water, and intrinsic factor are secreted primarily by ductal cells. The two most common disorders of the exocrine pancreas, acute pancreatic necrosis and EPI, are readily understood on the basis of these physiologic functions. With acute pancreatic necrosis, premature activation of digestive zymogen within pancreatic acinar cells leads to acinar cell necrosis (trypsin, chymotrypsin, carboxypeptidase), hemorrhage (elastase digestion of blood vessel elastin fibers), and fat necrosis and saponification (lipase digestion of pancreatic, peripancreatic, and mesenteric fat). With EPI, affected animals develop severe nutrient maldigestion, acid injury to the duodenal mucosa, cobalamin and fat-soluble vitamin malabsorption, and bacterial proliferation in the gut (summarized in reference 56).

Pancreatic acinar cells protect themselves from intraacinar activation of zymogen and acinar cell necrosis through several mechanisms: (a) Potentially harmful digestive enzymes are synthesized in the form of inactive precursors or zymogens in the rough endoplasmic reticulum. (b) Zymogens are then transported to the Golgi complex where they undergo selective glycosylations. Lysosomal hydrolases that are eventually packaged in lysosomes are separated from zymogens bound for export as they pass through the Golgi complex. Lysosomal hydrolases are first phosphorylated at the six position of mannose residues, bound to receptors specific for 6-phosphoryl mannose, and then transported to lysosomes where the acid pH favors their dissociation from the receptors. Digestive enzymes lack the 6-phosphoryl mannose label, and are instead transported vectorially into a different secretory fraction. (c) Packaging of zymogens into maturing zymogen granules sequesters them from contact with other subcellular fractions. (d) PSTI is incorporated into the maturing zymogen granules. PSTI inactivates trypsin should there be any intraacinar activation of trypsinogen. (e) Following stimulation (e.g., feeding and cholecystokinin secretion), mature zymogen granules and their contents are released from the cell into the ductal lumen in a process of membrane fusion and exocytosis. (f) Finally, zymogens are activated physiologically only after they enter the duodenum, where the brush-border enzyme enteropeptidase activates trypsinogen, and trypsin then activates other pancreatic zymogen (Figure 60-22).[56]

A large body of experimental, and some clinical, evidence suggests that the initiating event of acute pancreatitis is the premature activation of digestive zymogens within the acinar cell.[38,57-60] Premature activation of digestive zymogen results in acinar cell necrosis and pancreatic autodigestion. In acute pancreatic necrosis, protein synthesis and intracellular transport to the Golgi complex appear to be normal, but digestive zymogens then become colocalized along with lysosomal hydrolases in large vacuoles. Cell biology studies reveal that lysosomal and zymogen granule fractions become colocalized through a process known as *crinophagy*, a process used by

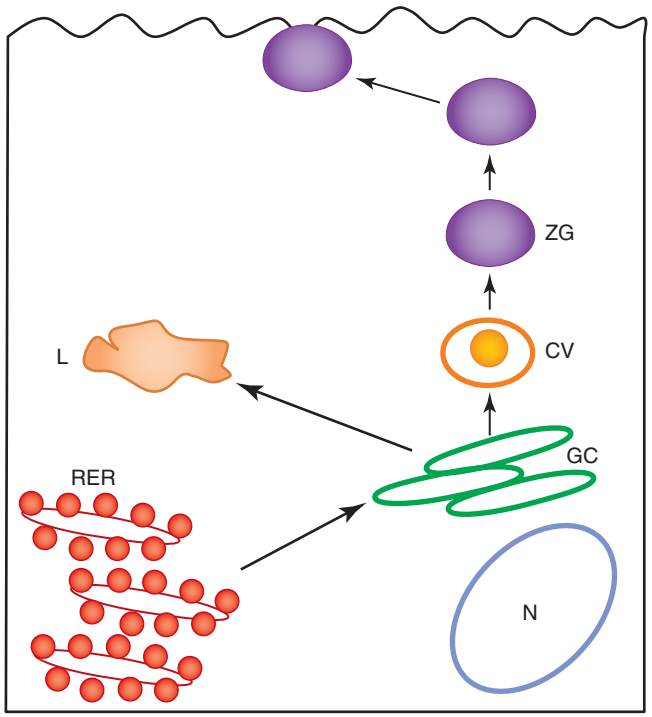

Figure 60-22 Intracellular trafficking of zymogens and lysosomal hydrolases in pancreatic acinar cells. Digestive zymogens and lysosomal hydrolases are synthesized on the rough endoplasmic reticulum (*RER*) and transported to the Golgi complex (GC) where they undergo selective glycosylation. Lysosomal hydrolases are phosphorylated at 6-mannose residues and transported to lysosomes (*L*) via receptors specific for 6-phosphoryl mannose. Digestive enzymes lack the 6-phosphoryl mannose label and are instead transported vectorially into condensing vacuoles (CV). Condensing vacuoles mature into zymogen granules (ZG) whose contents are released into the pancreatic ductal system following feeding. Trypsinogen is converted to active trypsin by intestinal enterokinase, and inactive zymogens are converted to active enzymes by tryptic hydrolysis. *N*, nucleus. (Modified from Steer ML: The early intra-acinar cell events which occur during acute pancreatitis. *Pancreas* 17:31, 1998.)

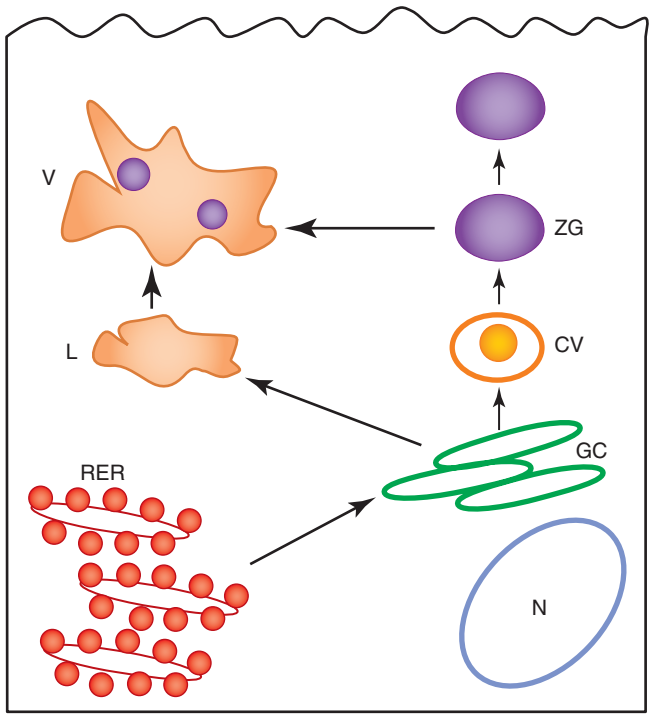

Figure 60-23 Cell biology of pancreatic acinar cell necrosis. Pancreatic enzyme secretion is inhibited and pancreatic zymogens become colocalized with lysosomal hydrolases within large vacuoles (*V*). Lysosomal hydrolases prematurely activate digestive zymogens within pancreatic acinar cells. (Modified from Steer ML: The early intra-acinar cell events which occur during acute pancreatitis. *Pancreas* 17:31, 1998.)

many cells to degrade accumulated secretory products when the need for secretion is no longer present. Although this process takes place in other cells without adverse consequences, it can be lethal in pancreatic acinar cells because of the peculiarity of their secretion products (digestive zymogens). Lysosomal hydrolases, such as cathepsin B and *N*-acetyl glucosaminidase, activate trypsinogen to the active trypsin form, and the enhanced fragility of these large vacuoles permits release of active enzyme into the cell cytoplasm (Figure 60-23). Trypsin acts autocatalytically to activate other trypsinogen molecules and other zymogens, each inducing a unique chemical pathology in pancreatic and extrapancreatic cells. A variety of inflammatory mediators and cytokines, interleukins, nitric oxide, and free radicals are involved in the further evolution of pancreatic acinar cell necrosis and inflammation and often determine the outcome.[56,61-64] Thus, a bout of pancreatitis begins with an *initiating event*, for example, ischemia, inflammation, or ductal obstruction, followed by *acinar events*, that is, colocalization, enzyme activation, and cell injury, the outcome of which is influenced by *severity determinants*, for example, inflammatory cytokines, reactive oxygen species, altered oxidation-reduction state, and apoptosis (Figure 60-24).[63] The further evolution of acute pancreatic necrosis to a SIRS and multiple organ dysfunction syndrome is determined by the balance of proinflammatory and antiinflammatory cytokines (Figure 60-25).[64]

Clinical Signs

History

Siamese cats were initially reported to be at increased risk for the disease in one of the first retrospective studies of feline pancreatitis.[2] Clinical case surveys of the past 10 years suggest that most cases of feline pancreatitis are seen in the Domestic Shorthair breed.[1-10,12] Anorexia (87%) and lethargy (81%) are the most frequently reported clinical signs in cats with acute pancreatitis, but these clinical signs are not pathognomonic for pancreatitis (Table 60-2). Anorexia and lethargy are the most important clinical signs in many feline diseases. Gastroenterologic signs are sporadic and less frequently reported in the cat. Vomiting and diarrhea are reported in only 46% and 12% of cases, respectively.[2-7,9,10,12] In dogs, vomiting (90%) and diarrhea (33%) appear to be more important clinical signs.[15,31,53]

Physical Examination Findings

Physical examination findings in cats with ANP (Table 60-3) include dehydration (54%), hypothermia (46%), icterus (37%), fever (25%), abdominal pain (19%), and abdominal mass (11%).[2-7,9,10,12] These findings suggest that a "classic textbook" description of acute pancreatitis (e.g., vomiting, diarrhea, abdominal pain, and fever) is not consistently seen in the domestic cat. Many of these physical examination findings are more commonly reported in canine acute pancreatitis. Abdominal pain (58% in dogs; 19% in cats) and fever (32% in dogs; 25% in cats), for example, are more commonly reported in dogs with acute pancreatitis.[15,31,53]

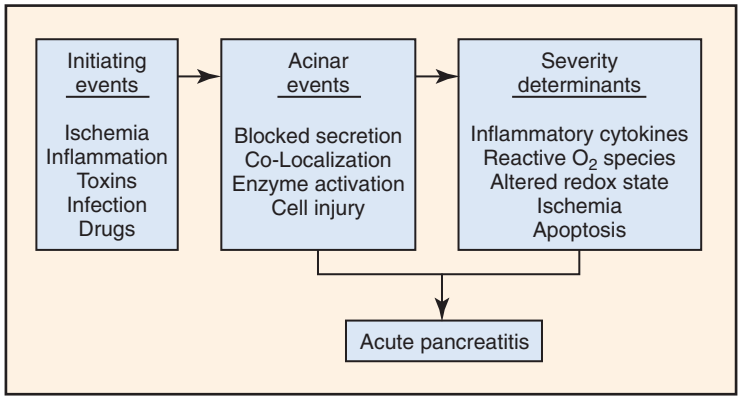

Figure 60-24 The three phases of acute pancreatitis. Pancreatic necrosis begins with an initiating event (e.g., ischemia, inflammation, or ductal obstruction), followed by acinar events (e.g., colocalization, enzyme activation, and cell injury), the outcome of which is influenced by severity determinants (e.g., inflammatory cytokines, oxygen free radicals, ischemia, and apoptosis). (Modified from Steer ML: The early intra-acinar cell events which occur during acute pancreatitis. *Pancreas* 17:31, 1998.)

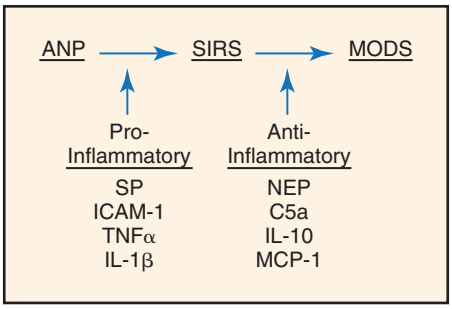

Figure 60-25 Final evolution of acute necrotizing pancreatitis. Severe cases of ANP may progress to a SIRS and multiple organ dysfunction syndrome. The balance between proinflammatory and antiinflammatory molecules determines the outcome. *C5a*, complement factor 5a; *ICAM-1*, intercellular adhesion molecule-1; *IL-1β*, interleukin-1β; *IL-10*, interleukin-10; *MCP-1*, monocytic chemotactic factor-1; *NEP*, neutral endopeptidase; *SP*, substance P; *TNFα*, tumor necrosis factor α. (Modified from Bhatia M, Brady M, Shokuhi S, et al: Inflammatory mediators in acute pancreatitis. *J Pathol* 190:117, 2000 with permission.)

Table 60-2 Historical Findings in Cats Affected with Acute Necrotizing Pancreatitis

Finding	Number of Cases	Incidence
Anorexia	131/150	87%
Lethargy	129/150	81%
Weight loss	75/159	47%
Vomiting	73/159	46%
Diarrhea	19/159	12%

Data from Hill R, van Winkle T: Acute necrotizing pancreatitis and acute suppurative pancreatitis in the cat. *J Vet Intern Med* 7:25, 1993; Akol K, Washabau RJ, Saunders HM, Hendrick MJ: Acute pancreatitis in cats with hepatic lipidosis. *J Vet Intern Med* 7:205, 1993; Simpson KW, Shiroma JT, Biller DS, et al: Ante-mortem diagnosis of pancreatitis in four cats. J Small Anim Pract 35:93, 1994; Swift NC, Marks SL, MacLachlan NJ, Norris CR: Evaluation of serum feline trypsin-like immunoreactivity for the diagnosis of pancreatitis in cats. *J Am Vet Assoc* 217:37, 2000; Kimmel SE, Washabau RJ, Drobatz KJ: Incidence and prognostic significance of ionized hypocalcemia in feline acute pancreatitis. *J Am Vet Assoc* 219:1105, 2001; Gerhardt A, Steiner JM, Williams DA, et al: Comparison of the sensitivity of different diagnostic tests pancreatitis in cats. *J Vet Intern Med* 15:329, 2001; Mayhew P, Holt D, McLear R, Washabau RJ: Pathogenesis and outcome of extrahepatic biliary obstruction in cats. *J Small Anim Pract* 43:247, 2002; Ferreri J, Hardam E, Van Winkle TJ, et al: Clinical differentiation of acute and chronic feline pancreatitis. *J Am Vet Assoc* 223:469, 2003; and Forman MA, Marks SL, De Cock HE, et al: Evaluation of feline pancreatic lipase immunoreactivity and helical computed tomography versus conventional testing for the diagnosis of feline pancreatitis. *J Vet Intern Med* 18:807, 2004.

Differential Diagnosis

The major differential diagnoses for feline ANP include GI foreign body, IBD, alimentary lymphoma, infectious gastroenteritis, GI intussusception and neoplasia, cholangitis, biliary tract neoplasia, and various forms of liver and biliary tract pathology.

Diagnosis

As with the same condition in the dog, diagnosis of ANP requires the careful integration of historical, physical examination, clinicopathologic, and imaging findings. Where appropriate, additional diagnostic support may be obtained at the time of laparoscopy or exploratory laparotomy. Diagnosis should not be made on the basis of a single laboratory or imaging finding.

Laboratory Findings

In cats affected with ANP, laboratory abnormalities (Tables 60-4 and 60-5) have included normocytic, normochromic, regenerative or nonregenerative anemia (38%), leukocytosis (46%), leukopenia (15%), hyperbilirubinemia (58%), hypercholesterolemia (72%), hyperglycemia (45%), hypocalcemia (65%), hypoalbuminemia (36%), and elevations in serum alanine aminotransferase (57%) and alkaline phosphatase (49%) activities.[2-7,9,10,12] Changes in red blood cell counts, serum activities of liver enzymes, and serum concentrations of bilirubin, glucose, and cholesterol are fairly consistent findings in feline ANP, just as they are in dogs.[15,31,53] Important differences between cats and dogs appear to be reflected in white blood cell counts and serum calcium concentrations. Leukocytosis is a more important clinical finding in the dog (62% in dogs; 46% in cats).[15,31,53] Leukopenia is sometimes seen instead of leukocytosis in cats, and a worse prognosis has been attributed to leukopenia in the cat.[2,5,7,10,12] Hypocalcemia also appears to be a more frequent finding in cats (3% to 5% in dogs[15,53]; 45% to 65% in cats[2,5,6,10,12]). Hypocalcemia (total and serum ionized) may result from several mechanisms, including

Table 60-3 Physical Examination Findings in Cats Affected with Acute Necrotizing Pancreatitis

Finding	Number of Cases	Incidence
Dehydration	50/92	54%
Hypothermia	23/54	46%
Icterus	51/138	37%
Fever	15/62	25%
Abdominal pain	30/159	19%
Abdominal mass	12/159	11%

Data from Hill R, van Winkle T: Acute necrotizing pancreatitis and acute suppurative pancreatitis in the cat. *J Vet Intern Med* 7:25, 1993; Akol K, Washabau RJ, Saunders HM, Hendrick MJ: Acute pancreatitis in cats with hepatic lipidosis. *J Vet Intern Med* 7:205, 1993; Simpson KW, Shiroma JT, Biller DS, et al: Ante-mortem diagnosis of pancreatitis in four cats. *J Small Anim Pract* 35:93, 1994; Swift NC, Marks SL, MacLachlan NJ, Norris CR: Evaluation of serum feline trypsin-like immunoreactivity for the diagnosis of pancreatitis in cats. *J Am Vet Assoc* 217:37, 2000; Kimmel SE, Washabau RJ, Drobatz KJ: Incidence and prognostic significance of ionized hypocalcemia in feline acute pancreatitis. *J Am Vet Assoc* 219:1105, 2001; Gerhardt A, Steiner JM, Williams DA, et al: Comparison of the sensitivity of different diagnostic tests pancreatitis in cats. *J Vet Intern Med* 15:329, 2001; Mayhew P, Holt D, McLear R, Washabau RJ: Pathogenesis and outcome of extrahepatic biliary obstruction in cats. *J Small Anim Pract* 43:247, 2002; Ferreri J, Hardam E, Van Winkle TJ, et al: Clinical differentiation of acute and chronic feline pancreatitis. *J Am Vet Assoc* 223:469, 2003; and Forman MA, Marks SL, De Cock HE, et al: Evaluation of feline pancreatic lipase immunoreactivity and helical computed tomography versus conventional testing for the diagnosis of feline pancreatitis. *J Vet Intern Med* 18:807, 2004.

Table 60-4 Hematologic Findings in Cats Affected with Acute Necrotizing Pancreatitis

Finding	Number of Cases	Incidence
Anemia	39/103	38%
Hemoconcentration	14/82	17%
Leukocytosis	46/99	46%
Leukopenia	14/94	15%

Data from Hill R, van Winkle T: Acute necrotizing pancreatitis and acute suppurative pancreatitis in the cat. *J Vet Intern Med* 7:25, 1993; Akol K, Washabau RJ, Saunders HM, Hendrick MJ: Acute pancreatitis in cats with hepatic lipidosis. *J Vet Intern Med* 7:205, 1993; Simpson KW, Shiroma JT, Biller DS, et al: Ante-mortem diagnosis of pancreatitis in four cats. *J Small Anim Pract* 35:93, 1994; Swift NC, Marks SL, MacLachlan NJ, Norris CR: Evaluation of serum feline trypsin-like immunoreactivity for the diagnosis of pancreatitis in cats. *J Am Vet Assoc* 217:37, 2000; Kimmel SE, Washabau RJ, Drobatz KJ: Incidence and prognostic significance of ionized hypocalcemia in feline acute pancreatitis. *J Am Vet Assoc* 219:1105, 2001; Gerhardt A, Steiner JM, Williams DA, et al: Comparison of the sensitivity of different diagnostic tests pancreatitis in cats. *J Vet Intern Med* 15:329, 2001; Mayhew P, Holt D, McLear R, Washabau RJ: Pathogenesis and outcome of extrahepatic biliary obstruction in cats. *J Small Anim Pract* 43:247, 2002; Ferreri J, Hardam E, Van Winkle TJ, et al: Clinical differentiation of acute and chronic feline pancreatitis. *J Am Vet Assoc* 223:469, 2003; and Forman MA, Marks SL, De Cock HE, et al: Evaluation of feline pancreatic lipase immunoreactivity and helical computed tomography versus conventional testing for the diagnosis of feline pancreatitis. *J Vet Intern Med* 18:807, 2004.

acid–base disturbances, peripancreatic fat saponification, and parathormone resistance.[65] Regardless of the mechanism, hypocalcemia appears to confer a worse clinical prognosis in cats.[6,10] This finding suggests that cats should be monitored fairly closely for the development of hypocalcemia and treatment should be initiated, accordingly.

Table 60-5 Serum Biochemical Findings in Cats Affected with Acute Necrotizing Pancreatitis

Finding	Number of Cases	Incidence
↑↑ ALT, AST	37/65	57%
↑↑ ALP	32/65	49%
↑↑ Bilirubin	38/65	58%
↑↑ Glucose	32/71	45%
↑↑ Cholesterol	28/39	72%
↓↓ Calcium	55/85	65%
↓↓ Albumin	14/39	36%

Data from Hill R, van Winkle T: Acute necrotizing pancreatitis and acute suppurative pancreatitis in the cat. *J Vet Intern Med* 7:25, 1993; Akol K, Washabau RJ, Saunders HM, Hendrick MJ: Acute pancreatitis in cats with hepatic lipidosis. *J Vet Intern Med* 7:205, 1993; Simpson KW, Shiroma JT, Biller DS, et al: Ante-mortem diagnosis of pancreatitis in four cats. *J Small Anim Pract* 35:93, 1994; Swift NC, Marks SL, MacLachlan NJ, Norris CR: Evaluation of serum feline trypsin-like immunoreactivity for the diagnosis of pancreatitis in cats. *J Am Vet Assoc* 217:37, 2000; Kimmel SE, Washabau RJ, Drobatz KJ: Incidence and prognostic significance of ionized hypocalcemia in feline acute pancreatitis. *J Am Vet Assoc* 219:1105, 2001; Gerhardt A, Steiner JM, Williams DA, et al: Comparison of the sensitivity of different diagnostic tests pancreatitis in cats. *J Vet Intern Med* 15:329, 2001; Mayhew P, Holt D, McLear R, Washabau RJ: Pathogenesis and outcome of extrahepatic biliary obstruction in cats. *J Small Anim Pract* 43:247, 2002; Ferreri J, Hardam E, Van Winkle TJ, et al: Clinical differentiation of acute and chronic feline pancreatitis. *J Am Vet Assoc* 223:469, 2003; and Forman MA, Marks SL, De Cock HE, et al: Evaluation of feline pancreatic lipase immunoreactivity and helical computed tomography versus conventional testing for the diagnosis of feline pancreatitis. *J Vet Intern Med* 18:807, 2004.

Special Tests of Pancreatic Function

Lipase and Amylase Activity Assays

Serum lipase activities are elevated in experimental feline pancreatitis,[66,67] but serum lipase and amylase activities do not appear to be elevated or of clinical value in the diagnosis of clinical pancreatitis.[68] Serum lipase activity may still have some clinical utility in the diagnosis of ANP in the dog.[15,69] Assays of serum lipase activity are complicated by the fact that there may be as many as five different isoenzymes circulating in the blood[70]; consequently general serum lipase activity assays have been superseded by the development of pancreatic lipase immunoreactivity assays (e.g., cPLI, fPLI).[70,71]

Trypsin-like Immunoreactivity

Serum TLI mainly measures trypsinogen but also detects trypsin and some trypsin molecules bound to proteinase inhibitors.[70] TLI assays are species-specific, and different assays for feline (fTLI) and canine (cTLI) have been developed and validated.[72] Serum TLI concentration is the diagnostic test of choice for feline EPI because it is highly sensitive and specific for this disease in the cat.[11] The use of this test in the diagnosis of feline ANP is less clear. Serum TLI concentrations are transiently elevated in experimental feline acute pancreatitis,[73] but elevations in clinical cases are less consistently seen.[5,7,68] The poor sensitivity (i.e., 33%) of this test precludes its use as a definitive assay for feline ANP.

Trypsinogen Activation Peptide

When trypsinogen is activated to trypsin, a small peptide, TAP, is split from the trypsinogen molecule. Under normal conditions, activation of trypsinogen takes place only in the small intestine and

TAP is undetectable in the blood. During pancreatitis, trypsinogen is activated prematurely in pancreatic acinar cells and TAP is released into the vascular space.[71] Urine TAP assays have shown some promise in experimental models of feline pancreatitis,[74] but serum and urine TAP assays are less promising in clinical studies.[75] Evidence-based data is needed to determine the true specificity and sensitivity of this assay.

Pancreatic Lipase Immunoreactivity

ELISA and radioimmunoassays for the measurement of PLI have been developed and validated in the cat.[76] fPLI elevations have been cited in preliminary reports of experimental[73] and clinical[12] feline ANP, but the true sensitivity and specificity of fPLI in the diagnosis of feline ANP have not yet been reported. As with fTLI assays, there are false positives and false negatives with fPLI in the diagnosis of feline ANP.

Imaging Findings

Radiography

The radiographic findings of feline ANP have not been very well characterized. The radiographic hallmarks of canine acute pancreatitis (e.g., increased density in the right cranial abdominal quadrant, left gastric displacement, right duodenal displacement, and gas-filled duodenum/colon)[15,77] have not been substantiated in the cat. Indeed, in several recent reports, many of these radiographic findings were not reported in cats with documented acute pancreatic necrosis.[1-10,12] In spontaneous clinical cases, hepatomegaly and abdominal effusion may be the only radiographic findings in some cases of feline ANP.[1-10,12]

Ultrasonography

Enlarged, irregular, and/or hypoechoic pancreas; hyperechogenicity of the peripancreatic mesentery; and peritoneal effusion have been observed with abdominal ultrasonography in many cats with spontaneous acute pancreatitis (Figure 60-26).[8,10,12,78] The specificity of this imaging modality appears to be high (>85%), but the sensitivity has been reported as low as 35% in some studies.[5,7,8,78] The low sensitivity suggests that imaging the pancreas in cats with pancreatitis is technically more difficult than imaging the pancreas in dogs or that the ultrasonographic appearance of pancreatitis in cats differs from that reported for dogs. Other potential ultrasonographic findings include corrugation of the duodenum, fluid/gas distended, hypomotile intestines (indicative of paralytic ileus), and ultrasonographic signs of extrahepatic biliary obstruction.[8,79-81]

Endosonography

Endosonography has been used to confirm the diagnosis of feline ANP in a small series of patients, but it appears to confer no additional advantage over routine transabdominal ultrasonography.[82]

Computed Tomography

CT scanning appears to be useful in identifying the normal structures of the healthy feline pancreas,[83] but preliminary clinical reports are somewhat disappointing.[7,12] The sensitivity of CT scanning in detecting lesions consistent with feline ANP may be as low as 20%.[7,12] Additional study is needed to determine the specificity and sensitivity of this imaging modality in the diagnosis of feline ANP.

Biopsy

If clinically indicated, pancreatic biopsy may be obtained by laparoscopy[84] or exploratory laparotomy. Clinicians should always bear in mind that many pancreatitis patients are poor anesthesia risks.

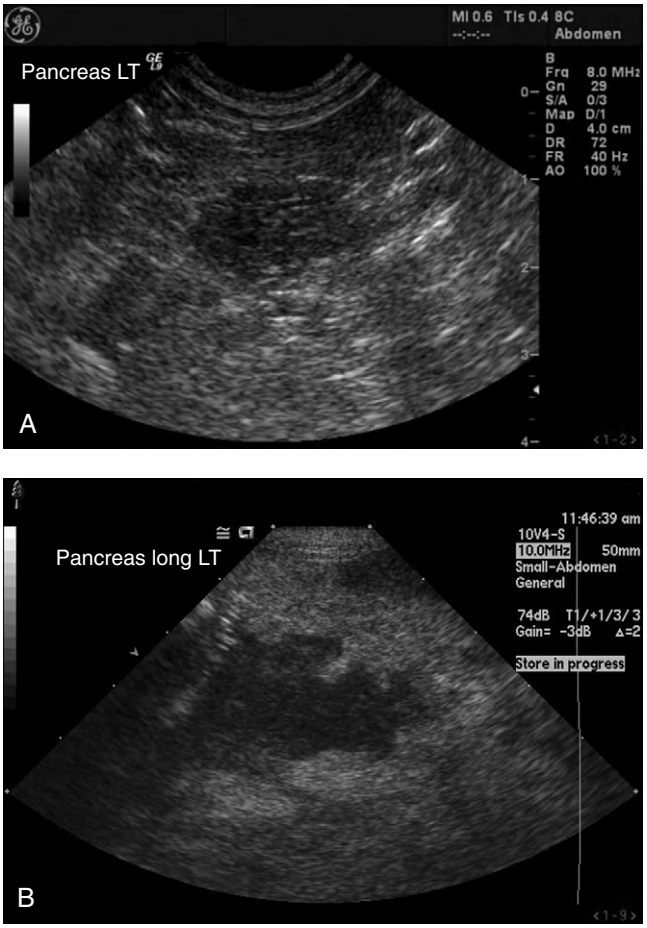

Figure 60-26 Ultrasonographic findings of feline acute necrotizing pancreatitis. A, The pancreas is severely enlarged and hypoechoic, with surrounding hyperechoic mesentery. **B,** Ultrasonographic findings of feline chronic necrotizing pancreatitis. The left lobe of the pancreas is irregularly thickened and hypoechoic.

Gross observation at the time of laparoscopy or exploratory laparotomy may confirm the diagnosis of ANP. In equivocal cases, biopsy may be safely performed as long as blood flow is preserved at the site of the biopsy. Single biopsy may be insufficient to exclude subclinical pancreatitis as inflammation of the canine pancreas occurs in discrete areas within the pancreas rather than diffusely throughout the whole organ.[85] Similar findings are reported in feline ANP.[2] Inspection of other viscera (e.g., intestine, biliary tract, liver) at the time of laparoscopy or exploratory laparotomy is of paramount importance in the cat because of the high rate of disease concurrence in this species.[2,3,9,10,18,24,25,84]

Species Differences

There are many important species differences between dogs and cats with regard to the clinical course and pathophysiology of acute pancreatic necrosis (summarized in Table 60-6 and reference 31). Fever, leukocytosis, vomiting, and abdominal pain are important physical examination findings in dogs with ANP, but these are relatively infrequent findings in cats with ANP. Cats more often have hypothermic reactions, and they may not necessarily manifest the classic gastroenterologic signs (e.g., vomiting, diarrhea, abdominal pain) reported in dogs. The imaging findings in cats are also less

Table 60-6 Clinical Difference between Feline and Canine Acute Necrotizing Pancreatitis

	Feline	Canine
Vomiting	46%	90%
Diarrhea	12%	33%
Fever	25%	32%
Abdominal pain	19%	58%
↑ White blood cell counts	46%	62%
↓ Calcium	65%	5%
Radiography	Not useful	Somewhat useful
Inflammatory bowel disease	Strong association	Weak association

Data from Hill R, van Winkle T: Acute necrotizing pancreatitis and acute suppurative pancreatitis in the cat. *J Vet Intern Med* 7:25, 1993; Akol K, Washabau RJ, Saunders HM, Hendrick MJ: Acute pancreatitis in cats with hepatic lipidosis. *J Vet Intern Med* 7:205, 1993; Simpson KW, Shiroma JT, Biller DS, et al: Ante-mortem diagnosis of pancreatitis in four cats. *J Small Anim Pract* 35:93, 1994; Swift NC, Marks SL, MacLachlan NJ, Norris CR: Evaluation of serum feline trypsin-like immunoreactivity for the diagnosis of pancreatitis in cats. *J Am Vet Assoc* 217:37, 2000; Kimmel SE, Washabau RJ, Drobatz KJ: Incidence and prognostic significance of ionized hypocalcemia in feline acute pancreatitis. *J Am Vet Assoc* 219:1105, 2001; Gerhardt A, Steiner JM, Williams DA, et al: Comparison of the sensitivity of different diagnostic tests pancreatitis in cats. *J Vet Intern Med* 15:329, 2001; Mayhew P, Holt D, McLear R, Washabau RJ: Pathogenesis and outcome of extrahepatic biliary obstruction in cats. *J Small Anim Pract* 43:247, 2002; Ferreri J, Hardam E, Van Winkle TJ, et al: Clinical differentiation of acute and chronic feline pancreatitis. *J Am Vet Assoc* 223:469, 2003; Forman MA, Marks SL, De Cock HE, et al: Evaluation of feline pancreatic lipase immunoreactivity and helical computed tomography versus conventional testing for the diagnosis of feline pancreatitis. *J Vet Intern Med* 18:807, 2004; and Hess RS, Saunders HM, Van Winkle TJ, et al: Clinical, clinicopathologic, radiographic, and ultrasonographic abnormalities in dogs with fatal acute pancreatitis. *J Am Vet Assoc* 213:665, 1998.

subtle than what has been reported in dogs; the classic radiographic hallmarks of canine ANP have not reported in the cat. Cats have a greater incidence and severity of hypocalcemia following bouts of acute pancreatic necrosis. Serum total and/or ionized hypocalcemia is significantly reduced in 45% to 65% of affected cats, whereas hypocalcemia is reported in only 5% of affected dogs. The pathogenesis of hypocalcemia in cats with ANP is incompletely understood, but it does carry a significantly worse prognosis for recovery.[6] Prior GI tract disease confers slight increased risk for the development of acute pancreatic necrosis in the dog[15,53]; this is especially true of the cat.[2,10,18,24,25]

Therapy

Supportive care continues to be the mainstay of therapy for feline acute pancreatitis (Box 60-3). Efforts should be made to identify and eliminate any inciting agents; sustain blood and plasma volume; correct acid–base, electrolyte, and fluid deficits; and treat any complications that might develop. Important life-threatening complications of acute pancreatitis in cats include hypocalcemia, DIC, thromboembolism, cardiac arrhythmia, sepsis, acute tubular necrosis, pulmonary edema, and pleural effusion.

Historically, a short period of food and water fasting has been recommended for cats with ANP. This recommendation should be applied only in those instances in which there is severe vomiting and risk for aspiration pneumonia. As obligate carnivores, cats develop fat mobilization and hepatic lipidosis during prolonged starvation. Moreover, recent studies suggest that it may be appropriate and necessary to stimulate pancreatic secretion (via feeding) in affected animals.[57-60] Esophagostomy, gastrostomy, and enterostomy tubes may be placed to facilitate nutrition in anorectic animals.

Box 60-3 General Principles in the Treatment of Feline Acute Necrotizing Pancreatitis

1. Eliminate the inciting agent
2. NPO *only* if severe nausea and vomiting
3. Intravenous fluids
4. Supportive therapy—plasma 10 mL/kg
5. Relieve pain—meperidine, butorphanol
6. Antiemetics—α_2-adrenergic antagonists, 5-HT_3 serotonergic antagonists, NK_1 neurokinin antagonists
7. Calcium gluconate supplementation
8. H_1- and H_2-histaminergic receptor antagonists
9. Low-dose dopamine infusion—5 µg/kg/min
10. Broad-spectrum antibiotics
11. Ductal decompression

Other therapies that may be of some benefit in the treatment of this disorder include:

- Relief of pain: Analgesic agents should be used when abdominal pain is suspected. Most cats do not manifest clinical signs of abdominal pain, but clinicians inspect for it. Meperidine at a dose of 1 to 2 mg/kg administered intramuscularly or subcutaneously every 2 to 4 hours or butorphanol at a dose of 0.2 to 0.4 mg/kg administered subcutaneously every 6 hours has been recommended.[86]
- Antiemetic agents: Nausea and vomiting may be severe in affected animals. The α_2-adrenergic antagonists and 5-HT_3 antagonists are somewhat effective antiemetic agents in the cat.[87] Cats may be treated with chlorpromazine (α_2-adrenergic antagonist) at a dose of 0.2 to 0.4 mg/kg administered subcutaneously or intramuscularly every 8 hours, or with any of the 5-HT_3 antagonists (ondansetron 0.1 to 1.0 mg/kg, granisetron 0.1 to 0.5 mg/kg, or dolasetron 0.5 to 1.0 mg/kg, orally or intravenously every 12 to 24 hours). Dopaminergic antagonists, for example, metoclopramide, are less-effective antiemetic agents in the cat.[87] NK_1 receptor antagonists (e.g., maropitant) have been used in the cat (see Chapters 23 and 35), but their comparative efficacy is still unknown.[88]
- Calcium gluconate supplementation: Hypocalcemia is a frequent complication of feline ANP and is associated with a worse prognosis.[6] Calcium gluconate should be given at doses of 50 to 150 mg/kg intravenously over 12 to 24 hours and serum total or ionized calcium concentrations should be monitored during therapy.
- H_1- and H_2-histamine antagonists: Histamine and bradykinin-induced increases in microvascular permeability are associated with the development of hemorrhagic necrosis in experimental feline pancreatitis.[89] Treatment with H_1 (mepyramine, 10 mg/kg) and H_2 (cimetidine, 5 mg/kg; ranitidine, 1 to 2 mg/kg; famotidine, 0.5 to 1.0 mg/kg) histamine-receptor antagonists protects against the development of hemorrhagic pancreatitis in these models.[89] Efficacy has not been established in clinical pancreatitis, but the use of these drugs in suspected or proven clinical cases would appear to have some rationale as they are associated with few side effects. Diphenhydramine (2 to 4 mg/kg) or

dimenhydrinate (4 to 8 mg/kg) are examples of clinically used H_1-histamine receptor antagonists. Cimetidine (5 mg/kg), ranitidine (1 to 2 mg/kg), famotidine (0.5 to 1.0 mg/kg), and nizatidine (2.5 to 5.0 mg/kg) are examples of clinically used H_2-histamine receptor antagonists.

- Low-dose dopamine infusion: Low-dose dopamine infusion (5 µg/kg/min) improves pancreatic blood flow and reduces microvascular permeability in feline experimental pancreatitis.[67] Low-dose dopamine infusion is effective treatment in experimental pancreatitis even when it is given up to 12 hours after induction of the disease.[67] Part of the appeal of dopamine as a potential treatment for feline pancreatitis lies in the diversity of its actions. Dopamine's effect on the kidney in promoting renal blood flow and urinary output, and its cardiac inotropic effect make it a useful agent, although it has not yet been studied in controlled clinical trials.
- Broad-spectrum antibiotics: ANP may begin as a sterile process, but necrosis and inflammation predispose to colonic bacterial translocation and colonization of the pancreas.[90,91] *Escherichia coli* and other coliforms are the principal pathogens.[90,91] High colonization rates suggest that bacteria may spread to the inflamed pancreas more frequently than is currently thought, and that broad-spectrum antibiotics may be appropriate in suspected cases of feline acute pancreatitis. Cefotaxime at a dose of 50 mg/kg administered intramuscularly every 8 hours prevents bacterial colonization of the pancreas.[92]
- Ductal decompression: Surgical decompression of the pancreaticobiliary duct should be considered in cases of acute ductal obstruction, for example, calculus, neoplasia, and fluke infection. Ductal decompression may also be useful in acute cases that have progressed to the more chronic form of the disease. Ductal decompression restores pancreatic blood flow, tissue pH, and acinar cell function.[35,36]

Prevention

In cases in which IBD is the underlying pathogenesis of ANP, therapy should be directed toward regulation of the IBD. The five components of feline IBD therapy are dietary modification, antibiotics, probiotics, antidiarrheal agents, and immunosuppressive therapy.[93]

Complications of Acute Necrotizing Pancreatitis

Chronic Nonsuppurative Pancreatitis

Recurring bouts of ANP may progress to a chronic nonsuppurative form of the disease. This chronic form of pancreatitis has generally been held to be of lesser clinical severity, lower mortality, and better long-term prognosis.[1] More recent reports suggest, however, that chronic pancreatitis cannot be differentiated from acute pancreatitis by clinical, clinicopathologic, or imaging findings.[10] The clinical signs, laboratory data, and imaging findings are indistinguishable between the two groups. Histopathology remains the only dependable method of differentiating acute and chronic pancreatitis. Not surprisingly, cats with chronic pancreatitis more frequently have concurrent systemic disease (e.g., cholangitis, IBD) compared with cats with acute pancreatitis.[10]

Exocrine Pancreatic Insufficiency

EPI is an uncommon cause of chronic diarrhea in cats. Insufficiency results from failure of synthesis and secretion of pancreatic digestive enzymes. The natural history of feline EPI is poorly understood, but most cases are believed to result from chronic pancreatitis, fibrosis, and acinar atrophy. As with dogs, clinical signs reported in cats with EPI include weight loss, soft voluminous feces, and ravenous appetite. Affected cats may have an antecedent history of recurring bouts of acute pancreatitis (e.g., anorexia, lethargy, vomiting) culminating in chronic pancreatitis and EPI.

The diagnosis of EPI in cats has been technically difficult. Clinical signs in affected cats are not pathognomonic for EPI, clinicopathologic data are fairly nonspecific, imaging findings are inconsistent, and the severity of pancreatic histologic changes are not always directly related to the severity of clinical signs. Serum TLI is believed to be diagnostic of the disease.[11,17] In that study, TLI concentrations less than 8 µg/L (reference range: 17 to 49 µg/L) were reported in 27 of 30 cats with clinical signs compatible with EPI (e.g., weight loss, loose voluminous feces, greasy soiling of the hair coat) and at least one other finding, for example, decreased fecal proteolytic activity, exploratory laparotomy or necropsy findings compatible with EPI, or favorable response to pancreatic enzyme replacement therapy.[11,17] Cats affected with EPI have predictable serum cobalamin deficiency because of pancreatic intrinsic factor deficiency and cobalamin malabsorption.[94] Therapy should include subcutaneous vitamin B_{12} injections (100 µg subcutaneously every 3 to 4 weeks) in addition to pancreatic replacement enzymes.

Hepatic Lipidosis

ANP is but one of many examples in which anorexia or starvation predisposes an obligate carnivore to the syndrome of fat mobilization and hepatic lipidosis.[1,3,95] The concurrence of these two syndromes is a particularly poor prognostic sign in that affected cats have high morbidity and mortality rates. This emphasizes the importance of early interventions in the treatment of pancreatitis before the development of the metabolic syndrome of hepatic lipidosis.

Diabetes Mellitus

Several studies have related severe chronic pancreatitis to the development of diabetes mellitus.[1,4,10,11] ANP per se may not necessarily be a risk factor for the development of diabetes mellitus, but disease progression to the chronic nonsuppurative form may increase that risk.

ABSCESS, NECROSIS, PSEUDOCYST, PHLEGMON, AND INFECTION

Michael Schaer

Pancreatic Abscess and Necrosis

Definition

Abscess and necrosis are discussed together in this section because abscess formation is always preceded by necrosis, although necrosis is not always followed by abscess formation. In 1992 the International Symposium on Acute Pancreatitis defined pancreatic necrosis as the presence of one or more diffuse or focal areas of nonviable pancreatic parenchyma.[1] Pancreatic glandular necrosis is usually associated with necrosis of peripancreatic fat. By definition, pancreatic necrosis represents a severe form of acute pancreatitis (Figures 60-27 and 60-28).[2] Pancreatic abscess is a collection of purulent and necrotic pancreatic tissue (Figure 60-29). Abscessation forms if an episode of pancreatitis is severe enough to cause parenchymal

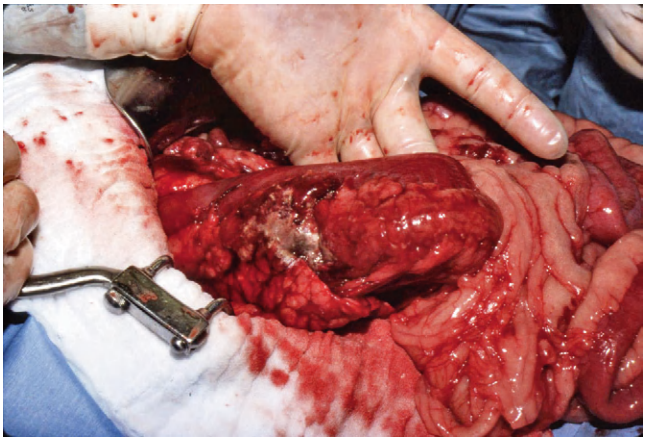

Figure 60-27 Surgical view of focal pancreatic necrosis in a dog.

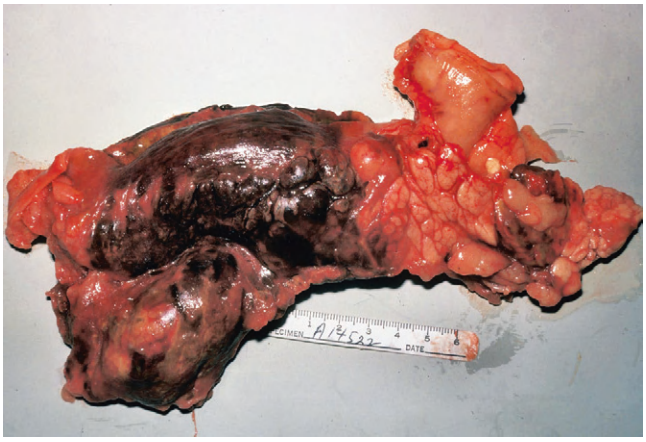

Figure 60-28 A postmortem depiction of severe ischemic necrosis of the pancreas and parapancreatic lymph node.

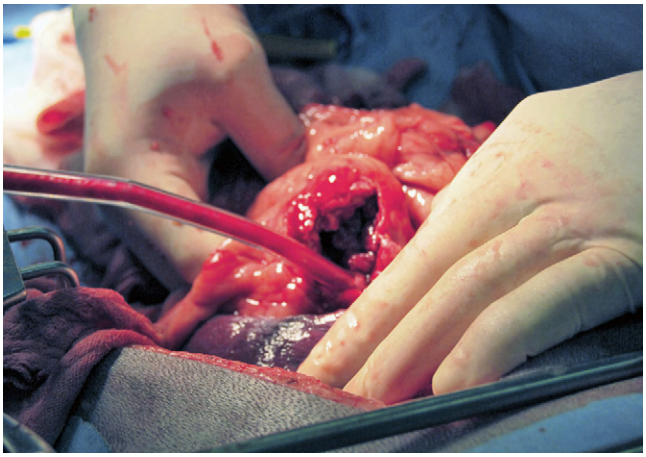

Figure 60-29 Pancreatic abscess at surgery.

necrosis.[3] In some cases, necrotic tissue is secondarily infected by bacteria. There can be multiple foci of necrotic debris rather than a recognizable discrete abscess cavity. In humans, a pancreatic abscess can also be caused by secondary infection of a pseudocyst, but the latter pathogenesis is apparently rare in dogs and cats.

Incidence

Pancreatic abscess is infrequently reported in the veterinary literature,[4] with only 73 total case reports in five separate references , most of which were reported in dogs.[5-9] The largest report of pancreatic abscess described clinical findings in 36 dogs.[9] Mortality numbers were high and ranged from 50% to 86%, but this parallels the high mortality that occurs in all cases of severe necrotic pancreatitis with and without secondary infection. Although viewed as a sequel to acute pancreatitis in some cases, abscess can be a continuation of a single severe inflammatory process with accompanying necrosis that becomes more clinically apparent in the dog 1 to 2 weeks after disease onset.

History and Physical Examination Findings

There is nothing particularly pathognomonic for pancreatic abscess in the dog. The history will always show a sudden onset of mental depression, anorexia, vomiting, and lethargy. Certain "triggers" of acute pancreatitis might be present, such as the ingestion of a fatty meal or other potential causes such as hyperlipidemia, hypercalcemia, or the ingestion of certain drugs such as potassium bromide.[10] Animals with hemorrhagic and necrotic acute pancreatitis are usually critically ill, and may have a spectrum of clinical signs including vomiting, abdominal pain, lethargy, diarrhea, and hypovolemia. Abdominal pain is often reflective of peritonitis that is associated with pancreatitis, but this sign might not be present in a recumbent patient in the advanced stages of acute necrotic pancreatitis. Icterus is seldom present acutely but may evolve with progressive cholestasis. Body temperature ranges from high fever to hypothermic reactions with hypothermia commonly reflecting an advanced decompensated stage of the systemic inflammatory response. Abdominal distention is usually caused by inflammatory ascites characterized as a sterile inflammatory exudate in most cases. Ileus is also present and contributes to abdominal distention. It is not uncommon for these dogs to be prostrate upon initial examination reflecting their grave status.

Clinicopathologic Features

There is nothing in the clinicopathologic profile that distinguishes pancreatic abscess from necrotizing pancreatitis.[3,5,7,9,11] In Anderson's review, anemia occurred in nine of 36 dogs and was likely associated with the anemia of inflammation.[9] Leukocytosis occurred in 25 of 36 dogs and this was likely caused by the systemic inflammatory response. Of these, 25% had increased circulating immature white blood cells. The leukopenia that was reported in three dogs should be seen as a grave sign associated with either insufficient bone marrow production, sequestration of white blood cells in the area of severe inflammation, or both.

Coagulation testing will yield variable responses. Acute pancreatitis itself may cause platelet consumption and thrombocytopenia in some patients. This was seen in 10 of 36 cases in Anderson's review.[9] Prolongations in the PT and activated partial thromboplastin times can occur in severe cases of acute pancreatitis often times reflecting DIC. This latter complication is thought to be an ominous sign if the parameters do not normalize after intense treatment.

Serum chemistry abnormalities accompanying pancreatic abscess cannot be distinguished from those reported in dogs with acute pancreatitis. Reported abnormalities include hypoproteinemia associated with plasma protein leakage into the abdominal cavity ("third spacing"); hyperglycemia (with or without ketoacidosis) as a result of relative insulin insufficiency; hypoglycemia secondary to sepsis or endotoxemia; hypocalcemia associated with hypoalbuminemia and saponification; elevated liver enzymes with or without

hyperbilirubinemia occurring as a result of cholestasis; and normal or below normal concentrations of serum sodium and potassium. Increases in renal parameters (BUN and serum creatinine) reflect a more guarded prognosis if acute renal failure has occurred.

Increases in the serum amylase and lipase concentrations can be present in some cases, but neither of these tests are sensitive or specific for this condition. They might even be normal by the time a pancreatic abscess has formed because of the failure of a damaged pancreas to produce digestive enzymes. Canine and feline pancreatic-specific lipase (cPLI, fPLI) tests have not proved useful in the diagnosis of pancreatic abscess. More discussion about clinicopathologic changes may be found in the section on pancreatic phlegmon.

Abdominal fluid is commonly present in hemorrhagic and necrotizing acute pancreatitis. The fluid is usually exudative but sterile.[12] Pancreatic infection occurs more commonly in humans than in dogs and cats, and in humans it is associated with a guarded to grave prognosis. Sterile cultures in dogs and cats might result from prior treatment with antibiotics. In Anderson's study,[9] two of 13 cases of necrotic pancreatitis were positive for bacterial (*Staphylococcus saprophyticus* and *Klebsiella pneumoniae*) infection while cultures of the abdominal fluid of 12 dogs were positive for bacteria in seven animals (*E. coli*, *Enterococcus*, *Pseudomonas*, *Streptococcus*, and *Bacteroides*). Johnson's review of 15 dogs detected *Staphylococcus epidermidis* in three dogs, but these were interpreted as contaminants.[7] Salisbury's review of six cases makes no mention of bacterial isolation.[5]

Diagnostic Imaging

Radiographic and ultrasonographic pancreatic abnormalities have been reported in dogs with pancreatic abscess, but there are no distinctive features for pancreatic abscess formation when compared with other forms of severe acute pancreatitis. Abdominal radiographs will show an increased fluid pattern in the anterior abdomen that can be diffuse or more localized to the upper right abdomen. This will cause a loss of serosal detail and occasionally a mass effect with organ displacement.

Chest radiographs are usually normal or they might show a pleural effusion consistent with migration of pancreatic fluid into the thoracic cavity and development of serositis. Acute pancreatitis is one cause of the acute respiratory distress syndrome that appears as a diffuse "whiteout" caused by diffuse alveolar infiltrates.

Abdominal ultrasonography usually reveals cavitation of a pancreatic abscess, but it is not readily distinguished from pancreatic pseudocyst or pancreatic phlegmon. In the Anderson study, only one dog had a nondiagnostic study while 26 of 27 dogs had abnormal pancreatic appearance described as hypoechoic, hyperechoic, or mixed echoic patterns (Figure 60-30). Fourteen of the 26 dogs had a "mass effect." Although the mass effect can be caused by an abscess, the same can be described for pancreatic phlegmon or any other combined effects caused by inflammation and adhesions. Abdominal ultrasound does give the radiologist an opportunity to do a transabdominal fine-needle aspiration biopsy of any abnormal abdominal tissue and tissue fluid for bacterial culture and cytology.

Treatment

Most patients will have been treated medically in intensive care for 7 to 14 days before any decision for surgery is made. The extent of sophisticated patient monitoring will be individualized according to the particular facility, the skill of the attending clinician, and the financial restrictions imposed by the pet owner. The medical treatment of many acute pancreatitis patients will require an intensive

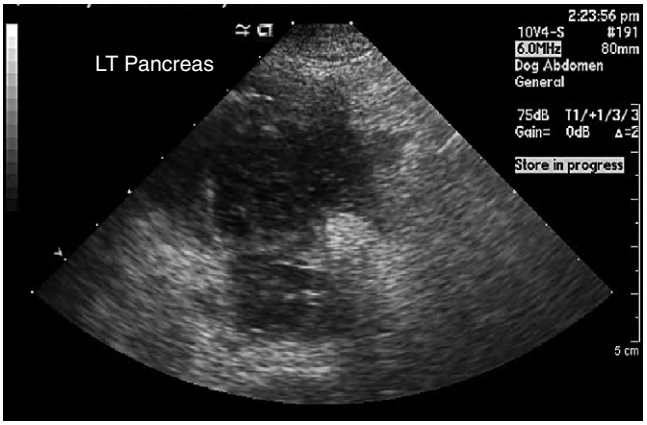

Figure 60-30 Abdominal ultrasound examination showing pancreatic abscess.

care setting because it entails meticulous parenteral fluid therapy, analgesics, plasma transfusions, and continuous patient monitoring. Pressor drugs might be necessary to stabilize the hypotensive patient that does not respond well to parenteral fluid therapy. Antibiotics are often administered because of concern about infection caused by transcolonic bacterial migration or the demonstration of bacteria on cytologic examination of a sample of the abdominal fluid.[13] Today, however, the routine use of antibiotics for severe ANP without the demonstration of sepsis is not recommended in human medicine because of a lack of influence on outcome between treated and untreated patient populations.[14-17] Glucocorticoid drugs might be of theoretical benefit because of their antiinflammatory effects, but they might predispose the patient to secondary infection that could have catastrophic effects. Antiemetic agents should be used in those patients that have multiple vomiting episodes per day, but attention to side effects should be made along with the necessary dosage adjustments. Many patients lack nutrition support for the first several days, and eventually require either total parenteral nutrition or jejunostomy tube feedings. The patient with pancreatic abscess and severe necrotizing pancreatitis frequently shows few signs of clinical improvement during the first week. A repeated abdominal ultrasound examination at that time will show the same or worsened abdominal abnormalities. In humans, the decision for abdominal surgery is made on the basis of continuing worsening clinical condition, the need for jejunostomy tube placement, the need to grossly assess the degree of pathology within the abdomen, the demonstration of infected pancreatitis.[18,19]

The accepted principles of surgical management of necrotizing pancreatitis are the removal of the necrotic pancreatic and peripancreatic tissue (necrosectomy), as well as providing drainage of ascites from the peritoneal cavity [2,7,9,11,18,19] Conventional drainage involves necrosectomy with placement of standard surgical drains and reoperation as required. Open or semiopen management involves necrosectomy and either scheduled repeated laparotomies or open packing, which leaves the abdominal wound exposed for frequent changes of dressing. Closed management involves necrosectomy with extensive intraoperative lavage of the pancreatic bed. The abdomen is closed over large-bore drains for continuous high-volume postoperative lavage.[20] Most surgeons in human medicine have abandoned the conventional surgical approach to debridement, as inadequately removed necrotic tissue becomes or remains infected, resulting in significant mortality as high as 40%.[21]

Johnson et al. compared the treatment of pancreatic abscesses via surgical omentalization with abdominal closure versus open

peritoneal drainage in 15 dogs.[7] Five of the eight dogs treated with omentalization survived while only one of four dogs treated with open peritoneal drainage survived. The other three dogs either died or were euthanized.

All 36 dogs with pancreatic abscess in the Anderson study went to surgery. The pancreas was debrided in 13 dogs and partial pancreatectomies were performed in three others. Duodenostomy tubes were placed in three dogs, and seven dogs received jejunostomy tubes. Sump-Penrose drains were placed in three dogs, and 11 were managed with open peritoneal drainage. Overall, 23 of the 36 dogs had one surgery and 13 of 36 had multiple surgeries. Multiple surgical procedures did not influence outcome nor was there any difference in outcome between dogs managed with open abdominal drainage or Sump-Penrose drainage and those managed with primary closure.[9]

Conclusion

The diagnosis of pancreatic abscess will usually not be made until the patient goes to surgery. This particular patient will be one that does not respond well to the standard of care for treating acute pancreatitis and may have evidence of a mass effect on abdominal imaging. The length of hospitalization is substantial, the risks of surgery rather daunting, the cost to the pet owner is often staggering, and the prognosis is fair to grave.

Pancreatic Pseudocyst

Definition and Incidence

A pancreatic pseudocyst is a collection of enzyme-rich pancreatic fluid containing variable amounts of tissue debris and blood. It results from autodigestion and liquefaction of pancreatic tissue during severe pancreatitis and is highly associated with necrosis and hemorrhage. A pseudocyst is not a true cyst in that it is lined by inflammatory tissue instead of epithelium.[3] It is an uncommon sequel to acute pancreatitis in humans, and is rare in the dog and cat.[22] In humans, a pancreatic pseudocyst can resolve spontaneously or it can rupture into the abdominal cavity with potentially life-threatening consequences. Complications in humans include infection, rupture into the peritoneal cavity, and acute hemorrhage. There are only a few case reports of this condition in the dog[22-25] and one in the cat.[26]

History and Physical Examination

Because this condition is a sequel to acute pancreatitis, the initial signs will represent the primary illness and be characterized by any combination of signs including vomiting, anorexia, fever, dehydration, abdominal tenderness, lethargy, mental depression, and occasionally diarrhea.[22] The acute pancreatitis can resolve uneventfully, or it can culminate in a pseudocyst over a period of a weeks. A small cyst might not cause any clinical signs, but a large mass will cause abdominal discomfort and displacement of abdominal organs. Additional signs reported in the literature include vomiting, diarrhea, anorexia, abdominal pain, and a palpable abdominal mass.[23,24]

Clinicopathologic Findings

The laboratory features of pancreatic pseudocyst will vary from normal to those similar to acute pancreatitis. Normal or minimally abnormal test results will depend on the time proximity to the most recent bout of pancreatitis. Minimal abnormalities will be present if the pseudocyst forms after the inflammatory phase has ceased. This trend would also pertain to serum pancreatic enzyme activities (amylase, lipase) or concentrations (cPLI).

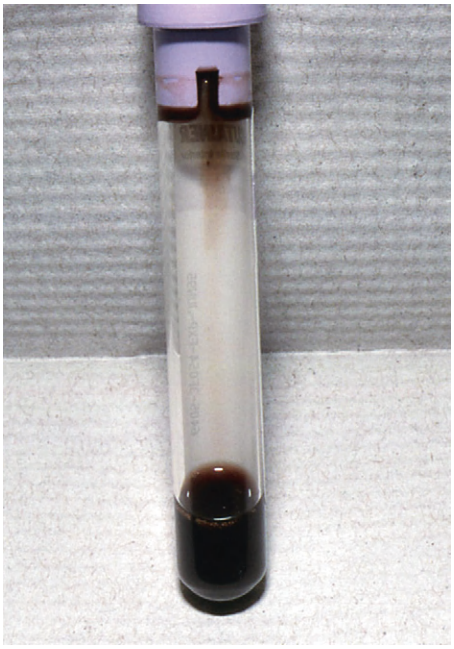

Figure 60-31 Pancreatic pseudocyst fluid containing amorphous debris.

A sample of the cystic fluid can be obtained by ultrasound-guided fine-needle aspiration. The character of the fluid will vary, especially if it is infected. Sterile cyst fluid can vary from being thin to viscous depending on the amount of necrotic debris present (Figure 60-31). In humans, the cyst can contain high concentrations of amylase and lipase, especially if the cyst is connected to the pancreatic duct. The cyst fluid from the canine case reported by Smith et al. contained high concentrations of amylase, lipase, and TLI.[22] This finding has been reported in other canine cases.[27] The cytologic features of the pancreatic cyst fluid can range from minimal cellularity to that of increased cellularity that reflects an inflammatory component. The latter finding in a clinically ill patient with fever might prompt a more aggressive treatment strategy including laparotomy.

Diagnostic Imaging

Pancreatic pseudocyst might have the radiographic appearance of a mass with fluid density in the area of pancreas. Large cysts will displace adjacent abdominal viscera. Radiographs will not distinguish pseudocyst from the inflammation pattern typical of acute pancreatitis. Abdominal ultrasonography has greatly facilitated this diagnosis in humans, and it will probably accomplish the same in veterinary medicine once the technology and the accompanying necessary skills become more widely available. The sonographic appearance of pseudocyst will likely be indistinguishable from other types of pancreatic masses such as pancreatic abscess or cystic neoplasia until a sample of the cyst fluid or the tissue itself is analyzed. Using this technique, it will appear as a hypoechoic mass containing hyperechoic sediment (Figure 60-32). One report showed that the size of the pseudocyst ranged from 2×2 to 7×6 cm,[27] and that the fine-needle aspiration procedure was a practical and efficient way to make this diagnosis, and in some cases to expedite its medical treatment.[11,28]

CT provides an excellent visualization of pancreatic pseudocyst. This technique is more commonly used in humans for general abdominal diagnostic evaluations, but abdominal ultrasound might be more feasible for veterinarians because of its availability, lesser cost, and high degree of diagnostic accuracy.

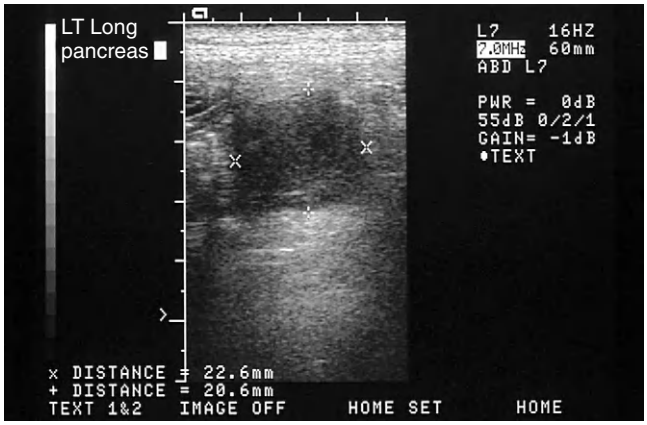

Figure 60-32 An abdominal ultrasound showing pancreatic pseudocyst.

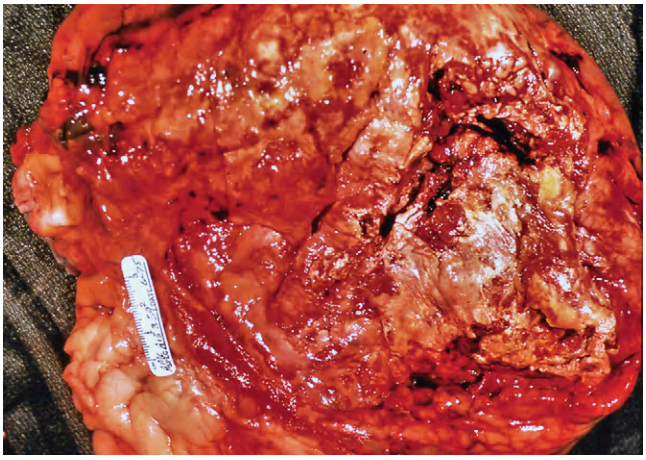

Figure 60-33 Pancreatic phlegmon at postmortem.

Treatment

Physicians will monitor human pancreatic pseudocyst for several weeks so long as they are not infected, not causing pressure on nearby structures, and not showing evidence of spontaneous rupture. In many cases, the cyst will resolve spontaneously.[3,11,28] The incidence of spontaneous resolution in small animals is not known either because of the rarity of the condition or its infrequency of diagnosis. It would seem prudent to conservatively monitor a small cyst for spontaneous resolution if it is of no immediate threat to the patient.

Transabdominal fine-needle aspiration of the cyst contents is commonly performed in humans and this technique has been reported in dogs.[11,23,27] The procedure is performed selectively on those patients who are clinically stable and who do not show signs of a surgical abdomen (fever, prostration, palpable tenderness, cytologic evidence of abdominal sepsis). Potential complications include leakage of cyst fluid into the peritoneal cavity, hemorrhage, and introduction of infection. Patients treated with this technique should be clinically reevaluated for 2 weeks. Other treatment techniques that are used in humans include percutaneous cystogastrostomy, and endoscopic cystogastrostomy, and duodenostomy. Surgical resection is done if the less-invasive techniques fail to resolve the problem or if bacterial infection is present.[3,8,22,26] Procedures include anastomosis of the cyst to an adjacent hollow viscus, Roux-en-Y anastomosis, and external drainage with creation of a pancreatic fistula to the skin.[3,20]

Conclusion

Pancreatic pseudocyst formation occurs as a sequel to acute pancreatitis. Small pseudocysts might be clinically asymptomatic and resolve spontaneously over a few weeks. Large cysts can cause a range of clinical signs related to their physical size, the possibility of secondary infection, or because of spontaneous rupture into the abdominal cavity. Treatment of large intact cysts can be accomplished by transabdominal ultrasound-guided fine-needle aspiration. Surgery is indicated for infected cysts and those that rupture.

Pancreatic Phlegmon

Definition

Adler and Barkin describe pancreatic phlegmon as a mass that results from acute intrapancreatic inflammation with fat necrosis and pancreatic parenchymal necrosis. They are usually found in association with necrotizing pancreatitis and are characterized by necrotic pancreatic and peripancreatic tissue.[11] "Pancreatic ascites" commonly accompanies this condition because of the substantial peritonitis that occurs with this condition. It is characterized as a sterile exudate in the absence of infection.[2] The largest number of reported cases describes this condition in seven dogs.[6] Because of the overlap in defining pancreatic necrosis and pancreatic phlegmon, Edwards et al. use the description provided by Warshaw where pancreatic phlegmon is a solid mass of indurated pancreas and adjacent tissue resulting from edema, inflammatory cells, and some tissue necrosis (Figure 60-33).[29] A fluid pocket is not present. Phlegmon develops within days after a severe bout of pancreatitis and is characterized by the presence of a palpable or radiographic abdominal mass and prolonged leukocytosis. Persistent fever and abdominal tenderness frequently are present. The terms *pancreatic necrosis* and *phlegmonous pancreatic slough* refer to the condition where glandular tissue becomes devitalized. These masses involve peripancreatic tissue more extensively than a phlegmon and can be associated with fluid-filled pockets produced by liquefaction necrosis.[6,30]

Incidence, History, and Physical Examination

There is nothing in particular that distinguishes one particular patient with pancreatic necrosis from another that has pancreatic phlegmon except for the eventual mass-like lesion that develops with phlegmon within 5 to 7 days of severe clinical illness. Edwards et al. reporting on seven dogs described all of them as seriously ill and showing signs typical of severe pancreatitis.[6] The ages ranged from 4 to 12 years (mean: 7.8 years) with a majority (five) in obese female dogs. All seven had signs of anorexia, lethargy or depression, and vomiting, which were present for a few hours to 3 days prior to being seen by a veterinarian. Five were admitted to the teaching hospital within 2 days of onset of clinical signs of acute pancreatitis while two were referred 9 to 10 days after the initial signs of pancreatitis. Fever occurred in five, abdominal pain in three, and diarrhea in two. All of the initial imaging and clinical pathology results were typical of most dogs affected with pancreatitis. One dog had a palpable abdominal mass that resolved, and this dog was discharged after 8 days of hospitalization. Because the pancreas was not grossly visualized in this dog, the diagnosis of a phlegmon was tentative based on imaging and laboratory results. The other six dogs were diagnosed at surgery, which was done after a protracted hospital stay that ranged from to 8 to14 days after initial signs of pancreatitis. The clinical course in some of these dogs fluctuated with varying degrees of illness, but they were persistently ill.

Clinicopathologic Findings

It is important to note that there are no laboratory tests to distinguish between severe acute pancreatitis, pancreatic necrosis, pancreatic abscess, and pancreatic phlegmon. They can all have the same clinicopathologic findings from normal to highly abnormal. All of these conditions cause a leukocytosis, many of which also have toxic changes in the white blood cells. Many cases have a lowered platelet count that is attributable to consumption of platelets because of inflammation. DIC can occur in any patient with severe acute pancreatitis as a result of the systemic inflammatory response or secondary sepsis. Patients with phlegmon usually have elevated serum liver enzyme concentrations and hyperbilirubinemia. Icterus can occur from either cholestasis or secondary to an obstruction of the common bile duct. Serum proteins might be increased initially but then decrease because of "third spacing" of plasma proteins in the peritoneal space because of increased vascular permeability associated with the marked inflammatory response. BUN and serum creatinine concentrations can increase as a result of prerenal effects from hypovolemia and renal hypoperfusion. Acute renal failure can occur as an ominous secondary complication because of acute tubular necrosis, antibody–antigen accumulation at the glomerulus, secondary to drug toxicity, and pathologic thrombi formation at the glomerulus.[20,31,32]

Diagnostic Imaging

The detection of an abdominal mass using diagnostic imaging is the main sign that suggests pancreatic phlegmon formation. In Edwards' review, pancreatic (anterior abdominal) masses were detected by radiography in five cases, with ultrasonography in two cases, and with abdominal palpation in one case. Today we expect a large majority of cases to be discovered using abdominal ultrasonography. The main radiographic abnormalities include a mottled appearance in the peritoneal cavity with a loss of serosal detail. The majority had a mass effect in the pancreatic region that often displaced the pylorus or ascending proximal transverse colon. The main ultrasonographic features were a hyperechoic mass in the pancreatic region containing hypoechoic and anechoic areas.[6]

Treatment

The treatment for pancreatic phlegmon and sterile necrosis can range from purely medical to those that require major surgery. When surgery is selected, it is essential to be aware that the procedure begins on a severely ill patient that might be near death prior to surgery, and that the postoperative outcome could be disastrous. This is evidenced in Edwards' report showing that all six patients that underwent surgery either died or were euthanized.[6] Perhaps part of the reason for this outcome might be the protracted care that was needed in each of those cases. In humans, the decision to operate is controversial, each based on valid opinions, but the one unanimous decision in favor of surgery is the presence of infected necrosis.

Infected necrosis is a serious and potentially lethal complication in humans.[18] Overall, the rate of mortality is 20% to 30%, and in some cases even higher, especially if the condition goes unrecognized until the postmortem examination. Surgery is essential for treating this condition where debridement is carried out by gentle finger dissection of necrotic material which consists of necrotic fat and pancreatic parenchyma. As discussed for pancreatic abscess, the various types of surgical drainage include necrosectomy with closed peritoneal lavage, necrosectomy with wide peripancreatic drainage, necrosectomy with staged reexploration, and necrosectomy with open packing.[20] These same procedures can be done in veterinary patients. Regardless of the species, one of the most important factors regarding surgery is to not delay the surgery while the patient continues to worsen because of sequestered necrosis. The postoperative morbidity in all of these procedures is substantial, and all are associated with a long postoperative stay.

The treatment of sterile necrosis is controversial when considering the option for surgery.[2,18,33] In such cases, intense medical treatment is done before surgery is considered. In humans, most patients found to have sterile necrosis heal successfully without debridement. However there are exceptions to this that usually involve patients who continue to deteriorate despite adequate medical support.

Infected Pancreatitis

Overview

The veterinary literature suggests that cultures of pancreatic tissue are usually negative.[5-7] In Anderson's review of 36 dogs with pancreatic abscess, only two of 13 cultures yielded bacterial growth.[9] However, 12 of the 36 dogs had peritoneal fluid cultured, and seven of these had positive bacterial growth. The results of Anderson's study population raises the possibility of the presence of an undiagnosed peritonitis in the face of ongoing sterile pancreatic necrosis. There is also the question of bacterial isolation from necrotic tissue which might not be conducive to pancreatic growth. It is possible that antibiotics administered to the pancreatitis patient could favor negative bacterial isolation on samples taken several days after the antibiotics have had a chance to take effect. Perhaps veterinary patients might show a higher incidence of infected pancreatitis if tissue and/or abdominal fluid samples were obtained initially by fine-needle aspiration prior to administering antibiotics. The remaining question regarding the indication for antibiotic treatment is also one with answers that have changed over time. Because there is experimental evidence for transcolonic migration of bacteria during acute pancreatitis, there are some clinicians who will administer broad-spectrum antibiotics in the hope of reducing the incidence of pancreatic and peripancreatic infections even though the benefits of doing so have not been proved.[33,34] In a recent study involving 100 human patients with severe necrotizing pancreatitis, using antibiotic treated and untreated controls, there was no statistically significant difference between the antibiotic treated groups and the untreated group for pancreatic or peripancreatic infection, mortality, or the requirement for surgical intervention therefore concluding that early prophylactic antimicrobial use provided no distinct advantage in human patients.[14]

Regardless of its rare occurrence, infected pancreatitis should be suspected in every case of pancreatic necrosis or phlegmon. Diagnosis is established by demonstrating bacteria with fine-needle aspiration of any abdominal fluid or parenchymal tissue samples (Figure 60-34). Treatment should begin with a broad-spectrum antibiotic(s) while the results of culture and sensitivity are pending.

INSUFFICIENCY

Maria Wiberg

Exocrine Pancreatic Insufficiency in Dogs

Exocrine pancreatic function may be diminished by chronic diseases leading to inadequate production of digestive enzymes and classic signs of maldigestion. EPI is a functional diagnosis based on

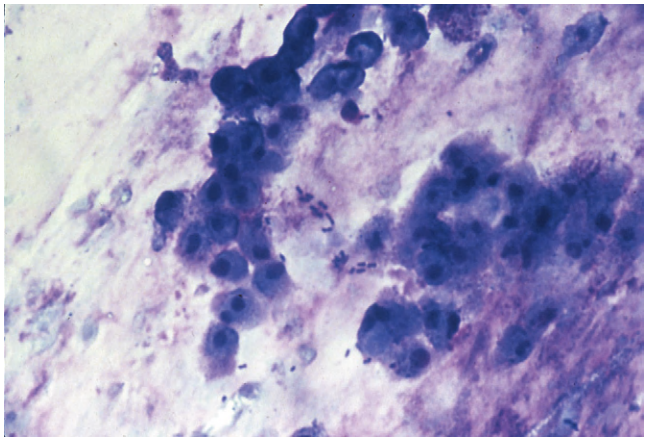

Figure 60-34 Bacteria detected on a fine-needle aspiration cytology sample from a dog with an infected pancreatic phlegmon that was confirmed at surgery.

measuring decreased pancreatic secretion capacity by pancreatic function test. The exocrine pancreas has a large reserve secretory capacity, and maldigestion signs are usually not seen until 90% of the secretory capacity is lost. Exocrine pancreatic diseases that may result in clinical signs of EPI include pancreatic acinar atrophy (PAA; dogs), chronic pancreatitis (dogs, cats), and very rarely reported pancreatic neoplasia (dogs, cats).[1-6]

Etiopathogenesis

EPI has been reported in many different breeds, but some breeds appear to be more predisposed than others. EPI is most commonly found in German Shepherds, followed by Rough-Coated Collies, Chow Chows, and Cavalier King Charles Spaniels.[3,5,7-10] Female association with EPI has been reported.[10] The prevalence of the various pancreatic diseases causing clinical signs of EPI is difficult to assess, because pancreatic morphologic examination is needed for the specific diagnosis. However, PAA is reported to be by far the most common cause of severe EPI in young adult dogs. Of all dogs diagnosed with EPI, approximately 50% to 70% were German Shepherds, and in Finland 20% of the cases are found in Rough-Coated Collies.[3,9,10] With German Shepherds and Rough-Coated Collies, the underlying cause for EPI is PAA. The estimated prevalence of the disease within these two breeds is approximately 1%.[3,8] Similar etiopathogenesis with PAA may also be suspected in other breeds with early onset EPI, such as the Chow Chow and Eurasian dog breeds.[10,11] In contrast, dogs that develop clinical signs of EPI later in life more likely have chronic pancreatitis as the underlying pathogenesis.[10]

Pancreatic Acinar Atrophy

The characteristic of PAA is a selective destruction of the digestive enzyme, producing acinar cells. Loss of acinar tissue leads to inadequate secretion of pancreatic enzymes and to signs of maldigestion typical of EPI. The endocrine function of the pancreas is usually spared in this process.[1,2,5,12] Canine PAA is a unique disease compared with other species. In humans, PAA has been reported, but in association with multiorgan diseases such as Sjögren and Shwachman-Diamond syndromes.[13] Congenital isolated deficiencies in pancreatic enzymes are reported in humans[13] but not in dogs. Experimental studies show that acinar atrophy can be an end result of multiple pathogenetic processes involving the exocrine pancreas, such as pancreatic duct obstruction, ischemia, toxicity, nutritional deficiencies or imbalances, and defective secretory and/or trophic stimuli.[6] That said, there is no evidence to support the involvement of these factors in naturally occurring PAA in dogs.[6,14] Congenital exocrine or compound exocrine and endocrine pancreatic hypoplasia in young puppies is sometimes found.[15-17] Westermarck et al.[18] followed the morphologic changes in the pancreas of a German Shepherd puppy bred from parents with PAA. The puppy was born with a grossly and histologically normal pancreas, but developed EPI later in life. This finding supports the hypothesis that PAA in this breed is neither hypoplastic nor congenital, but rather a progressive disease.

The clinical signs of EPI caused by PAA are usually seen in young adults, 1 to 4 years of age, although sometimes the clinical disease may develop later in life.[19] The hereditary nature of PAA has been demonstrated in German Shepherds, Rough-Coated Collies, and recently with Eurasian dogs. Pedigree analyses suggest that the disease in these three breeds is heritable by an autosomal recessive trait.[7,8,11,20,21] Preliminary results of a test mating between two German Shepherds with PAA showed that only two of the six offspring were affected, thus suggesting that EPI is not a single-gene disease but rather a polygenic disease (unpublished data). To date, two studies have attempted to identify the candidate genes for PAA. In German Shepherds, the gene for glycoprotein 25L, located at CFA3, is downregulated by 500-fold in affected pancreata. However, there were no mutations found in the coding sequence (that segregates with PAA).[22] In Eurasian dogs, linkage analysis of CFA3 and CFA23 as canine orthologs of the human cholecystokinin and cholecystokinin A receptor genes excluded them as candidates for PAA.[11] Therefore, additional studies are necessary to identify the molecular defect responsible for PAA in these breeds.

Recent etiopathogenetic studies showed that PAA has some features of autoimmune disease in German Shepherds and Rough-Coated Collies.[23,24] These features include genetic susceptibility to disease and characteristic morphologic and immunologic findings during progression of disease. The ability to diagnose PAA prior to development of total acinar atrophy and manifestation of clinical maldigestion signs, permits the progression to atrophy to be closely monitored.[9] The progression of PAA was divided into a subclinical phase characterized by partial acinar atrophy and a clinical phase with severe end-stage atrophy. In the subclinical phase, both atrophied and normal acinar parenchyma were found. Grossly, the normal pancreatic mass was diminished and scattered areas of atrophied tissue were found among the normal tissue. No hemorrhagic or fibrotic tissue was observed. The histologic findings during the progression of atrophy were typical for an autoimmune disease showing marked lymphocytic inflammation into the partially atrophied acinar parenchyma. The gradual destruction of the acinar structure was found in association with the inflammatory reaction. Lymphocytic inflammation was most extensive in the border zones of the normal and affected acinar parenchyma, and lymphocytes spread into the normal acinar parenchyma and intraacinar areas. As tissue destruction progressed, the findings became more typical of end-stage PAA.[23]

The clinical signs appear in the end stages of PAA. The gross pathologic findings are typical, showing thin and transparent pancreas with no signs of fibrosis. The normal glandular structure is hardly recognizable and the pancreatic ducts are clearly visible. Histologically, no normal acinar tissue is left in the end stages, or if normal tissue is present, it is found in small isolated lobuli. The normal acinar parenchyma is replaced by atypical tissue, and ductal structures are prominent. Fibrous tissue is not generally increased, and in some cases the normal tissue is replaced by adipose tissue.

Inflammatory cells, lymphocytes, and plasma cells may be found, but in general inflammation is less prominent than in the subclinical phase. The endocrine part of the pancreas in dogs with PAA is usually well preserved.[1,5,12,25]

Further immunologic studies with dogs with partial PAA have suggested that both cellular and humoral immune responses play a role in the pathogenesis of acinar atrophy, although tissue destruction appears to be largely mediated by cellular immune mechanisms.[24] Immunohistochemical analysis showed that at the onset of acinar cell destruction, the majority of the infiltrating lymphocytes were T cells, with an almost equal number of CD4+ T-helper and CD8+ cytotoxic T-lymphocytes. Cytotoxic T cells predominated in sections where the gradual destruction of the acinar parenchyma was present.[24] The role of the humoral immune response was previously studied, in which serum pancreatic-specific antibodies in dogs with clinical signs of EPI were compared with those of healthy controls, but the study found no differences between these two groups.[26] A recent study showed that serum autoantibodies reacting at low intensity with pancreatic acinar cells were found in some dogs with partial and end-stage PAA, but not in healthy control dogs, suggesting that the humoral immune response was also activated.[24]

As lymphocytic pancreatitis with active destruction of acinar structures preceded the end-stage atrophy, the term *autoimmune-mediated atrophic lymphocytic pancreatitis* has been suggested to describe the pathologic findings.[23,24] The rate of progression of the atrophy from the subclinical to the clinical phase is variable, and the factors affecting it are not yet identified. Long-term followup of dogs with partial PAA shows that they may remain in the subclinical phase for years or sometimes for life. No diagnostic markers predicting which dogs will develop clinical disease have been found.[27] Autoimmune diseases are often multifactorial. Genetic susceptibility, environmental factors, and immunologic abnormalities are all involved in this pathogenesis. Environmental factors, either microbial or nonmicrobial, are usually needed to initiate a clinical autoimmune disease in genetically susceptible individuals.[28] The possible contribution of various environmental factors, such as feeding, housing, training, stress, and viruses, in the pathogenesis of PAA has been proposed, but there are no comprehensive studies available on their roles. A survey failed to show any common triggering environmental factors in the histories of dogs with EPI.[19]

Chronic Pancreatitis

Chronic pancreatitis is probably an underestimated reason for EPI, because there has been lack of sufficient histologic data. Recent studies show that chronic pancreatitis may be more common in dogs than clinically suspected.[29,30] Unlike the situation in autoimmune atrophic pancreatitis, there is usually a progressive destruction of both exocrine and endocrine pancreas in chronic pancreatitis. Clinical history usually shows more nonspecific GI signs, or the signs of EPI also can develop later in dogs with previous diabetes mellitus. The pathologic findings in chronic pancreatitis are clearly different from those of PAA. Macroscopically, the pancreas is usually hard, shrunken, and nodular, and there may be adhesions. The characteristic histologic findings in chronic pancreatitis involve an increase in interlobular and intralobular fibrosis and disorganized acinar lobuli, with or without inflammatory cells in the interstitium.[1,2,5,29]

Clinical Signs

The typical clinical signs of EPI include increased fecal volume and defecation frequency, yellowish feces, weight loss, and flatulence. Other common signs are polyphagia, poorly digested, loose and pulpy feces, and coprophagia. Nervousness or aggressiveness may occur and these are suspected to result from abdominal discomfort because of increased intestinal gas. Severe watery diarrhea is usually only temporary. Skin disorders have also been reported. Although these signs of EPI are typical, they are not pathognomonic for the disease, as small intestinal diseases may show similar maldigestive or malabsorptive signs.[6,19]

Diagnosis

The diagnosis of exocrine pancreatic dysfunction is based on typical findings in clinical histories and clinical signs and is confirmed with a pancreatic function test. Complete blood cell count and routine serum biochemistry often show unremarkable changes. Serum amylase and lipase activities are not useful in the diagnosis of EPI. Various pancreatic function tests, which measure pancreatic enzyme concentrations in the blood and feces, have been used to diagnose canine EPI. The diagnostic value of these tests lies in their ability to distinguish whether the maldigestion signs are caused by exocrine pancreatic or small intestinal disease, as well as in their practicality. When needed to verify the underlying pathologic process causing the clinical signs, morphologic examination of the pancreas may be performed.[31]

The measurement of canine serum TLI has become one of the most commonly used pancreatic function tests in the diagnosis of canine EPI.[32] Serum TLI measurement is species- and pancreas-specific. The new reference ranges for cTLI in healthy dogs are 5.7 to 45.2 µg/L (Texas A&M, Gastrointestinal Lab, College Station, TX). Abnormally low serum cTLI concentrations (<2.5 µg/L), with the typical clinical signs of maldigestion, are considered highly diagnostic for severe EPI and indicate severe loss of the digestive enzyme-producing acinar cells.[32] Interpretation of the cTLI values is not always straightforward. The pathologic processes affecting exocrine pancreatic function are progressive, and cTLI levels can vary from normal to abnormal depending on the degree of pancreatic tissue lost. Overlapping results between normal and affected dogs can be expected, and a normal cTLI greater than 5.7 µg/L does not necessarily exclude mild to moderate pancreatic dysfunction.[9] In general, the lower the cTLI value, the more valuable a single measurement is in assessing pancreatic dysfunction. When the cTLI value is in a subnormal range (2.5 to 5.7 µg/L), further diagnostic procedures with repeat cTLI measurement are recommended.[9] In German Shepherds and Rough-Coated Collies, breeds predisposed to autoimmune atrophic pancreatitis, it was shown that repeatedly subnormal cTLI values (2.5 to 5.0 µg/L) in dogs showing no typical signs of EPI indicated subclinical EPI and suggested partial atrophy.[9,23]

Fecal proteolytic activity measurement has been used historically for the diagnosis of EPI. The reliability of the different tests varies, and a common problem with these tests is that sometimes normal dogs also showed decreased proteolytic activity.[6,33,34] To avoid this problem, fecal proteolytic activity was measured from repeated fecal samples and after using pancreatic stimulation by giving raw soybeans in the food during the test period.[34] A recent study showed that in dogs with protein-losing enteropathy, increased fecal loss of α_1-proteinase inhibitor is associated with a decrease in fecal proteolytic activity and may result in a false diagnosis of EPI.[35]

A new fecal test for diagnosing exocrine pancreatic dysfunction is the ELISA determination of fecal elastase. Canine fecal elastase is species- and pancreas-specific test with high sensitivity, but relatively low specificity. A single fecal elastase concentration greater than 20 µg/g can be used to exclude EPI in dogs with chronic diarrhea. Values less than 20 µg/g in association with typical clinical signs of EPI are suggestive of severe pancreatic dysfunction.[36-38] For

diagnosing subclinical EPI and partial PAA the fecal elastase measurement was not sufficiently sensitive enough.[39]

Treatment

Enzyme Replacement Therapy

When signs of maldigestion secondary to EPI appear, enzyme replacement therapy is indicated. The basic treatment includes supplementation of the dog's ordinary food with pancreatic enzyme extracts. Various pancreatic enzyme extracts are available in different countries. In dogs, the highest enzyme activity in the duodenum was achieved using nonenteric-coated supplements, such as powdered enzymes or raw chopped porcine pancreas, and these supplements are equally effective in controlling clinical signs.[40,41] The choice among preparations is based on practical properties, availability, and costs. In many countries the use of raw porcine pancreas is not permitted because of possible zoonotic disease. The maintenance dosage for the powdered enzyme is dependent on the preparation used (Viokase-V, Fort Dodge, Fort Dodge, KS, 1 tsp/meal). Raw frozen pancreas has been fed at 50 to 100 g/meal for dogs that weigh 20 to 35 kg.[6,40,41] The value of enteric-coated supplements is limited in dogs as a result of delayed gastric emptying of the preparations.[42] Despite accurate enzyme therapy the digestive capacity does not return to normal, because orally administered enzymes are largely destroyed by gastric acid. Sometimes the increase in enzyme dosage or change to another nonenteric-coated supplement may be beneficial. Inhibition of gastric acid secretion by H_2-histamine receptor antagonists has shown some positive effects. Even if routine use of H_2-histamine receptor antagonists is not needed, they may be indicated when the response to enzyme treatment alone is poor and especially when vomiting or inappetence appear.[6,41,43] A rare complication with oral enzyme powder supplementation is gingivitis and oral bleeding, which is treated either by decreasing the enzyme dose or by changing the supplement or preincubation enzyme in the food prior to feeding.[44,45]

Supportive Treatments

Supportive treatments should be considered when the treatment response to enzyme replacement therapy alone is not satisfactory. EPI also may be associated with secondary problems that may worsen the clinical signs. These include small intestinal bacterial overgrowth or antibiotic-responsive diarrhea, malabsorption of cobalamin, and the coexistence of small intestinal disease.

The most commonly used adjunctive medications in the treatment of EPI are antibiotics. An increased amount of substrates for bacteria in the small intestine, a lack of bacteriostatic factors in the pancreatic fluid, and changes in intestinal motility and immune functions are possible reasons for the accumulation of bacteria in the small intestine of dogs with EPI.[46-48] Antibiotics have been used during the initial treatment when clinical signs, such as diarrhea, increased intestinal gas, and flatulence have not resolved with enzyme therapy, or when these signs have recurred during long-term treatment. Antibiotics reported to be effective include tylosin (10 to 20 mg/kg BID) or metronidazole (10 to 15 mg/kg BID) for 1 to 3 weeks.[6,41]

Clinical feeding studies during long-term treatment of EPI show that the need for special diets is minimal and that dogs may continue to be fed their original diet. Radical dietary changes should be avoided and special attention should be focused on individual needs, since the response to different diets varies among dogs.[41,49-51] In those dogs that do not show satisfactory treatment response, dietary modification may be useful. The severity of some clinical signs of EPI can be decreased with dietary modification. A highly digestible, low-fiber and moderate-fat diet can alleviate clinical signs such as defecation frequency, increased fecal volume, and flatulence.[49] Highly digestible diets may be of particular value in the initial treatment until the nutritional status has improved and possible mucosal damage has been repaired. A low-fat diet was recommended, because enzyme supplements alone are unable to restore normal fat absorption.[52] Lipase is most easily destroyed by exposure to gastric acid during gastric transit. Fat absorption may also be affected by bacterial deconjugation of bile salts in small intestinal disease, producing metabolites, which, in turn, may result in diarrhea. However, feeding the low-fat diet did not significantly alleviate the clinical signs during the long-term treatment.[50] Dietary sensitivities may be a consequence of EPI, and therefore hypoallergenic diets may benefit some dogs, especially those with concurrent skin problems. No obvious clinical benefits were demonstrated by adding medium-chain triglycerides to food.[53]

Cobalamin deficiency in dogs with EPI is partly a result of increased uptake of cobalamin by the intestinal bacteria and partly to the lack of pancreatic intrinsic factor, shown to play a major role in the absorption of cobalamin. Enzyme treatment alone is not helpful for increasing serum cobalamin levels.[54-56] Because cobalamin deficiency is common in canine EPI, serum cobalamin should be measured in dogs that are clinically suspected of having EPI or that do not respond satisfactorily to enzyme treatment. Cobalamin is given subcutaneously and the dose currently recommended is 250 to 1000 µg, depending of the size of the dog.[57] The treatment should be repeated based on serum concentrations.

Although malabsorption of fat-soluble vitamins may be expected with EPI, the clinical importance of vitamins A, D, E, and K deficiency in this syndrome has not been reported. When the treatment response to enzymes and supportive therapies is still unsatisfactory, concomitant small intestinal disease should be suspected, and further diagnostic studies and treatment should be performed.[6]

Treatment of Atypical Cases

The diagnosis and treatment of EPI can be more complicated in dogs with pancreatic dysfunction as a result of chronic pancreatitis or with dogs having only partial PAA. These dogs may show nonspecific chronic or intermittent GI signs associated with serum TLI concentration in the subnormal area of 2.5 to 5.7 µg/L.[9] GI signs may be a result of subnormal pancreatic function or underlying small intestinal disease or a combination of both. The diagnostic workup and treatment for possible concurrent small intestinal disease is recommended (see Chapter 57), and serum TLI measurement should be repeated in 1 to 2 months. If no underlying small intestinal disorder is identified, a trial treatment with pancreatic enzymes should be initiated. Those dogs with diagnosed partial PAA caused by autoimmune pancreatitis, but showing no clinical signs of EPI, need no treatment. The value of early immunosuppressive treatment with azathioprine in slowing the progression of the autoimmune-mediated tissue destruction was shown to be questionable, and is thus not recommended.[27]

Prognosis

When the clinical signs of EPI appear, the loss of pancreatic tissue is already almost totally complete. Changes are considered to be irreversible, and lifelong enzyme replacement therapy is usually required. The response to enzyme treatment is usually seen during the first weeks of treatment, with weight gain, cessation of diarrhea, and decrease in fecal volume.[6,43]

The level of treatment response achieved during the initial treatment period remains fairly stable.[41] Although some dogs show short relapses of clinical signs, the permanent deterioration of the clinical

condition during long-term treatment is uncommon. During long-term treatment with nonenteric-coated enzyme supplements, the GI signs considered typical for dogs with EPI were almost completely controlled in half of the dogs. Although it was not always possible to eliminate all the signs, good resolution was found especially in the more serious signs. Those signs most commonly remaining were increased fecal volume, yellow and pulpy feces, and flatulence. Poor response to treatment was observed in 20% of the dogs, despite similar treatment regimens.[41]

Another study showed similar results, with favorable initial treatment response in 60% of dogs, partial in 17%, and poor in 23%.[58] Severe cobalamin deficiency was associated with shorter survival. Other predictors, such as breed, sex, age, clinical signs at the time of diagnosis, dietary modification, and fat-restricted diet did not affect the favorable initial treatment response or long-term survival. Interestingly, no difference in the treatment response or survival was found between enteric-coated and nonenteric coated supplements. This was clearly a different result than that previously reported[40] and thus should be further investigated.

Approximately 20% of dogs diagnosed with EPI were euthanized during the first year.[41,58] The most common reason for euthanasia was poor treatment response; another reason for euthanasia was owner reluctance for expensive and lifelong treatment. A rare, but severe, complication of EPI is mesenteric torsion.[59] Today mesenteric torsion is more seldom seen, probably because of more efficient enzyme preparations.

Exocrine Pancreatic Insufficiency in Cats

EPI in cats is rare. End-stage chronic pancreatitis is considered to be the most common cause of exocrine pancreatic dysfunction and clinical signs of maldigestion in the cat. Adenocarcinomas of the exocrine pancreas may cause obstruction of the pancreatic duct and thus decreased production of digestive enzymes.[60,61]

Clinical Signs

The clinical signs are similar to those of dogs, including loose and voluminous stools, weight loss, poor body condition, and polyphagia. Cats with EPI may have greasy, wet-looking hair coats, especially in the perineal region. The GI signs are often similar to those of small intestinal IBD and cobalamin deficiency. Other differential diagnoses to be considered are hyperthyroidism and intestinal neoplasia. Because chronic pancreatitis affects both the endocrine and exocrine pancreas, diabetes mellitus is commonly associated with EPI in cats.[60,61]

Diagnosis

The results of routine laboratory tests, abdominal radiography, and ultrasound are generally unremarkable, unless subtle changes of chronic pancreatitis can be recognized. The diagnosis of exocrine pancreatic dysfunction should be based on species-specific measurement of feline serum TLI. The reference ranges for fTLI are 12 to 82 µg/L (Texas A&M, Gastrointestinal Lab, College Station, TX). A severely decreased fTLI concentration equal to or less than 8 µg/L is considered diagnostic for EPI.[62] Fecal proteolytic activity tests can also be used for fEPI diagnosis, but in comparison to fTLI measurement these tests are impractical.[31,60]

Treatment

The basic treatment of feline EPI is pancreatic enzyme supplementation. Powdered formulations are the most effective in cats. With powdered enzyme extracts the initial dose is 0.5 tsp/meal. When possible, raw frozen pancreas can also be used. Tablets or enteric-coated supplements are usually less effective and thus not recommended. Dietary modification is not usually needed, and most cats with EPI can be fed with regular maintenance diets.[31,60] In cats with EPI, serum cobalamin concentrations are often severely decreased, and therefore serum cobalamin should be routinely measured in cats with suspected EPI and also during treatment of EPI in case of poor response to enzyme replacement alone. Some cats do not respond satisfactorily to enzyme treatment until cobalamin is also supplemented. The recommended dose for parenteral cobalamin is 250 µg subcutaneously weekly for 4 to 6 weeks, and thereafter based on the measurement of serum cobalamin concentrations.[31,60,63] EPI can also be associated with small intestinal disease, and in these cases treatment with oral prednisolone and/or antibiotics (oral metronidazole) may be needed.[31]

NEOPLASIA

Sandra Axiak and Kevin Hahn

Cats

Two types of feline exocrine pancreatic neoplasia are described: adenomas, which are usually incidental and benign, and adenocarcinomas. Adenocarcinomas are rare and can be diffuse throughout the pancreas,[1] although some reports show greater incidence in the head of the pancreas than the tail.[2] Age at presentation ranges from 4 to 20 years. Metastasis to the liver is common and less-common sites of metastatic spread include the lungs, lymph nodes, small intestine, and heart. Adenocarcinoma is also associated with diabetes mellitus and hyperadrenocorticism. Diabetes mellitus is thought to be secondary to compression of the islet cells, tumor-derived cortisol inducing β-cell degeneration, or decreased carbohydrate metabolism.[1]

Clinical Examination

Presenting clinical signs are anorexia, vomiting, abdominal pain, weight loss with a normal appetite, and icterus. Physical examination findings include icterus and cranial abdominal mass. Duration of signs is bimodal with 50% of cats having signs for less than 7 days and 50% having signs for more the 1 month.[1]

A rare paraneoplastic syndrome has been described in cats with pancreatic adenocarcinoma. It consists of nonpruritic, symmetrical alopecia of the face, ventral body, and medial limbs. Skin is glistening, but not fragile, and crusty lesions can be seen on the footpads. This syndrome is also reported in cats with bile duct carcinoma. Histopathologically, it is characterized by loss of the stratum corneum and severe follicular atrophy with miniaturized hair bulbs.[3] In one case report, the syndrome resolved following surgical excision of the pancreatic adenocarcinoma, but recurred when metastatic disease became evident, 18 weeks after surgery.[3]

Diagnosis

A CBC may show neutrophilia and serum biochemistry may reveal increased liver enzymes (alkaline phosphatase, alanine aminotransferase) and mild hyperglycemia. Chest radiographs may show pleural effusion indicative of metastasis.[1] Abdominal radiographs may show loss of serosal detail with or without a cranial abdominal mass. A pancreatic mass can be found on abdominal ultrasound. Definitive diagnosis requires fine-needle aspiration and cytology or exploratory laparotomy with biopsies and histopathology.[1]

Treatment and Prognosis

Supportive care is generally ineffective.[1] Surgical excision has been reported in one cat.[3] The prognosis is poor and most cats are euthanized within 7 days of diagnosis because of disease progression.[1] The cat in which surgical excision was reported did well for 18 weeks until euthanized for progressive disease.[3]

Dogs

The etiology of most canine exocrine pancreatic tumors is unknown and no predisposing factors have been identified. However, experimentally intraductal administration of *N*-ethyl-*N*′-nitro-*N*-nitrosoguanidine can induce pancreatic adenocarcinoma.[4]

Pancreatic exocrine tumors are derived from duct or acinar epithelium. Four types of pancreatic carcinoma have been described in the dog: adenocarcinoma, anaplastic carcinoma, alveolar carcinoma, and endocrine-like carcinoma.[5] An additional subset, hyalinizing pancreatic adenocarcinoma, has recently been described in a group of six dogs.[5a] There is no sex predilection, and breeds at higher risk include Airedales, Boxers, Labrador Retrievers, and Cocker Spaniels.[4] The overall incidence of exocrine pancreatic carcinoma is less than 1%, with an incidence of 12% in dogs with pancreatic disease.[5] Unlike the cat, benign neoplasms of the pancreas are not reported in the dog, although hyperplastic nodules are common in older dogs.[5] Location varies and grossly the tumor can appear singular, nodular, or diffuse. Hemorrhage and necrosis are common (Figure 60-35). Metastasis occurs early and affects the liver, omentum, and mesentery most frequently. Other sites of metastasis reported are lungs, thyroid gland, heart, duodenum, and subcutaneous tissue.[5] Histologically, there is extreme variation in cellular structure and central necrosis is common. Reduction in exocrine secretion does occur, however complete pancreatic insufficiency in dogs due to neoplasia has not been observed.[5]

Multifocal necrotizing steatitis has been reported in association with pancreatic carcinomas in three dogs.[6] In these cases, the presenting complaint was of panniculitis. Lesions ranged from ill-defined nondraining soft-tissue swellings to localized subcutaneous lesions with a purulent discharge. The mechanism of steatitis with pancreatic carcinoma is unknown, but is postulated to be a result of systemic release of lipase.[6] Panniculitis with polyarthritis and osteomyelitis also has been reported in two dogs, one with exocrine pancreatic adenoma, and the other with pancreatic adenocarcinoma.[7]

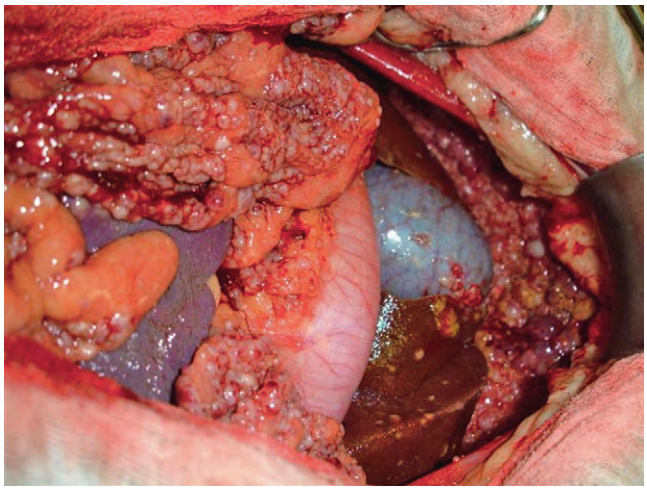

Figure 60-35 Carcinomatosis in a dog with pancreatic adenocarcinoma at surgery.

Clinical Examination

Clinical signs are nonspecific and bimodal, with duration of less than 1 month or of 2 to 4 months.[5] Most patients have a history of weight loss, anorexia, and vomiting. Other less-common signs include depression and weakness.[4] On physical examination, ascites, cranial abdominal mass, or icterus may be noted.[5]

Diagnosis

A CBC may reveal mature neutrophilia, while serum biochemistry may show increased alkaline phosphatase, lipase, or amylase. The increased lipase may occur from associated pancreatitis or from tumor production of lipase.[8] Chest radiographs are usually normal, whereas abdominal radiographs may show a loss of abdominal detail or cranial abdominal mass. Abdominal ultrasound may reveal a pancreatic mass, and can also be used to guide fine-needle aspiration and cytology. Cytology of abdominal fluid, if present, may also provide a diagnosis. Definitive diagnosis is based on ultrasound guided fine-needle aspiration and cytology (diagnostic in eight of 10 cases) or exploratory laparotomy and histopathology.[4] Immunocytochemical labeling for amylase and carboxypeptidase may be of value in diagnosing the primary tumor or metastasis.[9]

Treatment and Prognosis

Treatment is aimed at surgical removal of the pancreatic mass, however disease is usually advanced at the time of diagnosis.[10] One exception may be hyalinizing pancreatic adenocarcinoma, which may progress more slowly than other subtypes of exocrine pancreatic cancer. In one case series of six dogs, two lived greater than 15 months, one dog with no treatment and another with surgical excision. The other four dogs in this series died of complications related to concurrent disease or partial pancreatectomy.[5a] In general, chemotherapy and radiation therapy are ineffective.[10] Overall prognosis is poor as a result of location of the tumor and early onset of metastasis.[10]

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STRUCTURE AND FUNCTION

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CHAPTER 61

Liver

STRUCTURE AND FUNCTION

Robert J. Washabau

Liver Structure

The hepatic lobule is the anatomic unit of the liver. In the anatomic model, liver lobules are organized into irregular polygons demarcated by connective tissue and composed of plates of hepatocytes radiating outward from the central vein to the portal triads (Figure 61-1). The hepatic acinus is the functional unit of the liver. In the functional model hepatocytes are instead oriented around the afferent vascular system (portal veins and hepatic arteries) just as they anastomose into sinusoids (Figure 61-1), and the central vein is at the periphery of the acinus instead of centrally located as in the anatomic model. The acinus is divided into three contiguous zones (1, 2, and 3) that correspond to distance from the arterial blood supply. Those hepatocytes in closest proximity to the arterioles (zone 1) receive the greatest oxygen content, but are also first in line to be affected by toxins transported from the gut to the portal vein. Zone 3 hepatocytes reside at the periphery of the acinus near the central vein, and zone 2 hepatocytes are interspersed between zone 1 and zone 3 hepatocytes. The anatomic model is perhaps easier to understand, but the functional model serves as a better foundation for understanding liver pathology.[1] In either model portal venous and arterial blood flow centripetally, that is, toward the central vein, whereas bile flows centrifugally, that is, away from the central vein. Hepatocytes extract nutrients and oxygen from portal and arterial perfusion, respectively, and produce bile acids and other bile constituents that are transported from hepatocytes into bile canaliculi, ductules, and ducts.

Biliary Tract Structure

The basic elements of the biliary tract are the hepatic canaliculi, bile ductules, intralobular ducts, interlobular ducts, hepatic ducts, cystic duct, gallbladder, common bile duct, and the pancreaticobiliary sphincter (of Oddi).[2] There are many variations on this central theme, the most important of which are (a) the pancreaticobiliary sphincter is a common physiologic and anatomical channel at the duodenal papilla in the cat[3] and (b) there are many anatomic variations in the feline gallbladder, from single gallbladder to bilateral gallbladders, body duplication, fundic duplication, complete duplication, septate, and Y-shaped gallbladder.[4]

Cells of the Liver

Hepatocytes

Hepatocytes account for 60% to 80% of the liver cell mass (see Table 61-1) and contribute to a wide range of metabolic activity, including carbohydrate, protein, lipid, nucleic acid, porphyrin, metal, vitamin, glutathione, hormone, and xenobiotic metabolism; coagulation factor synthesis; biliary secretion; and immune surveillance.[1,5] Hepatocytes have an eosinophilic cytoplasm reflecting numerous mitochondria, and basophilic stippling caused by large amounts of rough endoplasmic reticulum and free ribosomes. Hepatocyte nuclei are round with dispersed chromatin and prominent nucleoli. Anisokaryosis is common and often reflects various degrees of polyploidy, a normal feature of more than 50% of hepatocytes. The average life span of the hepatocyte is 5 to 6 months reflecting their ability to regenerate. Hepatocytes are organized into plates separated by vascular channels (sinusoids), an arrangement supported by a reticulin (collagen type III) network. The sinusoids have a discontinuous, fenestrated endothelial cell lining. The endothelial cells have no basement membrane and are separated from the hepatocytes by the space of Disse, which drains lymph into the portal lymphatics. Hepatocytes are supported by a number of other cell types, which account for 40% of the liver cell mass.

Cholangiocytes

Representing 3% to 10% of liver cell mass, cholangiocytes are also known as biliary epithelial cells.[6] They secrete water, bicarbonate, and cations into the bile in the physiologic state, but they may also participate in the immune response as antigen-presenting cells in disease states. The biliary tract is a convergent system of canals that begins in the canaliculi, followed by the bile ducts, and ending with the common bile duct. Bile secretion depends on the function of membrane transport systems in hepatocytes and cholangiocytes and on the structural and functional integrity of the biliary tract. The hepatocytes, constituting the most abundant liver cell population, generate the so-called primary bile in their canaliculi. Biliary canaliculi are blind tubular structures, with a very high surface-to-volume ratio that by means of osmotic gradients favors the formation of bile flow. Cholangiocytes, which constitute 3% to 10% of the liver cells, modify the canalicular bile by secretory and reabsorptive processes as bile passes through the bile ducts, and they are responsible for approximately 30% of bile volume. In contrast to hepatocytes, where secretion is constant and poorly controlled, cholangiocyte secretion is broadly regulated.[5,6]

Table 61-1 Cells of the Liver and Their Functions

Cell Type	Other Names	Functions	Cell Markers
Hepatocytes	Liver cells	Intermediary metabolism	Albumin, cytokeratin 8 and 18
Cholangiocytes	Biliary epithelial cells	Line the bile ducts, secretion	Cytokeratin 7 and 19
Kupffer cells	Browicz-Kupffer cells, stellate macrophages	Phagocytosis of pathogens and particles	ED-1 and ED-2
Stellate cells	Ito cells, vitamin A–storing cells, lipocytes	Storage of vitamin A; production of myofibroblasts in injury	GFAP, desmin; α-smooth muscle actin
Natural killer (NK) cells	Pit cells, large granular lymphocytes, γδ T cells	Immune surveillance–infection, cancer	CD3
Vascular endothelial cells	Endothelial cells	Line blood vessels	CD34 and CD31
Lymphatic endothelial cells	Endothelial cells	Line lymphatic vessels	Podoplanin
Smooth muscle cells	Myocytes	Regulation of microcirculation	Myocardin, α-smooth muscle actin
Portal tract fibroblast	Fibroblasts	Integrity of portal triads, supporting function	Vimentin
Stem cells	Progenitor cells, oval cells	Bi-potential progenitor cell for hepatocytes and biliary epithelial cells	α-Fetoprotein

GFAP, Glial fibrillary acidic protein.
Adapted from Wallace K, Burt AD, Wright M: Liver fibrosis. *Biochem J* 411:1, 2008.

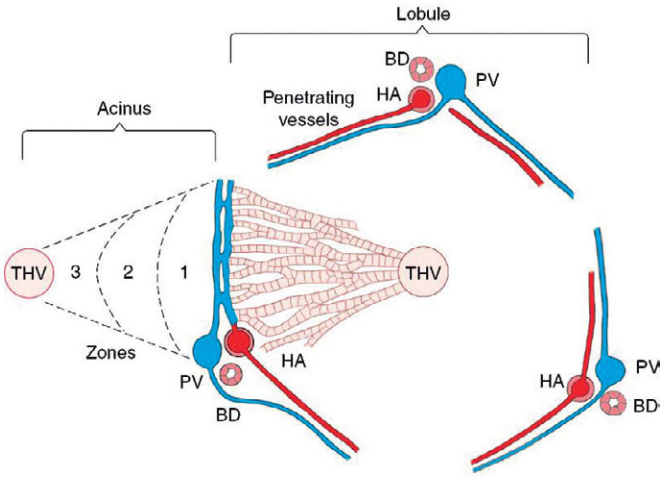

Figure 61-1 The anatomic unit of the liver is the hepatic lobule. The functional unit of the liver is the hepatic acinus. BD, bile duct; HA, hepatic artery; PV, portal vein; THV, terminal hepatic venule. (From Crawford JM: The gastrointestinal tract. In: Cotran RS, Kumar V, Robbins SL, editors: *Robbin's Pathologic Basis of Disease*, Philadelphia, 1994, Saunders.)

Kupffer Cells

Also known as *Browicz-Kupffer cells* or *stellate macrophages*, these cells represent 2% to 5% of the liver cell mass, and are specialized macrophages localized to the sinusoids as part of the mononuclear phagocyte system. Kupffer cells begin their development in the bone marrow with the genesis of promonocytes and monoblasts into monocytes, and then on to peripheral blood monocytes, completing differentiation into Kupffer cells within the liver. In health, Kupffer cells are involved in the metabolism of erythrocyte hemoglobin. During perfusion of the liver, senescent red blood cells are phagocytized by the Kupffer cells, and the hemoglobin molecule is further metabolized into its component parts. Globin chains and amino acids are reutilized; the iron-containing portion of heme is removed, transported, and stored; and heme is further oxidized into bilirubin, conjugated with glucuronic acid within hepatocytes, and secreted into the bile. Kupffer cells also express a complement receptor of the immunoglobulin family, without which the liver cannot clear complement system–coated pathogens.

In disease states, Kupffer cells contribute to the pathology of ethanol and other toxic principles through production of inflammatory mediators, activation of Toll-like receptors, and elaboration of tumor necrosis factor (TNF-α).[7] Kupffer cell activation is responsible for early ethanol-induced liver injury, common in chronic alcoholics. Ethanol activates the Toll-like receptor 4 and CD14, receptors on the Kupffer cell that internalize the endotoxin lipopolysaccharide. Internalization activates the transcription of TNF-α and production of superoxide (a prooxidant). TNF-α then enters the stellate cell in the liver, leading to collagen synthesis and fibrosis. Fibrosis eventually causes cirrhosis or loss of function of the liver (see the role of the stellate cell, which is discussed in "Stellate Cells" section that follows).

Stellate Cells

Hepatic stellate cells (HSCs) (also referred to as vitamin A–storing cells, lipocytes, interstitial cells, fat-storing cells, and Ito cells) exist in the space between parenchymal cells and liver sinusoidal endothelial cells of the hepatic lobule and store 50% to 80% of vitamin A in the whole body as retinyl palmitate in lipid droplets in the cytoplasm.[7-10] In physiologic conditions, these cells play pivotal roles in the regulation of vitamin A homeostasis. In pathologic conditions, such as hepatic fibrosis or liver cirrhosis, HSCs lose vitamin A and synthesize a large amount of ECM components, including collagen, proteoglycan, glycosaminoglycan, and adhesive glycoproteins. The morphology of these cells also changes from that of the star-shaped stellate cell to that of the fibroblast or myofibroblast. HSCs are now considered to be targets of therapy of hepatic fibrosis or liver cirrhosis.[11] Activation of HSCs, a key event in liver fibrosis, is caused by diminished adipogenic transcription.[12] Wnt signaling inhibits antiadipogenic activation of HSCs and liver fibrogenesis; wnt antagonism inhibits HSC activation and liver fibrosis.[9]

Pit Cells

Also known as natural killer (NK) cells or large granular lymphocytes, pit cells represent 1% of liver cell mass, and serve as part of the immune surveillance mechanism in the hepatic sinusoids. Pit

cells belong to the group of sinusoidal cells, together with Kupffer, endothelial, and fat-storing (stellate) cells. Pit cells use the FasL Fas ligand (FasL) and perforin/granzyme pathway to kill target cells. FasL on effector cells binds the Fas that is present on the target cell membrane, which results in oligomerization of Fas and activation of caspase 8. Perforin and granzymes, of which granzyme B is the most potent, reside in granules of the cytotoxic lymphocytes and are released by exocytosis. Intracellular delivery of granzyme B results in the initiation of the caspase cascade by proteolytic activation of caspase 3, either directly or through a mitochondrial-dependent pathway. Caspases play a central role in the execution of apoptosis.

Endothelial Cells

Lymphocyte recruitment from the circulation into tissue is dependent on the ability of the lymphocyte to recognize and bind molecules on the endothelial cell surface that promote transendothelial migration. A multistep model of leukocyte adhesion to vascular endothelium has been described and is broadly applicable, although the details of the signals involved differ between tissues.[13,14] In a generally accepted model, tethering or rolling receptors expressed on endothelial cells capture free-flowing leukocytes. These receptors may be either selectins or members of the immunoglobulin superfamily. Once captured, the leukocyte can receive activating messages presented by endothelial cells in the form of chemokines that activate specific G-protein–coupled receptors on the leukocyte surface. Occupancy of these receptors triggers a cascade of intracellular signals that results in the presentation of high-affinity integrin receptors on the leukocyte surface that bind to immunoglobulin family of counterreceptors on the endothelium to promote leukocyte arrest on the vessel wall. In the presence of the appropriate migratory signals the leukocyte will migrate across the endothelium into tissue, where it follows a hierarchy of chemotactic signals toward the focus of inflammation.

Smooth Muscle Cells

Representing 2% to 5% of the liver cell mass, smooth muscle cells are located primarily in the hepatic artery and portal vein and their tributaries, and serve primarily to regulate the hepatic microcirculation.

Hepatic fibrosis is a common outcome of hepatic injury in the dog. Activated fibroblasts that develop myofibroblastic characteristics play an essential role in hepatic fibrogenesis, and are comprised of three subpopulations: (a) portal or septal myofibroblasts, (b) interface myofibroblasts, and (c) the perisinusoidally located HSCs.

Stem Cells

It is difficult to arrive at a universally applicable definition of a stem cell because some of the defined properties of a stem cell can be exhibited by the stem cells in some tissues or organisms but not in others. In spite of that, a generally acceptable consensus defines a stem cell as an undifferentiated cell that has capacity to self-renew, for production of progeny in at least two lineages, for long-term tissue repopulation after transplantation, and for serial transplantability. In addition, stem cells exist in a mitotically quiescent form and clonally regenerate all of the different cell types that constitute the tissue in which they exist. They can undergo asymmetrical cell division, with production of one differentiated (progenitor) daughter and another daughter that is still a stem cell. The offspring of stem cells are referred to as progenitor cells, also named as transit amplifying cells and therefore cannot be serially transplanted, and are classified as early and late. The early progenitor or stem/progenitor cells have multilineage potential and similar characteristics to stem cells. The late progenitor cells have differentiated further and produce progeny in only a single lineage. Although they divide rapidly, they are capable of only a short-term tissue reconstitution and they do not self-renew.[15]

Early studies in hepatocyte turnover and liver regeneration showed that the parenchymal cell, the hepatocyte, was the primary and only cell involved in tissue renewal. However, new studies of liver regeneration, hepatocarcinogenesis, liver transplantation, and various cell lines show that a variety of cell types participate in maintaining hepatocyte number and mass. Recent studies indicate the presence of both intrahepatic and extrahepatic stem/progenitor cell populations that serve to maintain the normal organ and to regenerate damaged parenchyma in response to a variety of insults. The intrahepatic compartment most likely derives primarily from the biliary tract, particularly the most proximal branches, that is, the canals of Hering and smallest ductules. The extrahepatic compartment is at least in part derived from diverse populations of cells from the bone marrow. Embryonic stem cells are considered as a part of the extrahepatic compartment.[16] The precise role(s) of each of these individual cells remains to be determined, but it is clear that in the aggregate they confer the vast regenerative capacity of the liver .

Liver Function

Metabolism

The liver is involved in many aspects of intermediary metabolism.[1]

Carbohydrates

The liver is at the center of carbohydrate metabolism through its role in maintaining normoglycemia. Glucose is the primary energy source for most mammalian cells, and its metabolism is tightly regulated to guarantee that a sufficient supply is available to glucose-dependent organs, particularly the brain. Glucose can be made available from two sources: absorption of dietary glucose from the intestine, and release of glucose from organs such as the liver and kidney. Early in fasting, the majority of endogenous glucose is generated by glycogenolysis where glycogen in the liver is converted to glucose-6-phosphate under the regulation of debranching enzyme, hepatic glycogen phosphorylase, and phosphorylase kinase. With more prolonged fasting, endogenous glucose is generated by gluconeogenesis from certain substrates such as amino acids, lactate, and glycerol. Both processes generate glucose-6-phosphate, which must then be dephosphorylated in order to transport glucose out of the cell.

- Early fasting: glycogen → glycogenolysis → glucose → normoglycemia
- Prolonged fasting: amino acids → gluconeogenesis → glucose → normoglycemia

The enzyme responsible for the dephosphorylation of glucose-6-phosphate is glucose-6-phosphatase-α. Alterations in quantity, location, or activity of glucose-6-phosphatase, such as those seen in type 1 glycogen storage diseases, effectively result in a lack of all endogenous glucose production and severe hypoglycemia develops during periods of fasting.[17]

Proteins

The liver is an important site of protein metabolism. Amino acids and proteins absorbed from the intestine or produced in the body are delivered to the liver. The liver deaminates amino acids and

converts them to carbohydrates and lipids.[18-21] Deamination produces α-keto acids, which can be metabolized for energy or used for synthesis of monosaccharides and fatty acids.[20] The liver synthesizes amino acids from intermediates of carbohydrate and lipid metabolism by amination and transamination.[21] Examples of amino acid transaminations include:

- Alanine + α-ketoglutarate ↔ pyruvate + glutamate
- Aspartate + α-ketoglutarate ↔ oxaloacetate + glutamate

The liver synthesizes many proteins, including albumin and fibrinogen, most α globulins, and some of the β globulins. Prothrombin and clotting factors V, VII, VIII, IX, and X are produced in the liver, as well as ceruloplasmin, ferritin, and many serum enzymes.

Lipids

Lipid metabolism and transport is organized into three basic transport systems: (a) exogenous transport, which is associated with the metabolism of exogenous (dietary) lipids, (b) endogenous transport, which is associated with the metabolism of endogenously produced lipids, and (c) reverse transport, which is associated with the transport of lipids from the periphery (e.g., skeletal muscle, adipose, connective tissue) to the liver.

Exogenous Transport. Triglyceride is the major dietary lipid, along with cholesterol, phospholipids, and fat-soluble vitamins.[22] The digestion of dietary lipids begins in the proximal GI tract with the action of lingual and gastric lipases, and is completed in the small intestine with the actions of pancreatic lipase, cholesterol ester hydrolase, and phospholipase A_2. Lipid digestion and absorption is more complicated than carbohydrate and protein digestion and absorption because of lipid solubility characteristics, and involves emulsification of lipids by bile salts, hydrolysis by pancreatic lipase and colipase, solubilization of fatty acids and monoglycerides into mixed micelles, absorption, reesterification, chylomicron formation, and transport into the intestinal lymphatics or portal capillaries. Chylomicrons containing short- and long-chain triglycerides, and the newly incorporated B-100 apoprotein, are preferentially absorbed into the intestinal lymphatics where they are transported into the cisterna chyli, thoracic duct, and systemic circulation where they acquire apolipoproteins C and E from circulating high-density lipoproteins (HDLs). Apolipoprotein (apo) C-II activates lipoprotein lipase in the capillary beds of adipose and skeletal muscle, where they are stored as is or hydrolyzed into free fatty acids, β-monoglyceride, and glycerol. The cholesterol-rich remaining particles (now referred to as chylomicron remnants), return apo C-II molecule to HDL and are recognized by specific hepatic apo E and apo B-100 receptors that rapidly remove them from the circulation by endocytosis. The cholesterol found in chylomicron remnants can be used in very-low-density lipoprotein (VLDL), lipoprotein synthesis, bile acid formation, or cholesteryl storage.

Endogenous Transport. While chylomicrons are the apoprotein responsible for transport of dietary lipids, VLDLs, intermediate-density lipoproteins, low-density lipoproteins (LDLs), and HDLs are instead involved in the metabolism of endogenously produced lipids. Triglycerides and cholesterol produced by the liver combine with phospholipids, apo B-100, and apo B-48 to form VLDLs. When secreted from the liver, VLDLs acquire the apo C and apo E from HDL. VLDL apo C-II activates lipoprotein lipase located in the capillary beds, where once again triglyceride hydrolysis takes place with the production of free fatty acids and glycerol. The VLDL molecules remaining after hydrolysis of VLDL triglycerides are either removed from the circulation by the liver or undergo further transformation by lipoprotein lipase and/or hepatic lipase to form intermediate-density lipoproteins and LDLs. LDLs, which are relatively depleted of triglyceride and enriched in cholesteryl esters and phospholipid, circulate in the blood and bind to specific LDL receptors that are widely distributed throughout tissues in order to deliver cholesterol. HDLs produced by the liver play an important role as donors and acceptors of apo C, apo E, and various lipids from other lipoproteins in the circulation.

Reverse Transport. HDLs play an important role in the reverse transport of cholesterol from the periphey to the liver. Lecithin cholesterol acyl transferase esterifies HDL cholesterol and cholesteryl esters move to the core of the HDL molecule to allow more free cholesterol to be absorbed into the particle. Continued absorption of free cholesterol and subsequent esterification by lecithin cholesterol acyl transferase leads to the formation of the larger, cholesteryl ester-rich HDL2s. HDL2 molecules continuously acquire cholesteryl esters, resulting in the formation of the HDL1 molecules. On HDL1, cholesteryl esters are transferred from tissues to the liver for disposal or reuse, and not to LDL or VLDL molecules (as in humans), which transfer cholesterol to peripheral tissues. This function of HDL1s may account for the lower incidence of atherosclerotic disorders in dogs compared with humans.[23,24]

Nucleic Acids

Pyrimidine biosynthesis is one of the classic roles of the liver in nucleic acid metabolism. More recently, microRNAs have been impugned in the normal development and regeneration of the liver, as well as in hepatic pathology. microRNAs are small noncoding RNAs that regulate both messenger RNA and protein expression of target genes, which results in alterations in messenger RNA stability or translation inhibition. microRNAs influence at least one-third of all human transcripts and are known regulators of various important cellular growth and differentiation factors. microRNAs recently emerged as key regulatory molecules in chronic liver disease.[25]

Porphyrins

Porphyrins are intermediates of the heme biosynthetic pathway. Porphyrins are found in hemoglobin, myoglobin, cytochromes, catalase, and peroxidase enzyme. The liver and biliary tract serve as an excretory route for the porphyrins.

Metals

The liver stores iron, which can be toxic in excessive amounts (hemochromatosis). The amount of iron in the body is largely determined by regulation of its absorption in the upper small intestine. Iron is stored intracellularly as ferritin in a number of tissues, with the liver having a large storage capacity. When the capacity of the liver is exceeded, iron accumulates as hemosiderin.

The liver incorporates copper into specific copper proteins such as cytochrome c oxidase, mitochondrial monoamine oxidase, and ceruloplasmin. Mobilization of copper from hepatocytes takes place by at least two mechanisms: ceruloplasmin and bile secretion. Cholestatic liver disease is associated with secondary copper retention, which may then induce hepatocyte injury.[26,27]

Vitamins

The liver is importantly involved in vitamin metabolism. The liver produces bile for absorption of fat-soluble vitamins (A, D, E, K), and the liver is an important site for vitamin storage.

Vitamin A is stored in both stellate cells and hepatocytes. Approximately 95% of total body vitamin A is stored in the liver, representing a 1- to 2-year supply. The liver continues to release vitamin A to maintain normal blood concentrations despite reductions in its content. Liver and plasma vitamin A concentrations are reduced by malnutrition, liver disease, and intestinal malabsorption, but signs of deficiency do not appear until abnormalities become severe.

Fat-soluble vitamins A, D, E, and K require normal bile secretion for absorption. Vitamin K is particularly essential for synthesis of the prothrombin-complex clotting factors.

Water-soluble vitamins, with the exception of vitamin B_{12} (cobalamin), are readily absorbed from the small intestine. These vitamins are used primarily as coenzymes in metabolic processes. Vitamin phosphorylation, occurring primarily in hepatocytes, is required to produce some coenzymes. Thiamine is phosphorylated to thiamine pyrophosphate, for example, primarily in the liver and kidney. Nicotinic acid is a precursor in pyridine nucleotide synthesis, and an initial step in its conversion is nicotinamide synthesis in the liver. Pyridoxine is phosphorylated to its active form in the liver, as is the transformation of pantothenic acid to coenzyme A. Folic acid is converted to its active form in the liver. Large amounts of all water-soluble vitamins except vitamin C are stored in the liver.

Glutathione

Glutathione is synthesized in most if not all mammalian cells. The liver is particularly active and has relatively high levels of glutathione. Glutathione performs a variety of physiologic and metabolic functions, including thiol transfer reactions that protect cell membranes and proteins; thiol-disulfide reactions involved in protein synthesis, protein degradation, and catalysis; reduction of capacity; detoxification of hydrogen peroxide, organic peroxides, free radicals, and foreign compounds; and metabolism of various endogenous compounds.

Bile Secretion

Biliary secretions provide (a) a source of bile acids for fat digestion and absorption, (b) an excretory route for metabolites and xenobiotics, and (c) additional HCO_3^- for buffering of H^+ ion in the duodenum. Bile acids are the major components of bile accounting for about one-half to two-thirds of the total solutes. Bile also contains water, electrolytes, cholesterol, phospholipids, hormones, protein, and bilirubin (Figure 61-2).

Bile components are synthesized, stored, and secreted from the hepatocytes into the biliary ductal system.[28] In the absence of neural or hormonal input (as in the fasting state), the gallbladder is relaxed, the terminal biliary ductal sphincter (sphincter of Oddi) is contracted, and bile is largely stored in the gallbladder. While stored in the gallbladder, water and large portions of the electrolytes are reabsorbed by the gallbladder mucosa, concentrating the remaining constituents. During feeding, neural (acetylcholine) and hormonal (cholecystokinin) mechanisms activate gallbladder contraction, biliary ductal sphincter relaxation, and emptying of bile into the duodenum. Secretin and bile salts stimulate bile salt–independent and bile salt–dependent bile flow, respectively.[2,5,28]

Bile acids are synthesized from the cholesterol nucleus to which are attached a five- or eight-carbon side chain with a terminal carboxylic acid, and hydroxyl groups positioned at the C3, C7, or C12 carbon atom positions (Figure 61-3, *A* and *B*). The major primary bile salts are cholic acid and chenodeoxycholic acid in about equal molar quantities. When these primary bile acids are secreted into the lumen of intestine, a portion of each is dehydroxylated by intestinal bacteria to produce the secondary bile acids, deoxycholic acid, and lithocholic acid.[2,5,28] Prior to secretion, bile acids are conjugated with taurine and/or glycine to form tauro- and glycoconjugated bile salts (see Figure 61-3, *C*). Conjugation lowers the pK_a to well below the physiologic range of biliary and intestinal pH, and conjugated bile acids become ionized anions (referred to as bile salts) rather than undissociated bile acids. In the ionized form, they are less likely to be absorbed by the small intestine and so maintain a higher intraluminal concentration appropriate for emulsification, digestion, and absorption of lipids. Dogs and cats conjugate primarily with taurine. Dogs can convert to glycine conjugation if taurine is deficient, but cats cannot. Cats are obligate taurine conjugators, and have an essential dietary taurine requirement.[2,5,28]

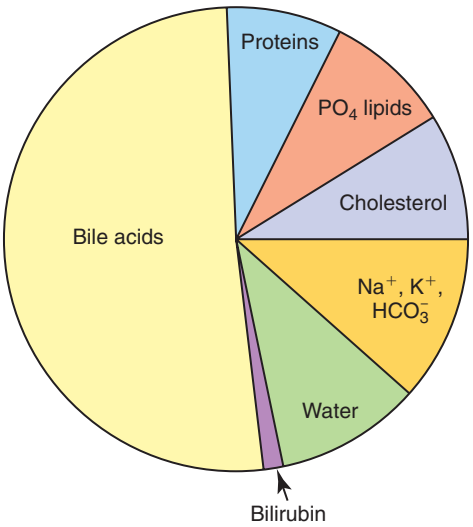

Figure 61-2 The chemical components of bile: bile acids, proteins, phospholipids, cholesterol, water, Na^+, K^+, HCO_3^-, and bilirubin.

Bile salts are amphipathic molecules with polar and nonpolar domains imparting two important functions. Bile salts have an initial detergent effect on fat particles in food permitting the breakup of fat globules into smaller sizes. This is the initial emulsification phase of bile salts that facilitates intraluminal lipid hydrolytic digestion. Bile salts further assist in the absorption of fatty acids, monoglycerides, cholesterol, and other lipids through the formation mixed micelles. These micelles serve to transfer digested lipids across the unstirred layer of the mucosa.

Following emulsification and micellarization of fat, most of the secreted bile salts are transported along the GI tract to the ileum where they are absorbed into ileal enterocytes and portal blood flow via Na^+–bile salt cotransporters.[2,28]

Coagulation Factors

The liver plays an important role in maintaining hemostasis. The liver produces procoagulant, anticoagulant, and fibrinolytic proteins, and also removes normal and abnormal clotting factors from the circulation.[29]

Hepatocytes synthesize most of the clotting factors including clotting factor I (fibrinogen), II (prothrombin), V, VII, IX, X, XI, and XIII. The site of biosynthesis of factor VIII remains controversial, but it is probable that the liver plays an important role in this factor, too. The liver is also responsible for the activation of the vitamin K–dependent factors II, VII, IX, and X and protein C. In addition to the production and activation of coagulation factors, the liver is also essential for the clearance of activated coagulation

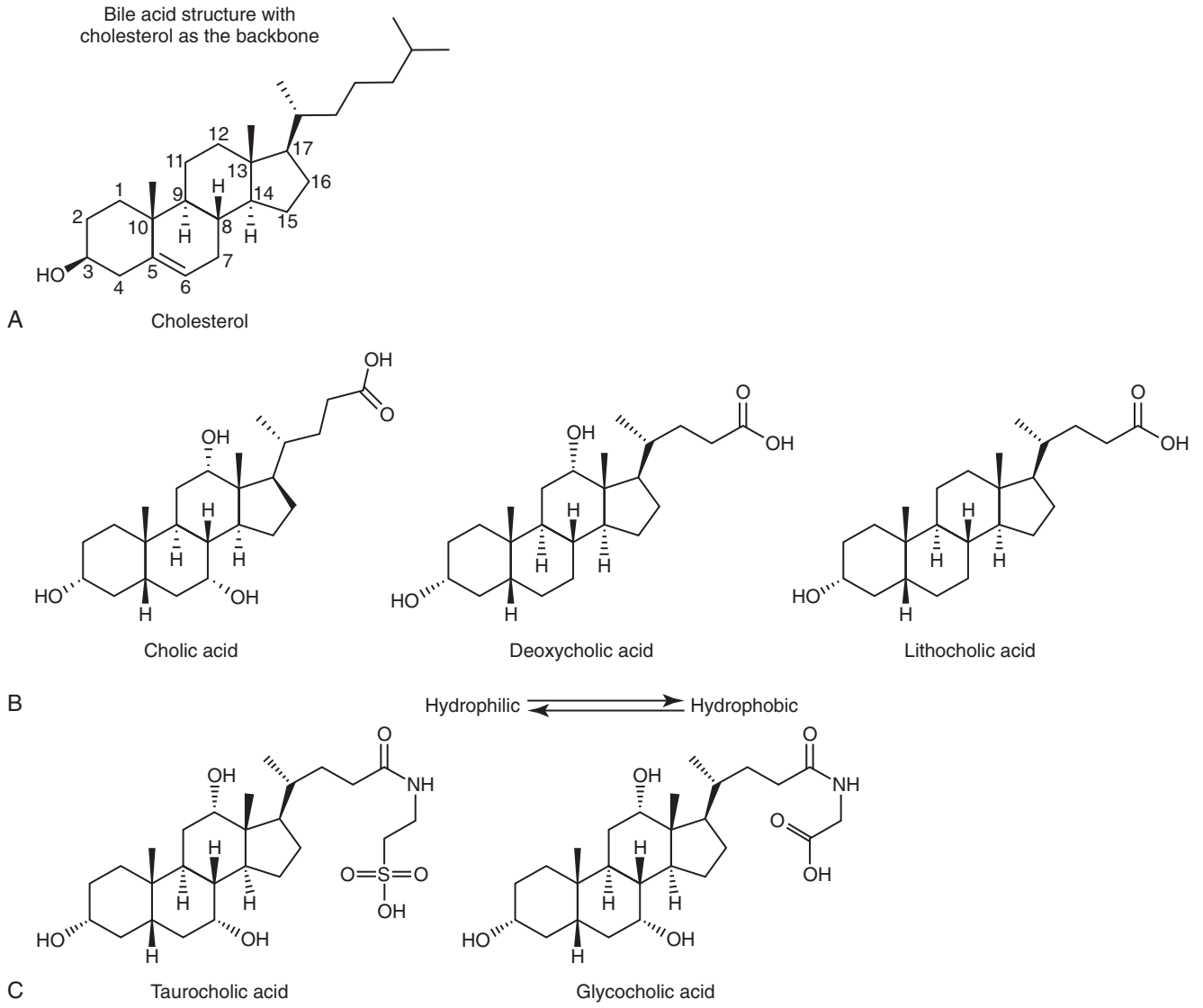

Figure 61-3 **A,** Cholesterol serves as the chemical backbone in bile acid synthesis. **B,** Hydrophilicity and hydrophobicity of bile acids. **C,** Glycine and taurine conjugation of bile acids.

products and the production of clotting factor inhibitors, such as antithrombin and α_1-antitrypsin, as well as fibrinolytic proteins like plasminogen.

In liver disease, factor and inhibitor synthesis and clearance of activated factors in both the coagulation factors and fibrinolytic system may be impaired. The extent of coagulation abnormalities depends upon the degree of disturbed liver function.[29] Patients with hepatic failure may present with the entire spectrum of factor deficiencies and may even develop disseminated intravascular coagulation.

In a study of 42 dogs with histologically confirmed liver disease, one or more coagulation abnormalities were found in 57% of dogs with liver disease.[29] Activated partial thromboplastin time was significantly prolonged in dogs with chronic hepatitis with or without cirrhosis. Mean platelet numbers, antithrombin, and factor IX activity were significantly lower in dogs with chronic hepatitis with cirrhosis, compared to dogs with other hepatopathies. D-Dimers were not significantly increased in any group. Only three dogs, all with different histologic diagnoses, satisfied the criteria for disseminated intravascular coagulation. Hemostatic abnormalities were primarily seen in dogs with chronic hepatitis plus cirrhosis, which may be a result of reduced synthesis rather than increased consumption of coagulation factors.

Detoxification

Xenobiotic Agents

Numerous foreign compounds, including drugs, are so hydrophobic that they would remain in the body indefinitely were it not for hepatic biotransformation. Cytochrome P450 (P450 or CYP) comprises a superfamily of enzymes that catalyze oxidation of a variety of xenobiotic chemicals such as drugs, toxic chemicals, and carcinogens, as well as endobiotic chemicals including steroids, fatty acids, prostaglandins, and vitamins. The cytochrome P450 enzymes in families one to three mediate 70% to 80% of all phase I–dependent metabolism of clinically used drugs and participate in the metabolism of a huge number of xenobiotic chemicals. There are 57 known active *P450* genes and 58 pseudogenes in the human genome. With 54 active genes, dogs are phylogenetically closest to the human. Although there are many similarities between dogs and humans, there also are many important differences.[30-33] Dogs present an

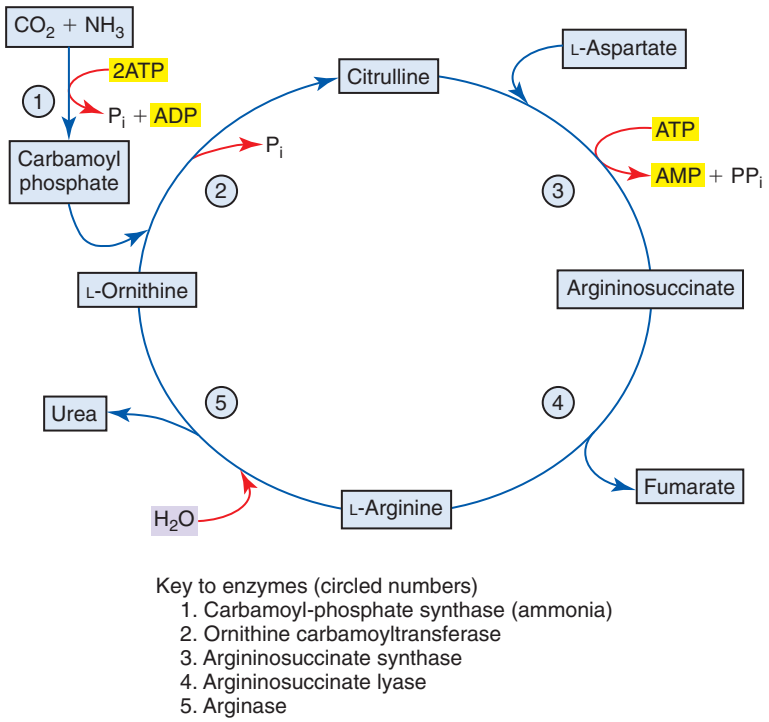

Figure 61-4 Urea cycle. Transformation of toxic ammonia into nontoxic urea.

interesting challenge in the assessment of P450-mediated drug–drug interactions because most of the enzymes have not been completely characterized, diet and aging induce significant changes in gene expression, and dogs are often treated off-label with a number of human drugs with little idea of risk for drug–drug interaction.

Drug metabolism takes two general forms: phase I metabolism (modification reactions) and phase II metabolism (conjugation reactions). Phase I metabolism typically subjects a drug to oxidation or hydrolysis. It involves the cytochrome P450 (CYP) enzymes, which facilitate reactions that include *N*-, *O*-, and *S*-dealkylation; aromatic, aliphatic, or *N*-hydroxylation; *N*-oxidation; sulfoxidation; deamination; and dehalogenation. Phase II metabolism conjugates the drug to hydrophilic substances, such as glucuronic acid, sulfate, glycine, or glutathione. Phase I metabolism usually precedes phase II metabolism, but this is not always the case.[34]

The liver is an important site of drug toxicity and oxidative stress because of its proximity and relationship to the GI tract. Seventy-five percent to 80% of hepatic blood flow comes directly from the GI tract and spleen via the main portal vein. Portal blood flow transports nutrients, bacteria and bacterial antigens, drugs, and xenobiotic agents absorbed from the gut to the liver in a more concentrated form. Drug-metabolizing enzymes detoxify many xenobiotics but might activate the toxicity of others. Hepatic parenchymal and nonparenchymal cells may all contribute to the pathogenesis of hepatic toxicity.

The toxicity of drugs can be considered in five contexts: on-target toxicity, hypersensitivity and immunologic reactions, off-target pharmacology, bioactivation to reactive intermediates, and idiosyncratic drug reactions.[35,36]

Ammonia

Ammonia is an important by-product of amino acid metabolism. Organisms that cannot easily and quickly remove ammonia usually have to convert it to some other substance, like urea or uric acid, which are much less toxic. Insufficiency of the urea cycle occurs in some genetic disorders (inborn errors of metabolism), or more typically, in liver failure. The result of liver failure is accumulation of nitrogenous waste, mainly ammonia, which leads to hepatic encephalopathy.

The GI tract, particularly the colon, is the most important source, through the action of bacterial urease on endogenous urea or dietary amines. Ammonia produced by colonic bacteria enters the portal circulation and is transported to the liver for urea cycle transformation (Figure 61-4). Ammonia is transformed into urea in the urea cycle in the overall equation:

$$2\,NH_3 + CO_2 + 3\ \text{adenosine triphosphate} + H_2O \rightarrow \text{urea} + 2\,ADP + 4\,Pi + AMP + 2\,H$$

where NH3 = ammonia; adenosine triphosphate = adenosine triphosphate; ADP = adenosine diphosphate; P_i = inorganic phosphate; and AMP = adenosine monophosphate.

Endogenous Hormones

Mineralocorticoids (aldosterone), glucocorticoids (cortisol, corticosterone), and sex steroids (androgens, estrogens, progesterone) are metabolized by the liver. Changes in the concentrations of total and free cortisol and of the binding capacity of corticosteroid-binding globulin have been reported in canine liver disease. As a consequence of hypercortisolemia, dogs with liver disease and hepatoencephalopathy have clinical and biochemical characteristics of PDH, including polyuria, high basal cortisol levels, and α-melanotropin.[37,38] Chronic hypercortisolism is associated with impaired osmoregulation of the release of vasopressin and inadequate urinary concentration.[39]

Immune Surveillance

The multiple physiologic functions of the liver require an immune response that is locally regulated. Pathogenic microorganisms must be efficiently eliminated, while the large number of antigens derived

from the GI tract must be tolerated. The liver favors the induction of tolerance rather than the induction of immunity. Although hepatocytes constitute the major cell population of the liver, direct interaction of hepatocytes with leukocytes in the blood is unlikely. Sinusoidal endothelial cells, which line the hepatic sinusoids and separate hepatocytes from leukocytes in the sinusoidal lumen, and Kupffer cells, the resident macrophage population of the liver, can directly interact with passenger leukocytes. In the liver, clearance of antigen from the blood occurs mainly by sinusoidal endothelial cells through very efficient receptor-mediated endocytosis. Liver sinusoidal endothelial cells constitutively express all molecules necessary for antigen presentation (CD54, CD80, CD86, major histocompatibility complex [MHC] classes I and II, and CD40) and can function as antigen-presenting cells for $CD4^+$ and $CD8^+$ T cells.[40,41] Thus, these cells probably contribute to hepatic immune surveillance by activation of effector T cells. Antigen-specific T-cell activation is influenced by the local microenvironment. This microenvironment is characterized by the physiologic presence of bacterial constituents such as endotoxin and by the local release of immunosuppressive mediators such as interleukin-10, prostaglandin E_2, and transforming growth factor-β.[42]

Regeneration

Liver regeneration after partial hepatectomy is a very complex and well-orchestrated phenomenon. It appears to be carried out by the participation of all mature liver cell types.[43,44] The process is associated with signaling cascades involving growth factors, cytokines, matrix remodeling, and several feedbacks of stimulation and inhibition of growth related signals.[45,46] The liver manages to restore any lost mass and adjust its size to that of the organism, while at the same time providing full support for body homeostasis during the entire regenerative process. In situations when hepatocytes or biliary cells are blocked from regeneration, these cell types can function as facultative stem cells for each other.

Gene expression in the regenerating liver is a multistep process with at least two critical steps: the transition of quiescent hepatocytes into the cell cycle ("priming"), and the progression beyond the restriction point in the G_1 phase of the cell cycle. Hepatocytes must first be primed before they can fully respond to growth factors. As many as 70 different genes participate in the early response to hepatectomy, but tumor necrosis factor (TNF), interleukin (IL)-6, and interleukin-22 (IL-22) appear to be the major cytokines involved in the priming of hepatocytes.[47] The proliferative effect of TNF on hepatocytes is further influenced by reactive oxygen species, nitric oxide, and glutathione content, and multiple transcription factors (e.g., nuclear factor kappa B, STAT3, AP-1, and C/EBPβ) play major roles in the initiation of early liver regeneration.[47] Progression through the cell cycle beyond the initiation phase requires growth factors, primarily hepatocyte growth factor and transforming growth factor-α (TGF-α). The subsequent expression of cell-cycle genes establishes the stage at which replication becomes growth factor-independent and autonomous. At this point, the hepatocyte is irreversibly committed to replicate and the cell cycle replication machinery takes over.

The proliferation of hepatocytes advances from periportal to pericentral ares of the lobules, as a wave of mitoses. Hepatocytes surrounding the central veins are the last ones to undergo cell replication. Proliferation of biliary epithelial cells occurs a little later than hepatocytes. Proliferation of endothelial cells starts at 2 to 3 days and ends around 4 to 5 days after partial hepatectomy. The kinetics of proliferation of stellate cells is incompletely understood. The regenerative capacity of the residual hepatocytes may restore liver mass and function after as much as 65% to 70% hepatectomy and it takes place over 7 to 14 days in most animal species.[48] A small wave of apoptosis in hepatocytes occurs at the end of regeneration.

HISTORY AND PHYSICAL EXAMINATION

Hein P. Meyer and Jan Rothuizen

Clinical Importance

The liver is the second largest organ in the body and performs an estimated 1500 essential biochemical functions.[1] These diverse functions include drug metabolism; removal of exogenous and endogenous toxins (e.g., ammonia, food antigens); synthesis of vital substances such as albumin and blood clotting factors; protein, fat, and carbohydrate metabolism; vitamin storage and activation; glycogen, triglyceride, and mineral (e.g., copper, iron) storage; activation, conversion, secretion, deactivation, and excretion of various hormones; bile salt synthesis; conjugation and excretion of bilirubin in bile; among others. Symptoms (defined here as abnormalities noted by the owner), clinical signs (defined here as abnormalities found during the physical examination), and diagnostic results reflect impairments in these functions. Hepatitis represented approximately 1% of the clinical population of the companion animal teaching hospital of Utrecht University. Box 61-1 summarizes the most common liver diseases with their possible etiologies in dogs and cats.

History of Dogs and Cats with Liver Disease

A properly taken history is pivotal to defining the most clinically relevant problems that need to be resolved. A structured interview process and understanding the basics of communication are important success factors to retrieve this crucial information. Fortunately, the knowledge about communication in the medical profession and the focus on the veterinary curriculum, has increased considerably during the last few years.[2,3]

Some basic principles should be kept in mind to understand the symptoms in dogs and cats with diseases affecting the hepatic parenchyma, portal vasculature, and the biliary system. First, for most of its functions, the liver has a tremendous (approximately 80%) reserve capacity and a remarkable potential to regenerate.[4] Symptoms occur only when progressive disease exhausts hepatic reserves. Diseases often remain subclinical for lengthy periods of time; symptoms may be relatively mild and nonspecific because the liver reserve prevents overt abnormalities. Symptoms such as lethargy, vomiting, or mild polyuria and polydipsia (PU/PD) may alert the clinician that a liver disorder could be developing. Serious symptoms may indicate loss of hepatic reserves. The onset of symptoms may be acute, but they may be the end result of a disease that has been present for many weeks or months. Because no specific physical abnormalities occur with most liver diseases, it is important to remember that liver disease may be present when symptoms of illness are unexplained or nonspecific. Sensitive and specific laboratory tests may easily detect such liver diseases.[5]

Second, most liver diseases cause similar signs and symptoms (Table 61-2). One of these is acholic feces, which occurs nearly exclusively in dogs with common bile duct obstruction.[6] Owners

Box 61-1 Causes of Acute Liver Disease in Dogs and Cats

Infectious Agents

Viral
- Infectious canine hepatitis (canine adenovirus I)
- Canine and feline herpesvirus (neonates)
- Coronavirus (feline infectious peritonitis virus)
- Feline *Calicivirus* (virulent form)

Bacterial
- Extrahepatic infections, septicemia, and endotoxemia
- Cholangitis
- *Clostridium piliforme* (Tyzzer disease)
- *Helicobacter canis* (dog)
- *Leptospira* spp.
- Liver abscess

Fungal
- *Histoplasma capsulatum*
- *Coccidioides immitis*
- Others

Protozoal
- *Toxoplasma gondii*
- *Neospora caninum*
- *Babesia* spp.
- *Cytauxzoon felis*

Rickettsial
- *Ehrlichia* spp.
- *Rickettsia* rickettsiae

Parasitic
- Liver flukes[a]
- Heartworms and caval syndrome

Drugs and Anesthetics

Anticonvulsants and Sedatives
- Diazepam (cats)
- Phenobarbital[a] (dogs)
- Primidone[a] (dogs)
- Phenytoin (dogs)

Antiinflammatory and Analgesic Drugs
- Glucocorticoids (dogs)
- Acetaminophen (dogs and cats)
- Carprofen and other nonsteroidal antiinflammatory drugs (dogs)

Antimicrobials and Parasiticides
- Diethylcarbamazine (dogs)
- Doxycycline (dogs)
- Griseofulvin (cats)
- Itraconazole (dogs and cats)
- Ketoconazole (dogs and cats)
- Mebendazole (dogs)
- Oxibendazole (dogs)
- Sulfonamides (dogs)
- Terbinafine (dogs)
- Tetracycline (dogs and cats)
- Thiacetarsamide (dogs)

Anesthetics
- Halothane (dogs)
- Methoxyflurane (dogs)

Miscellaneous
- Amiodarone[a] (dogs)
- Azathioprine (dogs)
- Danazol (dogs)
- Glipizide (cats)
- Lomustine[a] (dogs)
- Methimazole (cats)
- Methotrexate (dogs)
- Mithramycin (dogs)
- Mitotane (dogs)
- Phenazopyridine (dogs)
- Stanozolol (cats)

Herbal and Dietary Supplements
- α-Lipoic acid
- Black cohosh
- Comfrey[b] (pyrrolizidine alkaloids)
- Chaparral leaf[b]
- Chinese herbal medicines[b] (Jin Bu Huan, Ma huang)
- Kava[b]
- Pennyroyal oil
- St. John's wort

Biologic Toxins
- Aflatoxin
- *Amanita* mushrooms
- Blue-green algae
- Cycads (Sago palms)
- Hornet stings
- *Indigofera linnaei* (legume)

Food Additives
- Xylitol (sugar substitute)(dogs)

Chemicals
- Carbon tetrachloride
- Dimethylnitrosamine
- Dinitrophenol
- Pine oil
- Heavy metals (e.g., copper, lead, iron, arsenic)
- Organochloride pesticides
- Phenols
- Many others

Metabolic Disorders
- Acute pancreatitis
- Hemolytic anemia and disseminated intravascular coagulation
- Hepatic copper accumulation[a]
- Inflammatory bowel disease
- Feline hepatic lipidosis

Neoplastic Disorders
- Carcinoma (biliary, pancreatic)
- Lymphoma
- Malignant histiocytosis

Hypoxic/Ischemic Disorders
- Shock
- Liver lobe torsion
- Thromboembolic disease
- Congestive heart failure

Miscellaneous
- Trauma
- Heat stroke

[a]More likely to present with chronic rather than acute liver disease.
[b]Documented in humans, may occur in dogs and cats.

Table 61-2 Common Clinical Signs in Dogs with Liver Disease

Liver Disease with Relative Frequency (%)	PERCENTAGE OF DOGS AFFECTED BY DISEASE WITH SIGNS												
	Apathy, Depression	Inappetence	Reduced Endurance	Vomiting	Diarrhea	Weight Loss	Hepatic Encephalopathy	Polyuria/ Polydipsia	Dysuria	Anesthesia Intolerance	Acholic Feces	Distended Abdomen	Retarded Growth
Acute hepatitis (3)	44	49	–	61	21	12	–	11	–	–	–	–	–
Chronic hepatitis (10)	18	29	14	43	33	39	–	49	–	–	–	–	–
Cirrhosis (7)	25	53	39	61	37	58	9	56	–	–	–	55	–
Lobular dissecting hepatitis (2)	58	21	29	32	20	45	22	39	–	–	–	65	–
Reactive hepatitis (25)	10	34	–	48	77	39	–	9	–	–	–	–	–
Destructive cholangiolitis (1)	76	82	–	68	21	66	–	49	–	–	9	8	–
Portosystemic shunt (16)	99	68	62	31	12	81	91	52	3	9	–	–	39
Portal vein thrombosis (1)	25	10	–	38	44	15	5	32	–	–	–	33	–
Portal vein hypoplasia (4)	49	13	22	16	21	14	38	45	–	–	–	60	8
Liver cell carcinoma (4)	15	26	18	74	14	32	–	19	–	–	–	25	–
Metastatic tumor (10)	24	54	17	67	27	60	–	38	–	–	–	14	–
Malignant lymphoma (14)	18	75	32	70	21	85	–	55	–	–	–	5	–
Cholecystitis/ choleliths (1)	–	65	–	93	19	30	–	–	–	–	–	–	–
Extrahepatic cholestasis (2)	10	72	–	81	37	54	–	46	–	–	16	–	–

Figures are from the Utrecht University Clinic population. The relative frequencies are based on 2500 referred cases.

may note the light-gray appearance of stool, which in combination with icterus is virtually diagnostic for extrahepatic cholestasis. Different combinations of clinical signs and symptoms may occur with any liver disease. Statistically, one disease may be associated with a typical pattern of signs and symptoms in dogs and cats. However, overlapping patterns are so great that it is useless to try to identify the exact disease based on clinical signs and symptoms alone (Table 61-2). Clinical signs and symptoms associated with liver diseases of cats are similar to those in dogs, except for PU/PD, which is not clinically overt in most cats. Certain liver diseases cause neurobehavioral signs associated with hepatic encephalopathy,[7] and these signs may wax and wane in their frequency and severity. Any medication given may appear to be effective because of the natural fluctuation of signs. Therefore signs of hepatic origin may be easily missed. Seizures alone are never caused by hepatic encephalopathy; if they do occur, they occur in combination with other signs seen with this syndrome.[5] Furthermore, very few, if any, medications to treat liver diseases have been tested in double-blind, placebo-controlled studies, making decisions about the best therapeutic regimens difficult.[8]

It is usually not possible to differentiate between hepatic diseases and diseases of other organs based on symptoms and clinical signs. Signs associated with hepatic diseases are nonspecific; similar signs may occur in diseases of many other organ systems, most notably the GI, neurologic, renal, and hematologic systems (see Table 61-2).[9] Of the GI tract–related symptoms, nausea expressed as vomiting in acute cases or reduced, irregular appetite with occasional vomiting and weight loss over time, is very common in liver and biliary diseases of dogs and cats. For biliary diseases these are always the most prominent symptoms. Diarrhea, however, is not a major symptom of liver disease, and in cases in which diarrhea is the leading symptom the liver is only rarely the causative organ (except for rare cases with complete common bile duct obstruction). A rare sign (not included in Table 61-2) is an ulcerative form of dermatosis, so-called superficial necrolytic dermatitis, hepatodermal, or hepatocutaneous syndrome. This syndrome occurs rarely in dogs with liver cirrhosis and nodular hyperplasia and whose pathogenesis is poorly understood.[10] This symptom and the more common symptoms of lethargy, inappetence, vomiting, diarrhea, weight loss, PU/PD, and neurobehavioral symptoms are frequently associated with diseases of other organs. Therefore the history often discloses symptoms that may suggest hepatic disease, but may also be caused by other disorders.

Two main reasons account for the nonspecificity of liver-related symptoms. First, the liver is the central organ for many metabolic and detoxifying pathways; consequently, failing liver function may cause dysfunction of other organs. One example is hepatic encephalopathy; metabolic dysfunctions of the liver cause neurotransmitter dysfunctions of the brain, resulting in neurobehavioral signs.[11] Second, toxic factors resulting from diseases of other organ systems (especially from the GI tract) often secondarily affect the liver. Examples include hepatic lipidosis in diabetes mellitus, steroid-induced hepatopathy in Cushing syndrome, reactive hepatitis in GI diseases, and centrolobular liver necrosis in acute, severe anemia.[5] Therefore signs and symptoms of liver disease may be hidden within signs of other organ dysfunction, and vice versa. Because clinical and physical examination findings may be compatible with hepatic disease, and because laboratory tests to detect hepatic disease are also abnormal with primary and secondary hepatopathies, it is often necessary to make a histologic diagnosis of the liver disorder to resolve this dilemma.[12,13]

Lack of specific physical examination findings may prevent recognition of a primary liver disease. Most dogs with illnesses causing the clinical signs listed in Table 61-2 are candidates for having a primary hepatopathy. In all such cases, further diagnostic studies should be performed to confirm or exclude liver disease (Figure 61-5).

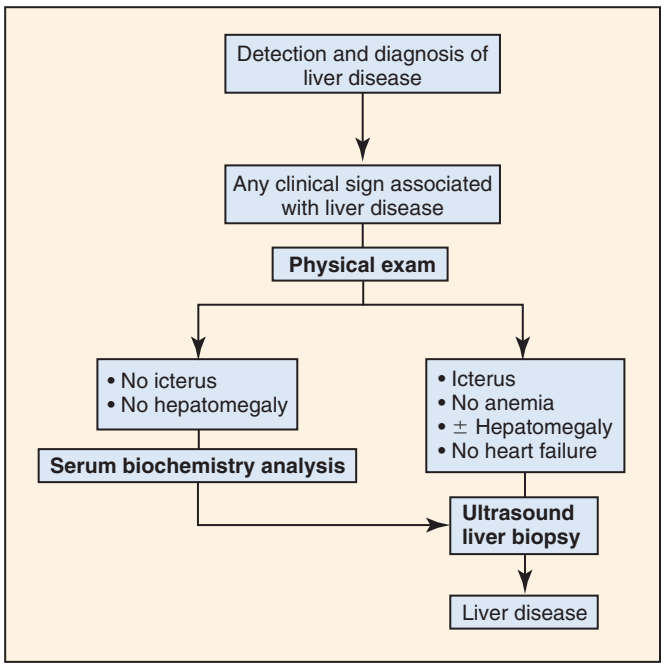

Figure 61-5 Algorithm for the detection and diagnosis of liver disease.

Predispositions

Breed, sex, age, and drugs may predispose dogs and cats to hepatopathies. The presence of numerous risk factors should be a stimulus for an extended diagnostic workup; other diseases should be investigated in the absence of such suspicions. Caused by hypersensitivity to sulfonamides, destructive cholangiolitis is the most common drug-induced liver disease.[14] A recent history of therapy with sulfonamides or other potentially hepatotoxic drugs, combined with icterus makes this condition likely and should prompt immediate discontinuation of the medication. Breed associations may occur when a disease is (in part) determined by genetic factors. Breeders may, by chance, increase the incidence of hepatic diseases by familial selection. Because dog breeds may represent more or less closed populations in a country, breed predispositions may vary among countries. Therefore this section only mentions generally applicable predispositions; locally, other breed associations may be more pertinent.

Chronic hepatitis and cirrhosis, both of which are, as a rule, different stages of one disease, occur more frequently in certain breeds.[15] Hepatitis may develop at any age, but typically not before 2 years of age. Only lobular dissecting hepatitis tends to occur at a young age (i.e., often before 1 year of age).[16] Breeds associated with hepatitis are Doberman Pinschers, Bedlington Terriers, West Highland White Terriers, American and English Cocker Spaniels, Labrador Retrievers, and many other breeds. Recent copper excretion studies have shown that hepatitis is caused by copper retention and not vice versa in Doberman Pinschers.[17] The cause of copper retention remains unclear; many of the tested candidate genes (including Murr 1, the affected gene in Bedlington Terriers) were excluded as monogenetic causes for copper-associated subclinical hepatitis in

Doberman Pinschers.[17] The hepatitis in Doberman Pinschers is sex linked, confined to females, and aggressive.[18] It is responsive to medication with penicillamine,[19] but may terminate in micronodular cirrhosis. This form of cirrhosis, predominantly seen in copper toxicosis, differs from other forms of chronic hepatitis, in which patients typically develop macronodular cirrhosis with large hyperplastic nodules. Hepatitis is overrepresented in female Doberman Pinschers by a factor of 10; a study in Finland showed that approximately 10% of Doberman Pinschers may be affected.[20] Inherited copper toxicosis is also a well described entity in Bedlington Terriers worldwide.[21] Both sexes may be affected. Clinical signs usually develop after 4 years of age as a result of the gradual accumulation of copper. It is caused by a defect in the Murr 1 gene, leading to a severely decreased excretion of copper by hepatocytes. Other affected breeds are West Highland White Terriers (particularly in the United States), Skye Terriers, Dalmatians, Anatolian Shepherd dogs, and Labrador Retrievers.[22-26] Siamese cats may also be predisposed to copper-associated hepatopathies.[9] Although essential for life, copper is usually ingested to excess and must be eliminated by the liver to prevent toxicity. The central role of the liver in copper homeostasis makes it vulnerable if elimination processes fail.[27] Furthermore, increased copper levels add to the oxidative stress, which is an important component in chronic inflammatory and cholestatic diseases in dogs.[25] Spaniels seem to have the form of chronic hepatitis unrelated to copper toxicosis and develop macronodular cirrhosis when left untreated. No sex predisposition exists, but there seems to be a worldwide overrepresentation of hepatitis in this breed.

Congenital portosystemic shunts (CPSS) are seen in both sexes in various breeds. Intrahepatic shunts predominate in large breeds, whereas extrahepatic shunts predominate in small and toy breeds. Although CPSS are most likely inherited in some fashion in all affected breeds, this has only been proven in Irish Wolfhounds[28] and Cairn Terriers.[29] Worldwide predispositions occur in Irish Wolfhounds, Australian cattle dogs, Labrador Retrievers, Dachshunds, Yorkshire Terriers, Cairn Terriers, Maltese Terriers, and Miniature Schnauzers.[7,9] In the United States, an increased prevalence of shunts has also been reported to occur in German Shepherd dogs, Doberman Pinschers, and Golden Retrievers. CPSS occur most often in mixed-breed cats; however, Persian and Himalayan cats are frequently overrepresented. Clinical signs are usually seen in young dogs and cats (<1 year old) with congenital shunts.[5,9]

Pathogenesis of Common Symptoms of Primary Liver Diseases

Vomiting

Vomiting is one of the most common symptoms noted in dogs and cats with liver disease. Vomiting may be caused by direct stimulation of the vomiting center via the chemoreceptor trigger zone in the fourth ventricle by (endo)toxins that are not cleared by the liver.[30] This typically occurs when toxins from the GI system bypass the liver and access other body systems. Vomiting is common in all conditions that share portosystemic shunting and liver dysfunction (e.g., congenital shunts and acquired shunts because of hepatitis, fibrosis, cirrhosis, and portal vein hypoplasia or thrombosis). Hepatic diseases that cause an abnormal liver shape may reposition the upper GI tract and induce nausea and vomiting by vagal stimulation. Causes include hepatic tumors, especially liver cell (or hepatocellular) carcinomas, and unilateral collapse and contralateral hypertrophy, which may occur with thrombosis of a main branch of the portal vein. The gallbladder and larger bile ducts have a rich sympathetic innervation; therefore dilation (e.g., extrahepatic cholestasis), cholecystitis, or cholelithiasis should be suspected in vomiting dogs and cats.[5]

Vomiting is also common in upper GI disease. In many GI diseases, translocation of bacteria and endotoxins may cause secondary, nonspecific, reactive hepatitis.[30] This occurs frequently in dogs, but rarely in cats. Reactive hepatitis is characterized by intrahepatic canalicular cholestasis, liver cell necrosis, and an exudative inflammatory reaction. Clinical signs, symptoms, and diagnostic results associated with primary liver disease and reactive hepatitis are similar; therefore, a further diagnostic workup is important to reveal the primary cause.

Diarrhea

Small bowel-type diarrhea occurs frequently with hepatic diseases (see Table 61-2). Two primary mechanisms may account for clinical signs. First, cholestatic diseases (intrahepatic or extrahepatic caused by common bile duct obstruction) disrupt the normal enterohepatic cycle of bile acids; therefore less bile reaches the duodenum.[30,31] Decreased resorption of dietary fat may cause hyperosmotic intestinal contents and diarrhea. However, studies in rats show that cholestasis must be severe before steatorrhea as a result of disruption of the enterohepatic bile acid cycle occurs. Another mechanism for diarrhea in liver disease is increased resistance to portal blood flow, resulting in portal hypertension and congestion of splanchnic organs. Intestinal vasculature congestion reduces intestinal water resorption and increases intestinal volume content. This is the predominant mechanism underlying diarrhea in diseases such as chronic hepatitis, lobular dissecting hepatitis, portal vein thrombosis, and portal vein hypoplasia.[5] Alternatively, when the primary cause of diarrhea is intestinal disease, the liver may be affected secondarily. In those cases, the hepatic macrophage system should remove the increased absorption of (endo)toxins or bacteria by the affected intestinal wall. Increased exposure, however, can lead to secondary, nonspecific, reactive hepatitis. Endotoxins also effectively inhibit bile formation and flow, leading to cholestasis. It is therefore common to find increased plasma liver enzyme activities and bile acid levels in cases of reactive hepatitis; clinical icterus may even be apparent. The cause of diarrhea can be determined only by further diagnostic methods, including histologic evaluation of liver biopsy specimens. Reactive hepatitis resolves rapidly when the primary disease is treated successfully. In the authors' experience it is very rare to find diarrhea as single or the leading symptom in cases of liver disease. If present, it is usually one of the less prominent symptoms in the spectrum of other more prominent symptoms such as apathy, PU/PD, or vomiting. One may therefore elect to follow liver laboratory values after treatment of the intestinal disease and perform a liver biopsy if liver parameters fail to improve within a few weeks.

Hepatic Encephalopathy and Related Anesthesia Intolerance

Hepatic encephalopathy is a complex of neurobehavioral signs resulting from portosystemic shunting of blood in combination with a reduction of functional liver mass.[11] It may occur in animals with CPSS or in those with APSCAPSC because of portal hypertension. Diseases associated with the latter form are chronic hepatitis, cirrhosis, portal vein hypoplasia, lobular dissecting hepatitis, and portal vein thrombosis.[32] Cats, because of their dependence on some essential amino acids (e.g., arginine), may develop hepatic encephalopathy without portosystemic shunting, especially when they have a severe form of hepatic lipidosis.[33]

Hepatic encephalopathy is caused by derangement of neurotransmitter systems caused by defective metabolic processes in the liver.[34] Inadequate metabolism of ammonia and aromatic amino acids by the liver may reduce the excitatory glutamatergic and monoaminergic neurotransmitter system tones, respectively.[35] In addition, there is an increased tone of the inhibitory γ-aminobutyric acid (GABA) system.[36] These neurotransmitter derangements make anesthesia risky in some animals with liver disease. The liver inactivates many anesthetics and the unforeseen delay of recovery from anesthesia may suggest an underlying liver disease as a cause for nonspecific clinical signs. This occurs especially in dog and cats with portosystemic shunting, either congenital or acquired. In addition to reduced hepatic clearance, anesthetics exert their action via various neurotransmitter systems in the brain, which may already be functioning abnormally as a consequence of hepatic encephalopathy.[34] This is especially true of drugs that act via the GABA-benzodiazepine pathway. That pathway is already overstimulated and may provoke an exaggerated and prolonged anesthetic effect.

Polyuria and Polydipsia

PU/PD is one of the most frequent signs (50% of cases) in dogs with liver disease, but is less common in cats. PU/PD is most common in diseases associated with congenital or acquired portosystemic shunting and, therefore, with hepatic encephalopathy. In affected dogs, abnormal neurotransmitter disturbances lead to increased secretion of adrenocorticotropic hormone (ACTH) from the anterior and intermediate pituitary lobes.[37] Chronically elevated ACTH stimulates increased levels of free cortisol. Increased levels of free cortisol, in turn, affect the posterior lobe of the pituitary creating an increased threshold for the release of arginine vasopressin.[38,39] Thus, a higher plasma osmolality is required to stimulate antidiuresis through arginine vasopressin, and before reaching that threshold, affected dogs become thirsty and start drinking.[38]

PU/PD is not only present in cases with hepatic encephalopathy, but also frequently in all other liver diseases. This may be caused by certain bile acids, which are often increased in plasma of animals with liver diseases. Bile acids may inhibit the activity of 11β-hydroxyl steroid dehydrogenase.[40] This enzyme protects the aldosterone receptor from occupation by cortisol, by converting cortisol into cortisone, which cannot bind to the receptor. Present in plasma in tenfold excess compared with aldosterone, cortisol can occupy and stimulate the aldosterone receptor thereby inducing pseudohyperaldosteronism and PU.[41]

Reduced hepatic formation of urea is another possible but undocumented mechanism that may play a role in the pathogenesis of PU/PD. In urea deficiency states, the kidney does not have sufficient urea available to build up an osmotic gradient in the medulla. Apart from this mechanism, PD also occurs in liver diseases not associated with hepatic encephalopathy (e.g., extrahepatic cholestasis and liver tumors). The mechanism is unclear; however, nausea with an impulse to drink and compensation of water loss by vomiting and diarrhea may play a role.[5]

Dysuria

Dysuria may occur as a result of insufficient liver function when nonmetabolized uric acid is excreted by the kidneys and precipitates to form uroliths. Such calculi are seen in dogs but rarely in cats.[42] There are two main categories of liver dysfunction that cause ammonium urate urolithiasis. Most frequently it is caused by congenital portosystemic shunting, whereby the liver is underdeveloped and fails to metabolize uric acid into allantoin. In urine, uric acid flocculates easily in the presence of high ammonia concentrations to form ammonium urate. Affected dogs usually have clinical signs related to shunting and liver dysfunction, such as hepatic encephalopathy, PU/PD, or vomiting. In the other category, the enzyme uricase, which forms allantoin, is inactive because of an inborn error affecting only this function. Ammonium urate urolithiasis occurs commonly in Dalmatians but may occur in other breeds.[43] Affected dogs only have signs related to urolithiasis (e.g., pollakiuria, stranguria, dysuria).

Acholic Feces

An owner may note acholic feces, which can provide a direct clue to the underlying diagnosis. Steatorrheic feces that do not contain normal bile pigment are seen only when bile flow into the intestinal tract is completely disrupted, usually as a consequence of extrahepatic obstruction of the common bile duct.[6] Destructive cholangiolitis is the only intrahepatic process severe enough to seriously disrupt bile flow. The latter disease is caused by a hypersensitivity reaction to sulfonamide-containing drugs. The smaller bile ductules become necrotic and liver lobuli may be disconnected from the biliary tract. Affected dogs have a history of recent medication with sulfonamides. Acholic feces contain excess fat because resorption is impaired. The lack of normal black-brown fecal pigments occurs because their precursor, bilirubin, does not reach the duodenum. Therefore, the feces from affected animals are gray-white and soft. Animals with this condition often are icteric. The presence of icterus reduces the likelihood of exocrine pancreatic insufficiency as a diagnosis.

Abdominal Distention

Abdominal distention may occur in dogs and cats with liver disease for several reasons. First, ascites is a frequent finding associated with liver disease in dogs as a result of portal hypertension, but is less common in cats. Abdominal distention may also result from organ enlargement, which in the case of liver disease may include the liver and, in the spleen in the presence of portal hypertension. In contrast to dogs, cats often have hepatomegaly with liver disease.

Other Symptoms

Nonspecific symptoms, such as apathy, reduced appetite or anorexia, and weight loss, may occur in dogs and cats with liver disease. Retarded growth is common in young animals. These problems reflect the central role of the liver in many metabolic and detoxifying functions. In addition, nausea, inappetence, vomiting, and diarrhea can result in a catabolic state, which, in turn, may aggravate hepatic encephalopathy. Signs of early hepatic encephalopathy include depression and other nonspecific problems. Anemia, another common finding in liver disease (see below), can cause general malaise. Dogs with liver cell carcinoma often are hypoglycemic,[44] which may be the primary problem underlying apathy and weakness. Production of insulin-like growth factors by the tumor may be responsible.

Physical Examination and Signs of Liver Diseases

As with historical findings, physical examination findings rarely provide enough information to pinpoint the liver as definitive cause of the presenting problems. Possible findings include icterus, hepatomegaly, splenomegaly, ascites, and pale mucous membranes. Petechiae of the skin or mucous membranes occur infrequently. Of these possible findings, only icterus and hepatomegaly are more or less specific for liver diseases; other abnormalities on the physical examination occur more frequently with diseases of other organ systems.

Ascites and hepato- and splenomegaly may have been noted by the owner as abdominal enlargement.[5] Biochemistry analyses are an integral part of the diagnostic process for liver diseases. Most of these analyses are not a decisive factor in the diagnosis of liver disease, but serve to rule out liver disease from the differential diagnosis.[8]

Icterus

Icterus is the most frequently encountered specific abnormality noted on the physical examination in dogs and cats with liver disease. However, only approximately 20% of dogs with hepatobiliary diseases and 30% to 40% of cats are icteric. Icterus results from bilirubin accumulation in the blood and extravascular space as a result of increased production, reduced clearance, impaired conjugation by the liver, and/or impaired bile flow. In most cases, a combination of these factors is involved. Cholestasis is predominant; therefore conjugated bilirubin is the fraction present in greatest quantity. Hemolysis alone does not result in icterus with normal liver function. When hemolysis is severe, however, it may result in such a degree of portal hypoxia that the centrolobular zones of the liver lobules become necrotic. In those cases, icterus results from the combination of increased production and reduced liver function and cholestasis.[45] If hemolysis is the primary cause of icterus, it must be severe, and the mucous membranes will be extremely pale. Primary liver diseases that may cause icterus are commonly accompanied by hemolysis. Whereas the erythrocyte lifetime is reduced to 6 to 10 days in dogs with severe primary hemolytic disease; it is 20 to 60 days (normally 100 days) in hepatobiliary disease. Increased production of bilirubin and liver dysfunction with cholestasis result in a combined conjugated and unconjugated hyperbilirubinemia in dogs and cats with primary hepatic or hemolytic disease.[46] Icterus caused by hemolytic disease is characterized by pale mucous membranes, whereas the mucous membranes in animals with primary liver disease are normal or only slightly pale. The combined evaluation of icterus and the color of the mucous membranes immediately reveal the nature of the underlying process.

Pale Mucous Membranes

As previously discussed, most hepatobiliary diseases are accompanied by increased degradation of red blood cells. The mechanisms behind hemolysis in liver disease are not completely clear. Hypersplenism and reduced portal blood flow due to portal hypertension may drastically prolong the transit time of erythrocytes through the spleen, with a greater chance that they will be trapped when they are slightly abnormal. Increased fragility of red cell membranes may be a result of the high bile acid levels in most liver diseases, whereas a reduced clearance of enteral endotoxins and bacteria by the liver may also induce immune-mediated hemolysis. Apart from hemolysis, nonregenerative anemia also may occur as part of the syndrome of anemia of chronic disease as an expression of catabolism and slight deficiencies of iron and B vitamins. Although common in liver diseases,[12] anemia, in contrast to icterus, is nonspecific.

Hepatomegaly

Like icterus, hepatic enlargement is a distinct sign of an abnormal liver. In dogs, most liver diseases do not cause hepatomegaly. Exceptions include tumors of the liver, liver congestion, and secondary liver involvement in metabolic diseases. Examples of the latter conditions are glycogen accumulation in the liver in Cushing disease, fatty liver with diabetes mellitus, and rare cases of amyloidosis of the liver.

The more chronic liver diseases of dogs tend to reduce liver size, and acute diseases cause little change in size. Liver enlargement as a result of congestive heart disease can, in most cases, be recognized easily by physical examination of the circulatory system. Measurement of central venous pressure is diagnostic. The exception is liver congestion caused by a thrombus in the caudal vena cava proximal to the liver, which is assessed by other methods. When the liver is overtly enlarged because of congestion, ascites is usually present. Ascitic fluid has the typical slightly hemorrhagic appearance of congestive fluid. Dogs with enlarged livers and no signs of congestive disease often have liver cancer, which may be primary, metastatic, or a form of malignant lymphoma. With most tumors, the liver is diffusely enlarged, but primary hepatocellular carcinomas or adenomas may cause enlargement of the affected lobe only. Bile duct carcinomas disseminate easily over the biliary system and usually cause pronounced icterus and hepatomegaly.

Most cats with hepatic disease develop pronounced enlargement of the liver. In cats, liver enlargement occurs with cholangitis, hepatic lipidosis, amyloidosis, hepatic tumors (primarily malignant lymphoma), and congestive disease. When the liver is involved in feline infectious peritonitis, it may not be enlarged. Cats with CPSS have small livers.

Splenomegaly and Ascites

Splenomegaly and ascites in association with liver disease are nonspecific findings. They occur especially with hepatic diseases causing portal hypertension. Both findings are frequent in dogs but rare in cats. There is a positive undulation test with distinct ascites; slight ascites can be found with ultrasonography rather than physical examination. The liver may be enlarged with central causes of venous congestion. Canine liver diseases associated with portal hypertension include chronic hepatitis and cirrhosis, portal vein hypoplasia, and lobular dissecting hepatitis. Portal hypertension is sometimes seen with cirrhosis because of advanced cholangiohepatitis in cats. In these diseases, hepatic encephalopathy is also common. Portal vein thrombosis is a prehepatic cause of portal hypertension that usually causes ascites. Although as a rule the liver is small in these cases, unilateral obstruction of a main branch of the portal vein may cause hypertrophy of the rest of the liver, which may be palpable.

Conclusion

Diseases of the hepatic parenchyma, hepatic vasculature, and biliary tract are relatively common in dogs and cats. Because the symptoms and signs accompanying liver disease are quite nonspecific, and the liver may be secondarily involved in diseases of other organs, liver disease can easily go undetected. Therefore, after taking a thorough history and performing a physical examination, it is critical to perform additional biochemical tests with the highest possible diagnostic accuracy whenever liver disease is included in the differential diagnosis. If liver disease cannot be ruled out based on these examinations, additional testing is necessary to define the type of liver disease, most notably ultrasonography of the cranial abdominal quadrant and examination of a liver biopsy specimen. The algorithm in Figure 61-5 summarizes this approach.

Diagnosis usually depends on histopathologic examination of liver tissue, especially for parenchymal liver diseases, many biliary tract diseases, and tumors of the liver or biliary tract. Although biopsy methods are beyond the scope of this chapter, excellent sources exist.[13] One note of caution: blood coagulation testing is vital before collecting a liver biopsy specimen for histopathology. Most animals, for example, have one or more abnormal coagulation tests.[47-52] Factors involved may include vitamin K deficiency, reduced

production of clotting factors, some degree of disseminated intravascular coagulation (DIC), and severe protein deficiency.[13,52] It should be noted that taking a fine-needle aspiration biopsy should be considered safe, even if abnormalities in coagulation are present. However, its diagnostic value is limited as the liver architecture is lost.

Diagnosis of circulatory hepatic diseases depends on information obtained from laboratory results, ultrasonography (most reliable diagnostic test to date), and histopathology.[13] A recent paper found that fasting ammonia concentration was superior to fasting bile acids for diagnosing portosystemic shunting in dogs.[53] Ammonia is easily measured in practice with dry chemical methods, some of which provide reliable results.[54] Another recent publication showed ultrasonography to be a reliable diagnostic method to noninvasively characterize the underlying hepatic disease in dogs with hyperammonemia.[55]

DIAGNOSTIC EVALUATION

Jonathan A. Lidbury and Jörg M. Steiner

Diagnostic evaluation of the hepatobiliary system has several aims: (a) to determine if hepatobiliary disease is present, (b) to assess liver function, (c) to determine if liver disease is primary or secondary, (d) to definitively diagnose hepatobiliary disease, and (e) to monitor response to treatment. Despite the apparent clarity of these aims, hepatobiliary disease can present a diagnostic challenge for a number of reasons. First, as clinical signs can be nonspecific, hepatobiliary disease should be a consideration when evaluating any patient with signs of systemic disease. Dogs and cats with hepatobiliary disease may not have any clinical signs. Furthermore, because of the liver's central role in metabolism and detoxification of endogenous toxins and xenobiotic agents, a number of extrahepatic diseases can secondarily affect the liver. It is important to distinguish these *secondary hepatopathies* from diseases that originate in the liver (*primary hepatopathies*). Additionally, serum markers of hepatocellular damage, cholestasis, and hepatic function can be abnormal in the absence of hepatobiliary disease. Finally, the liver's large reserve capacity means that detectable loss of liver function often occurs late in the course of disease. Thus, when assessing a patient with suspected hepatobiliary disease, it is important to consider the clinical presentation, results of laboratory testing, diagnostic imaging findings, and the results of cytologic and/or histopathologic evaluation together.

Laboratory Testing of the Liver

Hepatic Enzymology

Hepatic enzymes can be divided into markers of hepatocellular damage and markers of cholestasis. Serum alanine aminotransferase (ALT) and aspartate transaminase (AST) activities are the two most commonly measured markers of hepatocellular leakage, while serum alkaline phosphatase (ALP) and γ-glutamyltransferase (GGT) activities are the two most commonly measured markers of cholestasis.

Although increased serum hepatic enzyme activities are considered to be sensitive, they are not specific for primary liver disease because they are produced by extrahepatic tissues. The relative importance of these extrahepatic *isoenzymes* varies, but their extrahepatic release can lead to increased serum activities. Also, the production of some hepatic enzymes can be induced by certain hormones and drugs, leading to an increase in their serum activities in patients without primary hepatic disease. Additionally, serum hepatic enzyme activities can be increased as a consequence of secondary hepatopathies.

The magnitude of hepatic enzyme activity increases may aid in the assessment of the severity or the extent of hepatic injury but should not be considered to be prognostic. The liver has a large capacity for regeneration, so even in cases of severe hepatic injury, with dramatically raised hepatic enzyme activities, a full recovery is possible. This is especially true when the injury is acute. Conversely, in cases of chronic end-stage liver disease, such as cirrhosis, serum hepatic enzyme activities may not be markedly increased, or may even be within the reference interval as a result of the replacement of hepatocytes with fibrous tissue. Consequently, serial evaluation of serum hepatic enzyme activities is more useful for assessing prognosis than measurement at a single point in time. Consistent decreases of a previously increased activity are considered a favorable sign in acute liver injury, whereas a decreasing hepatic enzyme activity in a patient with chronic liver disease that is clinically deteriorating suggests loss of hepatocytes because of fibrosis. It is important to note that serum hepatic enzyme activities do not provide an assessment of liver function.

Markers of Hepatocellular Damage

ALT is an enzyme found primarily in the cytosol of hepatocytes. ALT is released into the serum when hepatocyte membrane permeability is increased, or if there is hepatocellular necrosis. ALT is considered to be the most liver-specific enzyme. ALT is also produced by cardiac muscle, skeletal muscle, and the kidneys.[1] Apart from the hepatic form, only the muscle isoenzyme is clinically significant. Although uncommon, severe muscle injury can result in an increased serum ALT activity. Hepatic microsomal induction in response to some drugs can also produce small increases in ALT activity.

Some controversy exists regarding the serum half-life for ALT in dogs. The mean serum half-life of ALT was reported as being 149 minutes in one study[1] and 59 hours in another.[2] The serum half-life of ALT is generally believed to be shorter in the cat than in the dog. A mean serum half-life of 207 minutes was reported in an experiment involving three healthy cats.[3] The shorter half-life in cats means that increases in serum ALT activity are considered more clinically important in this species. As ALT is metabolized in the liver its serum half-life may be longer in patients with liver disease.[4]

Increased cell membrane permeability in the absence of hepatocyte destruction can cause a rapid increase in serum ALT activity. Because of this, ALT activity is a considered to be a highly sensitive marker of hepatocyte injury. This also means that an increased ALT activity does not imply severe or irreversible hepatocellular injury. The highest increases in ALT activity are seen during acute hepatic inflammation or necrosis, but because of the capacity for the liver to regenerate these do not indicate irreversible damage. Consequently, a single measurement of ALT activity does not provide an accurate prognosis. However, the degree of the ALT activity increase is believed to have some correlation with the number of hepatocytes that have been injured. Cholestasis can also result in an increased serum ALT activity because of hepatocellular damage caused by the accumulation of bile acids. Certain drugs can lead to increases in serum ALT activity. These are usually minor, for example, phenobarbital used at therapeutic doses frequently leads to small increases in serum ALT activity, in the absence of hepatic insufficiency. These increases are thought to occur as a result of subclinical hepatic injury rather than induction of hepatic microsomal enzymes.[5] Toxic doses

of phenobarbital can cause dramatic increases of serum ALT activity and hepatic insufficiency. Prednisone and other glucocorticoids can cause an induction of ALT (and steroid hepatopathy) and consequently small increases in serum ALT activity. Serum ALT activity can also be increased with any secondary hepatopathy. However, a persistently increased serum ALT activity, even with an apparently normal liver function, is an indication for further diagnostic testing.

Serial evaluation of serum ALT activity can be helpful to prognosticate but must be done while considering the patient's clinical signs and other laboratory values. In general, a declining serum ALT activity after acute liver injury is considered a good sign.

AST is another aminotransferase enzyme that is used as a marker of hepatocellular leakage. AST is found in skeletal muscle, the brain, liver, kidney, cardiac muscle, and to a lesser extent within other tissues.[6] The extrahepatic isoenzymes of AST are relatively more important than they are for ALT. Muscle disease can cause an increase in serum AST activity. Because of this, AST is considered less liver specific than ALT. However, by looking at serum AST activity in conjunction with the activities of other hepatic enzymes and muscle enzymes, it is usually possible to differentiate increases caused by muscle damage from increases caused by hepatic damage.

Again, there is controversy regarding the serum half-life of AST. In dogs one study[1] reported the half-life to be a mean of 263 minutes; another study reported a mean of 22 hours.[2] One study reported the mean half-life to be 78 minutes for cats.[7] Unlike ALT, a considerable proportion of AST (approximately 30%) is found within hepatocyte mitochondria rather than the cytosol.[8] The cytosolic fraction of AST is released into the serum from hepatocytes when cell membrane permeability is increased, or in case of hepatocellular necrosis. In contrast, the mitochondrial fraction is only released during hepatocellular necrosis. Release of AST from hepatocytes into the serum parallels the release of ALT. Therefore, like serum ALT activity, serum AST activity is considered a sensitive marker for hepatocyte injury. It has been suggested that increased AST activity may be more sensitive than increased ALT activity for the detection of hepatocellular injury in cats.[9] Corticosteroids and phenobarbital may cause mild increases in serum AST activity. Because of the considerable overlap in the information provided by the measurement of serum ALT and AST activities, measurement of serum AST activity may be redundant.

Markers of Cholestasis

ALP is an enzyme bound to the membranes of the hepatocytes that comprise the bile canaliculi and the sinusoidal membranes. It is considered a sensitive marker for cholestasis, especially in the dog, but is not liver specific. Cholestasis, canalicular cell necrosis, and increased hepatic synthesis may lead to the release of this enzyme into the circulation. Synthesis of this enzyme can be induced by certain drugs, most notably corticosteroids. The possibility that an increase in serum ALP activity could be caused by extrahepatic disease, or could be induced by glucocorticoids in the dog, can make the interpretation of this finding challenging.

In the dog a wide variety of tissues exhibit ALP activity, including intestinal mucosa, kidney (cortex), bone marrow, pancreas, testicle, brain, lung, kidney (medulla), lymph node, liver, skin, spleen, skeletal muscle, and cardiac muscle.[6] There is disagreement in the literature regarding the relative contributions of ALP activity from each of these tissues in cats.[10-12] There are two genes encoding ALP in the dog. Different forms of ALP arising from the same gene are called *isoforms*. Differences among these isoforms arise because of differing posttranslational processing. Liver ALP (L-ALP), bone ALP (B-ALP), and kidney ALP (K-ALP) are transcribed from the tissue nonspecific ALP gene. The other gene encodes intestinal ALP (I-ALP) and probably glucocorticoid-induced ALP (G-ALP).[13] In dogs the serum half-lives of placental ALP, K-ALP, and I-ALP are less than 6 minutes.[14] In cats the serum half-life of I-ALP is less than 2 minutes. The half-lives of placental ALP and K-ALP are also assumed to be short in the cat as they have similar structures to I-ALP. Because of this, only L-ALP, B-ALP, and, in the dog but not the cat, G-ALP, are believed to contribute significantly to serum ALP activity. The serum half-life of L-ALP is approximately 70 hours in the dog[14,15] and 6 hours in the cat.[16]

L-ALP is bound to the membranes of the hepatocytes by glycosylphosphatidylinositol linkages. Cleavage of these links by glycosylphosphatidylinositol-phospholipase allows the enzyme to be released into the bloodstream.[17] As bile acids have detergent-like properties; accumulation of bile acids during cholestasis facilitates this process. Cholestasis can also result in the induction of synthesis of L-ALP (and G-ALP in the dog). Consequently, serum ALP activity is often severely increased in patients with cholestatic disorders. In the dog, ALP is considered to be a sensitive marker for cholestasis with a sensitivity of 85%.[18] The short half-life of L-ALP in cats means that increases in ALP during cholestasis are not as high as in the dog. Consequently, ALP is a less-sensitive marker of cholestasis in the cat than in the dog, with a reported sensitivity of only 48%.[19] However, the shorter half-life in cats and the absence of G-ALP means that any increase in ALP activity should be considered clinically important in this species. An increased serum ALP activity does not differentiate between intrahepatic or extrahepatic cholestasis. A wide variety of liver diseases can cause intrahepatic cholestasis. This is generally caused by hepatocyte swelling, causing obstruction of the small bile canaliculi. The increase of ALP following a hepatic insult is delayed compared to rises in markers of hepatocellular leakage. The reason for this is that it takes time for the enzyme to be synthesized and released into the systemic circulation. ALP often remains increased for some time after the resolution of liver injury.

B-ALP is released into the bloodstream as a result of the activity of osteoblasts. Therefore any condition that results in increased bone formation can lead to increased serum ALP activity. In animals that are skeletally immature, mild increases in serum ALP activity are commonly observed. Animals with increased osteoblast activity, such as those with hyperparathyroidism, neoplasia involving bones, and osteomyelitis, may have mild to moderate increases in ALP activity. These causes of increased B-ALP activity are unlikely to be confused with primary liver disease because the increases are smaller than would be expected with cholestasis, and because bone diseases are often clinically apparent. Finally, an increased serum activity of B-ALP was reported in a family of asymptomatic Huskies.[20]

In dogs, but not in cats, *G-ALP* and tissue-nonspecific ALP may be induced by corticosteroids. G-ALP is believed to be an isoform of I-ALP with a prolonged serum half-life that is produced by the liver.[13] Posttranslational glycosylation of the G-ALP is believed to be responsible the prolonged half-life. Induction of G-ALP may cause an increase in total serum ALP activity after administration of exogenous corticosteroids. Synthesis of this isoenzyme can also be induced by the administration of anticonvulsant drugs, such as phenobarbital. Similarly, hypercortisolemia frequently causes an increased serum ALP activity because of induction of G-ALP. However, in dogs with excess serum concentrations of endogenous or exogenous corticosteroids, hepatocyte swelling caused by glycogen accumulation (vacuolar hepatopathy) may lead to intrahepatic cholestasis, another potential contributor to increased serum ALP

activity. Before diagnosing primary liver disease in a dog with an increased serum ALP activity, induction of G-ALP by endogenous or exogenous steroids should be ruled out. Recently a group of Scottish Terriers were found to have increased serum ALP activity with no identifiable underlying cause.[21]

It is technically possible to selectively measure the activity of G-ALP using techniques such as levamisole inhibition. Measurement of G-ALP activity was initially investigated as a way to differentiate increases in ALP caused by corticosteroids from those caused by cholestasis. Unfortunately, measuring G-ALP is not clinically useful as G-ALP activity may be increased in a variety of conditions, including hepatic disease, diabetes mellitus, hypothyroidism, and pancreatitis.

GGT is a glycoprotein enzyme that is bound to the membranes of those hepatocytes that form the bile canaliculi and bile ducts and also periportal hepatocytes. In comparison to ALP its distribution includes more distal areas of the biliary tract, but measurement of serum GGT activity is not useful to distinguish between intrahepatic and extrahepatic cholestasis. GGT is also produced by a number of extrahepatic tissues. Most of the GGT activity in serum is thought to be a result of the hepatic isoenzyme. Colostrum also contains GGT, which is responsible for the mild increases in serum GGT activity that are seen in suckling animals.[22]

Changes in serum GGT activity generally parallel those in serum ALP activity, in that activity is often increased in patients with cholestasis. Because GGT is also induced by glucocorticoids, its activity may be increased in patients with hyperadrenocorticism or those exposed to exogenous steroids. In dogs, an increased serum GGT activity is considered to be more specific, but less sensitive than ALP activity for the presence of liver disease.[18] In cats, measurement of serum GGT activity is more sensitive but less specific for the detection of liver disease than ALP. Cats with hepatic lipidosis may be an exception to this as they often have a normal serum GGT activity but an increased serum ALP activity.[19]

Markers of Protein Metabolism

The liver plays a central role in protein metabolism. It is responsible for the synthesis of plasma proteins, deamination of amino acids, conversion of ammonia to urea, amino acid synthesis, and interconversion of amino acids.[23] Consequently, in patients with hepatic disease these functions may be compromised.

Plasma Proteins

Albumin is an important plasma protein that is produced exclusively by the liver. The rate of albumin synthesis must equal the rate of albumin loss to maintain serum albumin concentrations. Mild decreases in serum albumin concentration can occur from a variety of conditions. However, the differential diagnoses for severe hypoalbuminemia (<2 g/dL) are limited to hepatic insufficiency, severe exudative skin disease, protein-losing enteropathy, and protein-losing nephropathy. It is possible to determine the cause of severe hypoalbuminemia from a combination of clinical findings, measurement of the serum globulin concentration, urinalysis (including protein creatinine ratio), tests of GI protein loss, and tests of liver function. As albumin contributes significantly to colloid oncotic pressure,[24] severe hypoalbuminemia can lead to ascites, pleural effusion, and/or subcutaneous edema. The liver has a large reserve capacity for the synthesis of albumin and albumin has a serum half-life of approximately 7 days in dogs.[25] Consequently, hypoalbuminemia is a relatively insensitive marker for hepatic insufficiency and is only likely to be seen in patients with advanced chronic liver disease or *portosystemic shunts* (PSSs).

Globulins are produced in the liver, but not exclusively so. The liver produces α-globulins and β-globulins, whereas lymphoid cells produce immunoglobulins (γ-globulins). Hepatic insufficiency rarely leads to a decrease in serum globulin concentration. Conversely, inflammatory liver disease may be associated with hyperglobulinemia because the nonimmunoglobulin fraction produced by the liver includes several *acute-phase proteins* (C-reactive protein, haptoglobin, and serum amyloid A). The hepatic synthesis of these proteins is increased during systemic inflammation[26-29] possibly leading to a rise in the total serum globulin concentration. Additionally, immunoglobulin production may be increased in infectious, neoplastic, or autoimmune diseases.

Coagulation factors (except factor VIII), anticoagulation factors (antithrombin and protein C), and the fibrinolytic protein plasminogen, are all synthesized by the liver. The liver is also the site of activation of the vitamin K-dependent clotting factors: II, VII, IX, X, and protein C. Furthermore, as bile acids are needed to emulsify fat and aid in the absorption of vitamin K from the intestine, vitamin K malabsorption may develop secondary to cholestasis. Consequently, hepatobiliary disease can affect hemostasis in more than one way.

In canine and feline liver disease, coagulation parameter abnormalities have been reported in specific clotting factor activities, prothrombin time, aPTT,[30-32] proteins induced in the absence of vitamin K,[33,34] fibrin degradation products, fibrinogen, and protein-C activity.[35] These abnormalities of hemostasis are not specific for liver disease but may support its presence. Patients with liver disease may develop DIC, which can be difficult to distinguish from coagulopathy because of reduced hepatic synthesis of clotting factors alone. Although spontaneous bleeding seldom occurs in patients with liver disease, the assessment of the coagulation status of these patients is important, especially when an invasive procedure such as a liver biopsy is being considered.

A recent study investigated the diagnostic value of serum protein C as a marker for hepatobiliary disease and portosystemic shunting in dogs. Serum protein-C measurement was reported to aid in the differentiation of portal vein hypoplasia without portal hypertension (formerly called microvascular dysplasia) from portosystemic shunt (PSS). Dogs with portal vein hypoplasia without portal hypertension had a significantly higher serum protein-C concentration than those with portosystemic shunting.[35]

Protein Catabolism

Urea is produced from ammonia in the liver, released into the systemic circulation, and subsequently excreted by the kidneys. Serum urea nitrogen concentration may be close to or below the lower limit of the reference interval in patients with hepatic insufficiency, PSS,[36] or urea cycle enzyme deficiencies. However, serum urea nitrogen concentration may also be decreased because of medullary solute washout caused by diuresis, malnutrition, or a protein-restricted diet, and is a normal finding in neonates. In a patient with liver disease, a high fasting serum urea nitrogen concentration relative to the serum creatinine concentration suggests GI hemorrhage.

Ammonia (NH_3) is produced in small intestinal enterocytes from the catabolism of glutamine and in the colon as a consequence of bacterial deamination. Ammonia is a highly diffusible gas and passes readily through the bowel wall into the bloodstream. In the blood, at a pH of 7.4, most of the ammonia exists in the form of ammonium ions (NH_4^+). The ammonium is transported in the blood from the intestines through the hepatic portal circulation to the liver. The extraction of ammonia from the portal circulation is highly efficient. Endogenous ammonia is produced from the breakdown of

nitrogenous substances in the body, especially glutamine. In the liver the ammonium is converted to urea by the enzymes of the urea cycle, or is used during the conversion of glutamate to glutamine.[37] Urea enters the circulation and is excreted by the kidneys. Ammonium that is not removed by the liver enters the systemic circulation.

The liver has a large reserve capacity for the conversion of ammonia into urea. Because of this, plasma ammonia measurement is a relatively insensitive marker for hepatic insufficiency. However, measurement of blood ammonia concentration is a sensitive test for congenital PSSs and APSC shunts (also known as acquired PSSs). This is because when portosystemic shunting occurs, the ammonia absorbed from the intestines bypasses the liver and reaches the systemic circulation directly. The sensitivity of plasma ammonia measurement for the detection of PSS is reported to be between 81% and 100% in dogs[38-41] and 83% in cats.[41] The measurement of postprandial venous ammonia is more sensitive than the measurement of fasting ammonia (sensitivities of 91% and 81%, respectively) for the detection of congenital PSS.[42] However, the sensitivity for detecting dogs with hepatocellular disease is only 36%. Generally, hyperammonemia is considered specific for hepatic insufficiency or PSS. However, although they are uncommon, urea-cycle enzyme deficiencies may also cause an increased blood ammonia concentration. These enzyme deficiencies can be hereditary as a result of the absence of a particular enzyme[43] or secondary to cobalamin or arginine deficiency.[44,45] Arginine deficiency is especially relevant in cats with hepatic lipidosis. Ammonia is one of the substances that cause *hepatic encephalopathy* (HE). Therefore blood ammonia measurement is a useful marker for HE. However, other substances can also cause HE and the plasma ammonia concentration of a patient with HE may be within the reference interval.

Ammonium ions are labile in plasma, so sample handling is critical when measuring plasma ammonia concentration. Samples should be collected, placed immediately on ice, and the plasma separated from the red blood cells as soon as possible. The plasma must be kept cooled and should be analyzed within 30 minutes of collection. These handling requirements have meant that ammonia measurement has been mainly confined to practices with immediate access to a commercial laboratory. Measurement of plasma ammonia is available on an in-house dry chemistry analyzer (VetTest, Idexx Laboratories, Westbrook, ME) although this method was only considered to reliably agree with a reference method for serum ammonia concentrations greater than 150 μM.[46] A recent study found that a point of care blood ammonia analyzer (PocketChem BA, Menarini Diagnostics, Florence, Italy) may be suitable for the measurement of blood ammonia concentrations in dogs and cats.[47]

Ammonia tolerance tests (ATTs) have been investigated in an attempt to increase the sensitivity of ammonia measurement for detecting hepatic insufficiency and PSS. However, the oral administration of ammonium salts can cause vomiting and potentially worsen HE signs. Ammonium chloride or sulfate can also be given rectally, which is less likely to produce adverse. This method is sensitive for the detection of PSS in dogs.[48]

Markers of Lipid Metabolism

The liver plays a central role in lipid metabolism and is responsible for oxidation of fatty acids, synthesis of cholesterol, synthesis of lipoproteins, and synthesis of fatty acids from proteins and carbohydrates.[23]

Serum cholesterol concentrations may be increased, normal, or decreased in patients with liver disease. Increased or decreased fasting serum cholesterol concentrations are not sensitive or specific for hepatobiliary disease in dogs or cats. In patients with severe hepatic insufficiency or PSS[49] serum cholesterol, concentration may be decreased as a consequence of impaired hepatic synthesis. Hypocholesterolemia might also occur as a result of inadequate dietary intake, maldigestion, malabsorption, or hypoadrenocorticism. The serum cholesterol concentration of patients with hepatobiliary disease may be within the reference interval. Patients with cholestatic disease can become hypercholesterolemic.[50] Fasting hypercholesterolemia also may be observed in patients with various endocrinopathies, obesity, protein-losing nephropathy, pancreatitis, or primary hyperlipidemias.

Serum triglyceride concentration may be increased or normal in patients with liver disease. However, an increased fasting serum triglyceride concentration is not a sensitive or specific marker for hepatobiliary disease in dogs or cats. A mild increase in serum triglyceride concentration may develop in patients with cholestasis. There is some evidence that hypertriglyceridemia is associated with gallbladder mucocele formation.[51] Hypertriglyceridemia is associated with increased serum hepatic enzyme activities in Miniature Schnauzers.[52] Increased fasting serum triglyceride concentrations are also observed in patients with endocrinopathies, obesity, pancreatitis, and primary hyperlipidemias.

Markers of Carbohydrate Metabolism

The liver plays a central role in carbohydrate metabolism and is responsible glycogen storage, conversion of galactose and fructose into glucose, gluconeogenesis, and the synthesis of many compounds from carbohydrates.[23]

Blood glucose measurement is not a sensitive or specific marker for liver disease. The liver has a large reserve capacity for glucose production. Consequently, hepatic insufficiency must be severe for hypoglycemia to occur. Hypoglycemia occurs in a proportion of patients with congenital PSS.[53] Hepatic neoplasia can also lead to hypoglycemia. This is thought to be caused by release of insulin-like substances.[54] A variety of extrahepatic conditions can also lead to hypoglycemia.

Other Tests of Liver Function

Bilirubin is a yellow pigment produced from the breakdown of *heme*-containing compounds. Measurement of serum bilirubin concentration can be used to assess liver function. Hyperbilirubinemia can be the result of hepatobiliary or extrahepatic disease. Icterus is the yellowish pigmentation caused by the retention of bilirubin in the soft tissues. Laboratory assessment is the most sensitive way to detect increased serum bilirubin concentrations. Hyperbilirubinemia is classified as *prehepatic*, *hepatic*, or *posthepatic* in origin. Bilirubin may be artifactually increased by in vitro hemolysis or by the administration of synthetic hemoglobin polymers. When assessing a hyperbilirubinemic patient it is critical to localize the underlying cause.

Bilirubin is the major product of the degradation of heme-containing compounds by cells of the *mononuclear phagocyte system*. Bilirubin is released from the mononuclear phagocyte system and is transported in the plasma. The bilirubin is reversibly bound to albumin as it is water insoluble. The unconjugated bilirubin is absorbed through the hepatocyte cell membranes and is bound to glucuronic acid (conjugation). Conjugated bilirubin is water soluble and is actively excreted from the hepatocytes into the bile canaliculi, eventually being excreted into the intestines. Once in the intestine some of the bilirubin is converted into urobilinogen by bacteria. Some of the urobilinogen is reabsorbed from the intestines, but most of this is immediately reexcreted by the liver. When

exposed to air the urobilinogen remaining in the intestines is altered and oxidized into the brown pigment sterocobilin.[23]

Prehepatic hyperbilirubinemia is caused by increased production of bilirubin as a result of hemolysis. The liver has a large reserve capacity for bilirubin excretion so, for hemolysis to cause hyperbilirubinemia, hepatic bilirubin clearance must be decreased.[55] This occurs if the hemolytic anemia results in hepatocyte dysfunction because of hypoxia. If hepatic hypoxia occurs serum hepatic enzymes activities are often increased. Prehepatic hyperbilirubinemia is mainly distinguished from other causes of hyperbilirubinemia by the presence of severe anemia. Other supportive evidence includes the presence of a regenerative erythroid response, characteristic changes in red blood cell morphology, and possibly the detection of red blood cell bound antibodies.[56]

Hepatic hyperbilirubinemia is caused by a decreased rate of hepatocyte bilirubin uptake, conjugation, or excretion (as a result of *intrahepatic cholestasis*). Usually, hepatocyte dysfunction and intrahepatic cholestasis occur concurrently. Hepatic enzyme activities (both hepatocellular leakage markers and cholestatic markers) are often increased, although they can also be increased with both prehepatic and posthepatic hyperbilirubinemia. Because of the hepatic reserve capacity, hepatic disease must be severe in order to cause hyperbilirubinemia. A range of primary and secondary hepatopathies can cause hepatic hyperbilirubinemia. Hepatic hyperbilirubinemia can usually be distinguished from prehepatic hyperbilirubinemia by assessment of the patient's hematocrit, and from posthepatic hyperbilirubinemia by abdominal ultrasound. Other markers of hepatic insufficiency, when present, provide additional support for the presence of hepatic hyperbilirubinemia.

Posthepatic hyperbilirubinemia is a result of extrahepatic bile duct obstruction. This is often caused by pancreatic inflammation or, much less commonly, neoplasia. The main diagnostic tool for documenting extrahepatic bile duct obstruction is abdominal ultrasound. Typically, extrahepatic bile duct obstruction leads to dramatic increases in serum cholestatic enzyme activities (compared to hepatocellular leakage enzyme activities) and hypercholesterolemia. When the bile duct is completely obstructed, acholic (pale-colored) feces may be noted. Rupture of the biliary tract frequently leads to hyperbilirubinemia as bilirubin accumulates in the abdomen.

It is possible to measure the concentration of serum conjugated bilirubin. However, this test is not considered to be clinically useful for distinguishing between prehepatic, hepatic, or posthepatic hyperbilirubinemia, and is thus rarely performed.

Bilirubin can covalently (nonreversibly) bind to albumin. This biliprotein cannot be cleared by the liver and thus persists in the plasma. Biliprotein has a serum half-life comparable to albumin. This is of clinical importance because it means hyperbilirubinemia (and icterus) may persist for several weeks after the resolution of its cause.[57]

Bile acids (or bile salts when they are deionized) are formed from cholesterol in the liver and are the major constituent of bile. *Serum bile acids* (SBAs) measurement is a useful test of liver function in dogs and cats. SBAs are either measured as a fasting sample (after withholding food for 12 hours) or by collecting paired fasting and 2-hour postprandial samples.[58] Both of these tests are simple to perform and safe. Enzymatic measurement of the concentration of total bile acids in serum has become widely available and has replaced other techniques such as radioimmunoassays.[59,60] Once collected, the samples of serum can be stored at room temperature, making it possible to send them to an outside laboratory for evaluation. Lipemia and hemolysis of the blood samples should be avoided as both can interfere with the assay. Increased SBA concentrations

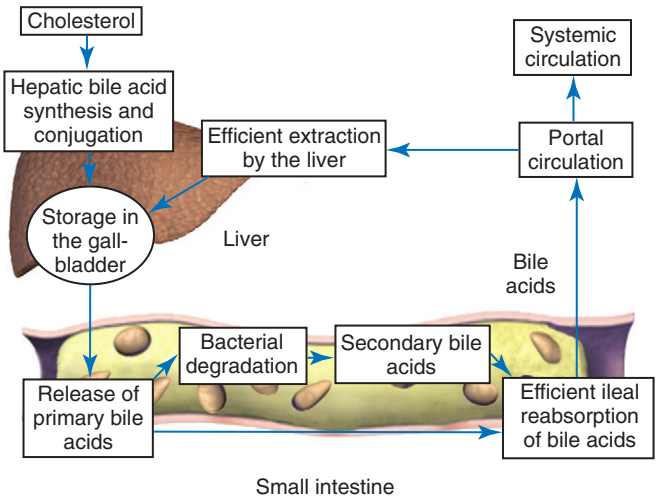

Figure 61-6 The enterohepatic circulation of bile acids.

(fasting or postprandial) suggest hepatic dysfunction, PSS, or cholestasis, but they are not specific for any particular liver disease.

Bile acids are exclusively synthesized in the liver from cholesterol. Nearly all of the bile acids that are produced by the hepatocytes are conjugated to an amino acid. In both dogs and cats conjugation is primarily to taurine, but dogs may also convert to a conjugation with glycine.[61] In contrast, even taurine depleted cats conjugate their bile acids almost exclusively to taurine.[62] The conjugated bile acids produced by the liver are called *primary bile acids*. These are secreted in the bile, and then stored in the gallbladder. *Cholecystokinin* is released from endocrine cells in the small intestine. This hormone stimulates gallbladder contraction and the flow of bile into the duodenum. When the gallbladder contracts the bile acids are released into the intestines. Spontaneous gallbladder contraction also occurs during the interdigestive phase.[63] Bile acids act as ionic detergents, aiding the emulsification of dietary lipids and their subsequent intestinal absorption in micelles.[64]

Bile acids are recycled in a process known as *enterohepatic circulation* (Figure 61-6). Primary bile acids are lipid insoluble and thus are only absorbed from the intestines when they bind to specific high affinity ileal mucosal receptors.[64] This ileal reabsorption is very efficient. The reabsorbed bile acids enter the portal circulation and upon reaching the liver they are efficiently extracted from the plasma and subsequently reexcreted. The total bile acids pool can be recirculated several times in a day. Consequently, the rate of hepatic bile acid synthesis and the fasting serum bile acids concentration in dogs and cats with normal hepatic function is low. Because of the increased release of stored bile acids during the postprandial period, small increases in total SBA concentration occur in animals with normal hepatic function.

Primary conjugated bile acids can undergo bacterial deconjugation in the intestinal lumen. The resulting unconjugated bile acids are called *secondary bile acids*. These are readily absorbed from the colon by passive diffusion. First-pass extraction and reexcretion of secondary bile acids is less efficient than that for primary bile acids. Consequently, secondary (unconjugated) bile acids are often present in postprandial serum samples.[65]

Hepatobiliary disease can cause increased SBA concentrations by interfering with hepatocellular function, by causing decreased bile flow (cholestasis), or by altering the hepatoportal blood flow. The main clinical use of SBA measurement is to assess hepatic function in patients suspected to have hepatic disease, with serum

bilirubin concentrations that are within the reference interval. Measurement of postprandial SBA concentration does not seem to have an advantage over fasting SBA concentrations or *vice versa*. Sensitivity can be increased by collecting paired preprandial and two-hour postprandial samples.[66] Numerous studies show that SBA measurement is a useful test for diagnosing hepatobiliary disease, including PSS in dogs and cats.[41,66-70] A recent study found the sensitivity of fasting SBA measurement for diagnosing PSS (using a cutoff value of 20 µmol/L) to be 93% for dogs and 100% for cats. The reported specificities were 67% for dogs and 71% for cats.[41] However, the sensitivity of SBA measurement for detecting hepatic insufficiency is lower than that for detecting PSS.

Measurements of SBA concentrations have several limitations. First, this test does not allow differentiation between various types of hepatobiliary disease. Also, measurement of serum bile acids in a patient with proven cholestasis is of no clinical benefit. Additionally, there is limited utility in measuring SBAs concentrations in patients with hyperbilirubinemia, although potentially SBA measurement could be useful in distinguishing prehepatic from hepatic or posthepatic causes of hyperbilirubinemia. With prehepatic causes of hyperbilirubinemia, the bile acid concentrations should be within the reference interval. However, in most cases prehepatic hyperbilirubinemia is easily distinguished by the presence of severe anemia. It should also be noted that the magnitude of increases of SBA concentration are not correlated with prognosis or disease severity.

It is important to note that fasting SBA concentrations may be higher than the upper limit of the reference interval or higher than the postprandial value because of spontaneous contraction of the gallbladder in the fasting state, or because of delayed gastric emptying. This could result in an increased fasting SBA concentration in the absence of hepatobiliary disease. Increased fasting and postprandial serum bile acids concentrations can be the result of increased bacterial deconjugation of primary bile acids into secondary bile acids.[71] False-negative results may occur if enterohepatic circulation of bile acids does not occur from a lack of gallbladder contraction. This could be a problem if a patient is anorectic, does not eat enough food, consumes a diet with insufficient protein or fat, vomits the test meal, or has delayed gastric emptying.

Ceruletide is an injectable cholecystokinin analogue that has been used to stimulate gallbladder contraction when using SBA measurement to diagnose hepatobiliary disease.[72,73] This test circumvents many of the factors that influence postprandial SBA concentrations. *Urine bile acids* measurement has been described in dogs and cats. The diagnostic performance was similar to that of SBA measurement in both species. This test does not offer any advantages over SBA measurement.[74-77]

Excretion of exogenous tracers, such as the anionic cholephilic dyes, bromsulphalein, and indocyanine green have been used historically to assess hepatic function in veterinary patients. However, these tests are considered unreliable and have been replaced by the measurement of SBA concentrations.

The metabolism of exogenous substances can be used to assess liver function. A variety of substances have been investigated as markers for hepatic metabolism in human medicine. Assessment of the metabolism of *aminopyrine* has been investigated in dogs and to a lesser extent in cats. The ^{13}C-labeled aminopyrine demethylation blood test involves intravenous administration of ^{13}C-labeled aminopyrine to the subject. The aminopyrine is metabolized by the liver, resulting in the production of $^{13}CO_2$. This is measured in the blood by fractional mass spectroscopy.[78,79] Further investigation of the utility of this test for assessment of liver function is needed. A recent study did not support the use of a ^{13}C-labeled galactose breath test for assessment of liver function in dogs.[80]

The metabolism of endogenous substances has been investigated to find possible markers of hepatic cellular metabolism. Dogs with hepatic disease (hepatitis and neoplasia) had significantly higher serum L-phenylalanine concentrations than did healthy dogs and those with nonhepatic diseases.[81] Further investigations are needed to determine the utility of these tests for assessing liver function in veterinary patients.

Urinalysis

Urine specific gravity can be decreased in patients with hepatic insufficiency or PSS. This can be caused by an inability to fully concentrate urine, resulting in PU, or from primary PD.

Bilirubin is commonly measured semiquantitatively in canine and feline urine using urine dipsticks. Bilirubinuria (<2+ on a dipstick) can be a normal finding in dogs (especially males).[82] Bilirubinuria in dogs without hemolytic or hepatobiliary disease can occur as a consequence of the loss of unconjugated bilirubin that is bound to albumin in proteinuric patients and renal filtration of small amounts of conjugated bilirubin that has leaked from the liver. Additionally, the renal tubular cells of male dogs have the enzymes needed to produce and conjugate bilirubin. As cats have a higher renal threshold for bilirubin than dogs, bilirubinuria should always be considered abnormal in cats. Bilirubinuria in cats and excessive bilirubinuria in dogs implies hemolytic or hepatobiliary disease. Because dogs have a relatively low renal threshold for bilirubin, bilirubinuria is often detected before bilirubinemia or jaundice.

Ammonium biurate crystals are detected in the urine sediment by light microscopy. Uric acid is a product of purine catabolism and is converted to allantoic acid by hepatic urate oxidase. In cases with severe hepatic insufficiency or PSS, the serum uric acid concentration may be higher than the renal threshold. This combined with hyperammonemia may lead to ammonium biurate precipitation in the urine. Urate urolithiasis seems to be more common in patients with PSS than those with other types of hepatic dysfunction. Between 40% and 70% of dogs with PSS were found to have urate crystalluria.[83] However, it should be noted that urate crystalluria is not specific for hepatobiliary disease.

Hematology

The erythrocyte series may be affected by hepatobiliary disease, resulting in erythrocyte dysmorphias and anemia. These abnormalities are suggestive of, but are not specific for, hepatobiliary disease.

Patients with hepatobiliary disease can be anemic as a result of blood loss, in which case signs of a regenerative response are normally present within 3 days of hemorrhage. Acute, severe hemorrhage may occur in patients with hepatobiliary disease following invasive procedures such as liver biopsy or as a consequence of hemorrhage from a hepatic neoplasm or hepatic rupture. Less-severe anemia may occur as a result of GI bleeding.[84] Chronic GI blood loss may eventually lead to iron-deficiency anemia. This is characterized by microcytic hypochromic erythrocytes and a variable regenerative response. Additionally, hepatobiliary disease may lead to anemia of chronic disease, which is typically nonregenerative with normocytic normochromic erythrocytes.

Red blood cell morphologic changes are sometimes observed in dogs with hepatobiliary disease. Poikilocytosis, characterized by the presence of acanthocytes and target cells, may be seen in patients with chronic hepatic disease. This is thought to be a result of altered phospholipid metabolism. Patients with PSS can have microcytic red blood cells. This is more common in dogs than in

Table 61-3 Typical Patterns of Clinicopathologic Changes Associated with Liver Disease in the Dog

Laboratory Test	Acute Hepatitis/ Hepatic Necrosis	Chronic Hepatitis	Cirrhosis	CPSS	Biliary Tract Obstruction	Nonobstructive Biliary Tract Disease	Hepatic Neoplasia
ALT	↑↑-↑↑↑	↑-↑↑↑	N-↑↑	N-↑	N-↑↑	N-↑↑	N-↑↑
ALP	↑-↑↑	↑-↑↑	N-↑↑	N-↑	↑↑↑	↑-↑↑↑	N-↑↑
Total bilirubin	N-↑↑↑	N-↑↑	N-↑↑↑	N	↑↑-↑↑↑	N	N-↑
Preprandial SBA	N-↑↑	N-↑↑	↑-↑↑↑	N-↑↑	↑↑-↑↑↑	N	N-↑
Postprandial SBA	N-↑↑	N-↑↑	↑-↑↑↑	↑↑-↑↑↑	↑↑-↑↑↑	N	N-↑
Ammonia	N-↑↑	N-↑↑	N-↑↑	↑-↑↑↑	N	N	N-↑

↑, Mild increase; ↑↑, moderate increase; ↑↑↑, severe increase; ALP, serum alkaline phosphatase activity; ALT, serum alanine aminotransferase activity; CPSS, congenital portosystemic shunt; N, within the reference interval; SBA, serum bile acid concentration.

cats.[83] Microcytosis also occasionally occurs in patients with hepatocellular disease. Altered iron metabolism is thought to lead to a delay in red blood cell precursors gaining a sufficient amount of hemoglobin to be released into the circulation. This delay leads to the precursors undergoing an extra cell division in the bone marrow, resulting in microcytosis.[85] Microangiopathy can occur as a result of hepatic neoplasia or DIC, and may lead to the formation of schistocytes.

The leukocyte series may be affected by hepatobiliary disease in a variety of ways. The resultant abnormalities are inconsistent and are not specific for hepatobiliary disease. Leukocytosis, leukopenia, and sometimes an inflammatory leukogram may be present when infectious and, less commonly, inflammatory or neoplastic processes affect the hepatobiliary system. A leukocytosis was found to be present in 44% of dogs with chronic hepatitis.[86]

The thrombocyte series is occasionally affected by hepatobiliary disease, but changes are both inconsistent and nonspecific. Mild to moderate thrombocytopenia may occur in patients with severe liver disease.[86] This may be the result of a decreased production of thrombopoietin by the liver. Disseminated intravascular coagulopathy associated with liver disease also may lead to thrombocytopenia. Additionally, infectious diseases affecting the liver, such as leptospirosis may result in thrombocytopenia.[87]

Other Diagnostic Tests for Hepatobiliary Disease

Genetic testing for copper hepatotoxicosis has been developed in Bedlington Terriers. Affected Bedlington Terriers have an autosomal recessive defect of their COMMD1 gene. Dogs with a homozygous affected genotype develop copper hepatopathy as a result of impaired biliary excretion of copper. Initially, a microsatellite marker that is in linkage disequilibrium with the mutation was discovered and used to identify affected dogs and select dogs homozygous unaffected dogs for breeding.[88] Subsequently, a mutation of the COMMD1 gene (a deletion of exon 2) was identified as the cause of the condition in the majority of Bedlington Terriers.[89] A genetic test for this disease has become commercially available (VetGen, Ann Arbor, MI). This test is run alongside the linked marker as a small proportion of Bedlington Terriers do not have the deletion but are nevertheless affected by the disease. These dogs are likely to have a rare second mutation of their COMMD1 gene which the linkage markers may track.

Hyaluronic acid is a major constituent of the ECM and hyaluronic acid (HA) concentration in blood has been used as a marker for hepatic fibrosis in humans. A recent study investigated the use of HA concentration as a marker for hepatic disease in dogs.[90] This study found that blood HA concentrations were significantly higher in dogs with liver disease than in dogs with extrahepatic disease, and were higher in dogs with cirrhotic liver disease than in dogs with noncirrhotic liver disease. Blood HA concentration may prove be a useful marker for hepatic fibrosis in dogs but further studies are necessary to evaluate its clinical utility.

Patterns of Clinicopathologic Change Associated with Liver Disease

Histopathologic analysis of liver biopsies or identification of a shunting blood vessel is often required to definitively diagnose hepatic disease. However, the pattern of laboratory test abnormalities, particularly when interpreted in conjunction with the patient's clinical presentation, and the results of diagnostic imaging, can increase or decrease a clinician's index of suspicion for specific liver diseases (Table 61-3). It is important to note that there is considerable overlap between the patterns for different diseases. To avoid misinterpretation and misdiagnosis when evaluating a patient for liver disease, it is essential to consider the limitations of the laboratory tests discussed above.

Diagnostic Imaging of the Liver

Diagnostic imaging is an important part of the investigation of hepatobiliary disease in dogs and cats. Diagnostic imaging may help to determine whether or not hepatobiliary disease is present, identify the cause of a secondary hepatopathy, aid in the diagnosis of specific hepatobiliary diseases, and provide prognostic information. However, with the exception of diagnosis of a PSS, imaging seldom yields a definitive diagnosis. Radiography and abdominal ultrasound are the most frequently used imaging modalities for assessment of the hepatobiliary system in dogs and cats, but alternative imaging techniques are now being used more frequently.

Abdominal Radiographs

Abdominal radiographs allow assessment of hepatic size, shape, opacity, and location in most patients.[91] Radiography may also allow identification of extrahepatic abnormalities that affect the liver. However, radiographs provide limited information about the hepatic parenchyma. It is important to note that patients with hepatobiliary disease often have normal abdominal radiographs.

Radiography allows subjective assessment of liver size. Cranial displacement of the gastric axis may be observed on lateral abdominal radiographs when microhepatia is present. However, subtle microhepatia is unlikely to be appreciated radiographically. PSSs and hepatic cirrhosis are the most common conditions causing microhepatia. Mild bilateral renomegaly may also be

appreciated radiographically for patients with PSS. Urate uroliths can be radiolucent so they might not be visible on plain abdominal radiographs.

Hepatomegaly can be generalized or focal. Generalized hepatomegaly can be caused by a number of conditions including neoplasia, vacuolar hepatopathies, congestion, or amyloidosis. Focal hepatomegaly can be caused by neoplasia, abscesses, granulomas, or a liver lobe torsion. Radiographic signs associated with hepatomegaly are rounded hepatic borders, caudal displacement of the gastric axis, and extension of the hepatic silhouette beyond the costal arch. Radiography does not allow appreciation of mild hepatomegaly. Additionally, it can be normal for the hepatic silhouette to extend beyond the costal arch in brachycephalic breeds, chondrodystrophic breeds, neonatal animals, or geriatric animals.[91]

The liver is normally appreciated as an area of homogenous soft-tissue opacity on radiographs. Radiolucent areas within the liver indicate accumulation of gas within the hepatic parenchyma, biliary tract, or portal vasculature. Gas in the parenchyma of the liver can be associated with an hepatic abscess.[92] Gas in or around the gallbladder has been reported in dogs with emphysematous cholecystitis.[93] Although uncommon in dogs and cats, if choleliths or choledocholiths contain enough calcium, they may be appreciated as mineral opacities within the hepatic silhouette.[94] Mineralization of the gallbladder wall can be associated with a biliary adenocarcinoma in the dog.[95] Parenchymal mineralization can be associated with granulomas, abscesses,[96] hematomas, neoplasia, or hepatic necrosis.[91]

Angiography allows the visualization of the hepatoportal vasculature, including abnormal vessels. This often provides a definitive diagnosis of PSS and is indicated in patients that are suspected of having a PSS, where the shunt cannot be adequately evaluated by abdominal ultrasound. Anatomical characterization of congenital PSS is important when planning attenuation, and angiographic procedures often allow this. There are several techniques for mesenteric portography. Operative mesenteric portography is commonly performed immediately prior to surgical attenuation of a congenital PSS and involves catheterization of a mesenteric vein and injection of a contrast agent. Operative contrast portography allows evaluation of the portal vasculature before and after shunt attenuation. This technique has the disadvantage of being relatively invasive. Cranial mesenteric portography can be accomplished less invasively by using ultrasound guidance to percutaneously catheterize the splenic vein.[97] However, this can be technically demanding and may not be possible in smaller patients. Transvenous retrograde portography has been described and involves the catheterization of the jugular vein.[98] This technique allows selective catheterization of the shunting vessel and measurement of portal pressures (Figure 61-7). Transvenous retrograde portography has been applied during percutaneous transjugular coil embolization of intrahepatic shunts.[99] Percutaneous splenoportography involves percutaneous injection of contrast media into the spleen. This technique is simple to perform, but there is a risk of complications such as splenic infarction or hemorrhage.

Abdominal Ultrasound

Abdominal ultrasonography is the most commonly used imaging modality for evaluating small animal patients with suspected hepatobiliary disease. Ultrasonography allows assessment of the hepatic parenchyma and biliary tract. Evidence of extrahepatic disease causing a secondary hepatopathy may also be detected. Additionally, ultrasound guidance is often used when collecting samples for cytologic and histologic evaluation of the liver.

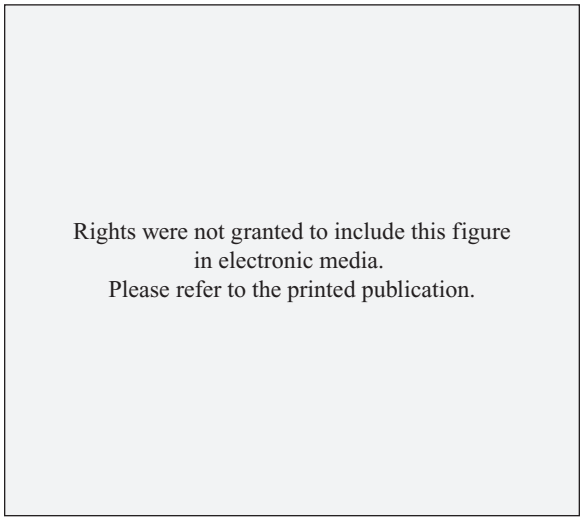

Figure 61-7 Lateral transvenous retrograde portogram of a dog with a single extrahepatic shunt. A balloon-tipped catheter positioned immediately cranial to the diaphragm was used for contrast injection. There is retrograde filling of some hepatic veins (*arrowheads*), there is also a large PSS that filled in a retrograde fashion (*arrows*). (From Miller MW, Fossum TW, Bahr AM: Transvenous retrograde portography for identification and characterization of portosystemic shunts in dogs. *J Am Vet Med Assoc* 221:1586, 2002.)

The size of the liver can be subjectively assessed by abdominal ultrasonography. The findings of a small liver and cranial displacement of the stomach suggest microhepatia. Hepatomegaly is another subjective finding and can be generalized or focal. The finding of rounded liver lobe margins suggests hepatomegaly.

Hepatic parenchymal changes can be classified as being diffuse, multifocal, or focal. A wide variety of disease processes can cause diffuse changes to the hepatic parenchyma. These changes can be isoechoic, hypoechoic, hyperechoic, or of mixed echogenicity. In some cases the architecture of the liver will not be altered, but in other cases changes will occur. Examples of diseases in which the echogenicity of the hepatic parenchyma is diffusely changed but no changes in architecture occur include cholangitis, neoplasia, hepatic lipidosis, other vacuolar hepatopathies, toxic hepatopathy, and early micronodular hyperplasia with various degrees of fibrosis.[100] Hyperechogenicity of the liver compared to the falciform fat, poor visualization of the intrahepatic blood vessels, and increased attenuation of the ultrasound beam have been used as criteria for the sonographic diagnosis of feline hepatic lipidosis.[101] Diseases where the hepatic architecture is altered are easier to detect sonographically. These include neoplasia, micronodular hyperplasia, and chronic hepatitis with fibrosis. Cystic structures, abscesses, hematomas, and granulomas are examples of focal parenchymal liver disease. These lesions are usually easily detected sonographically. Sonography seldom allows a definitive diagnosis of hepatic parenchymal disease to be made. In one study the overall accuracy of ultrasound for discrimination among different categories of diffuse liver disease was 36.5% for dogs and 54.6% for cats. Hepatic lipidosis in cats could be diagnosed slightly more accurately than other diffuse hepatic diseases.[102] Cytologic or histologic evaluation of a hepatic tissue sample is usually needed to make a definitive diagnosis.

Hepatic neoplasia, whether primary or metastatic, can be diffuse, multifocal, or focal in its distribution. Round cell tumors are the most likely tumor type to diffusely infiltrate the liver. These tumors can cause hypoechoic, hyperechoic, or mixed-echoic changes, or

may not affect the echogenicity of the liver at all. Neoplasia can also lead to the appearance of nodules within the hepatic parenchyma. Malignant liver nodules have a variable appearance and size and can be difficult to distinguish from nonmalignant conditions such as cysts, hematomas, benign hyperplastic nodules, granulomas, or abscesses. The finding of one or more target lesions in the liver or spleen had a positive predictive value of 74% for detecting malignancy, and thus should not be considered a specific finding.[103] Cytologic or histologic evaluation of a tissue sample is needed to differentiate between malignant and benign liver nodules. Tumors, such as hepatoma or hepatocellular carcinoma, can also focally infiltrate the liver.

Contrast-enhanced harmonic ultrasound allows assessment of tissue perfusion patterns. Gas-filled microbubbles are administered intravenously to the patient. The microbubbles are relatively echogenic. When they reach the tissue of interest, they produce a more potent harmonic signal than the surrounding tissue. This technique allows enhanced differentiation between tissues with varying perfusion patterns. In one study the sensitivity of contrast enhanced ultrasound for differentiation between benign and malignant liver nodules in dogs was reported to be 100% and the specificity was reported to be 94.1%.[104]

Sonography is also a valuable tool for the evaluation of the biliary system. Biliary disease can be classified as being obstructive or nonobstructive.

The term *cholangitis* refers to a group of nonobstructive biliary diseases, which are more common in cats than in dogs. Typical ultrasound findings in cats include a hypoechoic hepatic parenchyma and prominent portal vasculature.[105] Additional findings can include evidence of pancreatic inflammation, thickening of the gallbladder wall, and dilation of the intrahepatic and extrahepatic biliary system. It is important to note these changes are not always present. Cytologic or histologic confirmation and bacterial culture are needed to confirm this diagnosis. Generalized gallbladder wall thickening can occur as a result of cholecystitis, cholangitis, or hepatitis. However, the gallbladder wall can also appear to be thickened when peritoneal effusion or hypoproteinemia are present. Gall bladder wall masses can be identified sonographically as a focal thickening of the gallbladder wall. Sonography has also been used to assess gallbladder motility in dogs.[106] It should be noted that gravity dependent gallbladder sludge can be found in dogs without hepatobiliary disease, so this finding should be considered incidental.[107]

Abdominal ultrasound is the most commonly used imaging modality for the detection of biliary obstruction in dogs and cats. Findings consistent with biliary obstruction include common bile duct distention, intra- and extrahepatic bile duct distention, and/or gallbladder dilation. A retrospective study showed that common bile duct dilation greater than 4 mm was 97% sensitive for the detection of biliary obstruction in cats.[108] Sonography can also aid in identifying the cause of biliary obstruction. Biliary obstruction can be classified as being luminal or extraluminal. Extraluminal causes include nonneoplastic pancreatic disease, abdominal adhesions, and, rarely, pancreatic neoplasia. Luminal causes include gallbladder mucocele, biliary neoplasia, inflammation, and cholecystolithiasis. Biliary tract obstruction can progress to biliary rupture and bile peritonitis. Sonographic signs of biliary rupture include loss of gallbladder wall continuity, free peritoneal fluid, and signs of localized peritonitis. Gallbladder mucoceles occur in the dog, but have not been described in cats. Mucoceles have a variable sonographic appearance; typical findings include a stellate or finely striated bile pattern with a hypoechoic rim, which is not gravity dependent, and

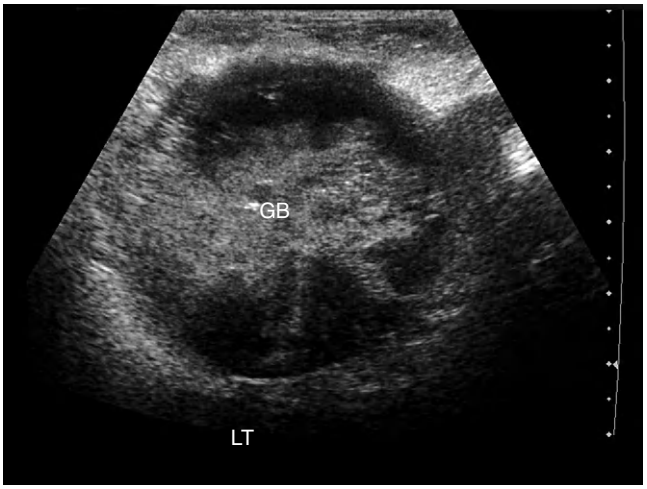

Figure 61-8 Abdominal ultrasound image of a dog with a gallbladder mucocele. There is organized hyperechoic bile within the distended gallbladder (*GB*). The periphery of the bile is stellate in appearance and the gallbladder wall is thickened.

distention of the gallbladder (Figure 61-8). Gallbladder mucoceles can also lead to biliary obstruction, which might also be appreciated sonographically. The sensitivity of ultrasound for the detection of a gallbladder wall rupture in dogs with gallbladder mucoceles is reported to be 85.7%.[109]

Abdominal ultrasound can be used to assess the liver for vascular disease. Congenital PSS is classified as being intrahepatic or extrahepatic. Although angiographic techniques are considered to be the gold standard for the detection and characterization of PSS, abdominal ultrasound is being used increasingly for this purpose. Sonographic assessment of the portal vasculature is time-consuming and highly operator dependent. Because of this there should be a high index of suspicion for PSS before performing these studies. Secondary findings consistent with PSS include mild bilateral renomegaly, urolithiasis (because of urate crystalluria), and microhepatia. Ascites and hepatic parenchymal changes are not consistent with congenital PSS. Extrahepatic shunts typically occur in small-breed dogs and arise from the splenic vein or the right gastric vein while intrahepatic shunts typically occur in larger breeds of dogs and arise from the right or left portal branch. An intrahepatic PSS is usually easier to detect sonographically than an extrahepatic PSS in dogs. Cats typically have single extrahepatic shunts with a wider degree of anatomical variation than in the dog. Ultrasonography has been reported to have a sensitivity of 92% and a specificity of 98% for detecting PSS in dogs.[110] Portal hypertension can develop as a result of chronic hepatitis with fibrosis, hepatic arterioportal fistulas, portal vein thrombosis, primary portal vein hypoplasia, extraluminal compression of the portal vein, or after ligation of a congenital PSS. The finding of hepatofugal or reduced velocity hepatopetal blood flow using Doppler ultrasound is consistent with portal hypertension.[111] However, not all patients with portal hypertension will have these changes. Ascites frequently, but not always, develops secondary to portal hypertension and this can be readily detected on abdominal ultrasound examination. Acquired portosystemic collaterals (also known as acquired PSS) may develop when sustained prehepatic or hepatic portal hypertension is present.[112] Sonography may allow detection of portal hypertension and APSCAPSC although APSC vessels are more difficult to identify than congenital PSS. Posthepatic portal hypertension does not result in the development of

APSC vessels, but can lead to a distention of hepatic veins and ascites.

Nuclear Scintigraphy

Nuclear scintigraphy involves administering a radioactive tracer substance (radiopharmaceutical) to the patient, which localizes to a specific organ or tissue. The radioactive decay of this substance is detected by a gamma camera and used to form images. Scintigraphy has been used to detect PSS and to assess gallbladder emptying in small animals. However, specialized equipment and a license for the use of radioisotopes are required. Consequently, availability of this imaging modality is currently limited to academic institutions and specialty referral hospitals.

Technetium-99m pertechnetate is the most commonly used radiopharmaceutical for assessing the portal circulation of small animal patients. Two techniques have been described: per-rectal portal scintigraphy and transsplenic portal scintigraphy. By analyzing the radiation emitted from regions of interest drawn over the patient's liver and heart, PSS can be detected and a shunt fraction can be calculated. This allows for the minimally invasive diagnosis of PSS, differentiation of PSS from portal vein hypoplasia without portal hypotension (previously known as microvascular dysplasia), and comparison of the degree of shunting before and after shunt attenuation. Transsplenic portal scintigraphy is preferred over per-rectal portal scintigraphy as it is simpler to perform, uses lower doses of the radiopharmaceutical, and is more sensitive (Figure 61-9). Transsplenic portal scintigraphy is 100% sensitive and specific for the diagnosis of congenital PSS, and significantly more likely than per-rectal portal scintigraphy to detect shunt number and termination in dogs.[113]

Nuclear scintigraphy has been used to quantify liver function and to assess biliary tract patency in dogs. In a retrospective study hepatobiliary scintigraphy was found to be 83% sensitive and 94% specific for the detection of extrahepatic biliary obstruction in dogs and cats.[114]

Computed Tomography and Magnetic Resonance Imaging

Computed tomography (CT) (Figure 61-10) and magnetic resonance imaging (MRI) have been used to detect hepatic parenchymal neoplasia in humans. Compared to abdominal ultrasound these techniques have an improved accuracy for the diagnosis of hepatic neoplasia in humans. However, there is limited data in the veterinary literature evaluating their diagnostic performance. In one study the diagnostic accuracy of CT for detecting hepatic masses was not found to be significantly different from that of abdominal ultrasound in dogs.[115] In another study MRI was found to have a sensitivity of 100% and a specificity of 86% for the differentiation between benign and malignant liver lesions in dogs.[116]

CT angiography is being used increasingly in dogs for the diagnosis of congenital PSS and other hepatic vascular diseases. It offers the advantage of being less invasive than operative angiography, allows for improved assessment of the portal vasculature, and allows the creation of a three-dimensional reconstruction. The vasculature detail afforded by CT angiography is particularly useful when planning attenuation of a congenital PSS. The diagnostic utility of CT angiography for detecting and characterizing PSS in dogs was shown to compare favorably to that of other techniques, including surgical exploration.[117] Transsplenic CT portography has been described in dogs without PSS. This technique offers more intense enhancement of the splenic and portal veins than CT angiography.[118] MRI angiography diagnoses PSS in dogs with a sensitivity of 80% and a specificity of 100%.[119] The disadvantages of CT and MRI include their limited availability, cost, and the need for anesthesia.

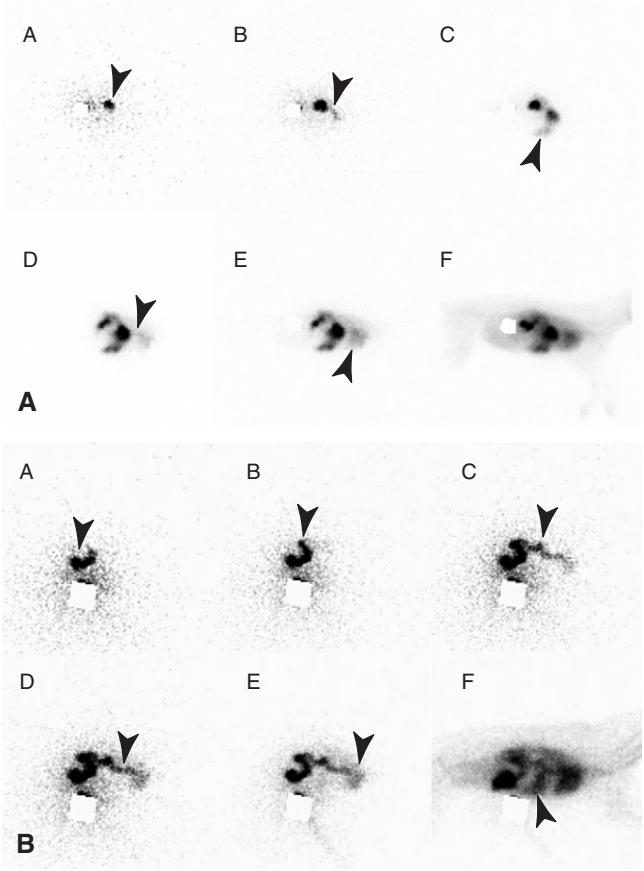

Figure 61-9 **A,** Transsplenic portal scintigraphy of a dog with normal portal vasculature. Images were acquired following ultrasound-guided intrasplenic injection of 2 mCi ^{99m}technetium pertechnetate. The radionuclide exits the spleen via blood flow in the splenic vein then enters the portal circulation. Blood first reaches the liver before entering the caudal vena cava and heart. Frames a to e document progression of radionuclide from the spleen to the heart: (a) splenic injection site; (b) portal vein; (c) liver; (d) caudal vena cava; (e) heart. Frame f is a summed image providing anatomic landmarks for reference. **B,** Transsplenic portal scintigraphy of a dog with a portocaval shunt. Images were acquired following ultrasound-guided intrasplenic injection of 2 mCi ^{99m}technetium pertechnetate. The radionuclide exits the spleen via blood flow in the splenic vein then enters the portal circulation. Blood bypasses the liver and enters the caudal vena cava and heart. Frames a to e document progression of the radionuclide from the spleen to the heart: (a) splenic injection site; (b) portal vein; (c) shunting vessel; (d) caudal vena cava; (e) heart. Frame f is a summed image providing anatomic landmarks for reference. (Courtesy of Dr. Benjamin D. Young, Texas A&M University, College Station, TX.)

Cytologic Evaluation of the Liver

Although cytologic evaluation of the liver provides a definitive diagnosis, often histologic examination is also required. There are a variety of techniques to collect cytologic samples of the hepatobiliary system. Abdominal effusion, when present, can be collected percutaneously. Fine-needle aspirates (FNA) of the liver can be collected percutaneously under ultrasound guidance. Cholecystocentesis can also be performed percutaneously with ultrasound

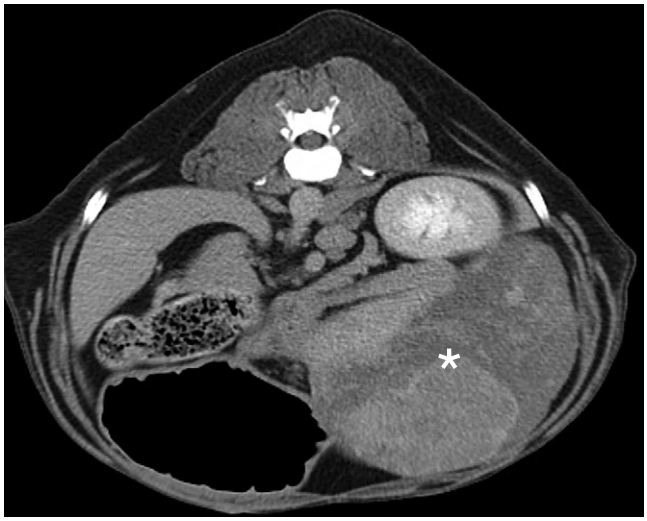

Figure 61-10 Abdominal computed tomography image of a dog with a massive hepatocellular carcinoma. There is a large irregularly shaped mass associated with the ventrolateral right side of the liver (*).

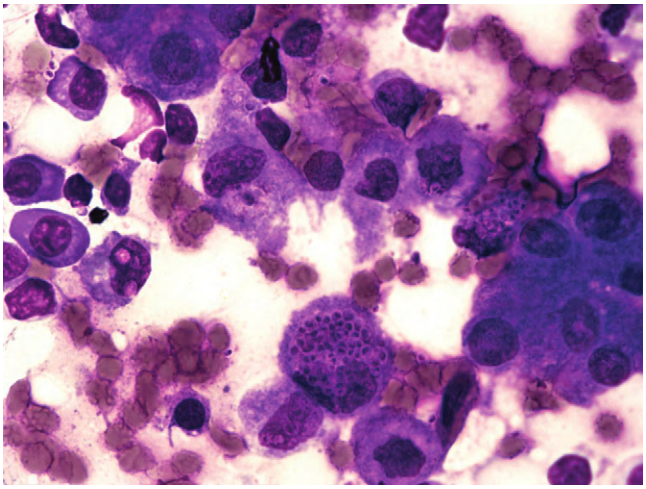

Figure 61-11 **Fine-needle aspirate from the liver of a cat with disseminated histoplasmosis.** Erythrocytes, hepatocytes, lymphocytes, plasma cells, and macrophages containing large numbers of *Histoplasma capsulatum* organisms can be seen (*). Diff-Quik 100× objective. (Courtesy of Dr. Kathrin F. Burke, Texas A&M University, College Station, TX.)

guidance. These techniques are minimally invasive and the risk of complications is relatively low but caution should be exercised in patients with bleeding disorders.

Liver disease can cause abdominal effusion by several mechanisms. In cases with hepatic insufficiency, severe hypoalbuminemia (<1.5 g/dL) can occur. This can lead to the formation of a pure transudate as the result of a reduced plasma colloid oncotic pressure. Increased capillary hydrostatic pressure because of portal hypertension may lead to formation of a pure or modified transudate. Hepatic neoplasia can also lead to a formation of a modified transudate. Biliary tract rupture can lead to bile peritonitis and abdominal effusion. An exudate with a bilirubin concentration greater than twice that of the plasma is suggestive of bile peritonitis.[120]

Cytologic evaluation of hepatic FNA can aid in making a diagnosis of liver disease. Suppurative, mixed inflammatory, lymphocytic and, more rarely, eosinophilic patterns of inflammation can be appreciated cytologically. Each pattern of inflammation suggests a group of possible diagnoses. The finding of dark green or black bile casts suggests cholestasis. Infectious diseases such as histoplasmosis can be definitively diagnosed based on the cytologic finding of the infectious agent (Figure 61-11). Hepatocellular vacuolation can be classified as being caused by lipid or not. Lipid vacuolation of hepatocytes is characterized by colorless cytoplasmic vacuoles. Severe lipid vacuolation is suggestive of hepatic lipidosis in cats (Figure 61-12). However, feline hepatic lipidosis often occurs secondary to another disease process. A group of cats with cytologic findings suggestive of hepatic lipidosis were reported to have underlying infiltrative liver disease.[121] Nonlipid vacuolation is characterized by generalized hepatocyte swelling and lacy vacuolation (Figure 61-13). Vacuolar hepatopathy occurs secondary to a wide variety of extrahepatic disease processes in dogs.[122] Metastatic tumors and round cell tumors, such as lymphoma (Figure 61-14), affecting the liver can often be diagnosed cytologically. Additionally, cytologic evaluation can aid in distinguishing liver nodules because of extramedullary hematopoiesis from those caused by neoplasia. However, it is not possible to distinguish hepatic nodular hyperplasia from hepatic adenoma or well-differentiated carcinoma cytologically. Some cases of hepatocellular carcinoma can be diagnosed cytologically if criteria for malignancy are present.

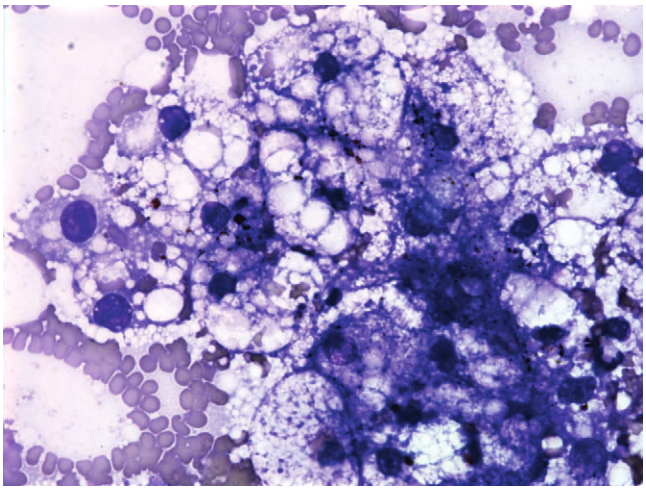

Figure 61-12 **Fine-needle aspirate from the liver of a cat with hepatic lipidosis.** The cytoplasm of the hepatocytes is severely distended by many variably sized clear vacuoles (both microvesicular and macrovesicular type) consistent with lipid that has been cleared during the staining procedure. Diff-Quik 100× objective. (Courtesy of Dr. Mark C. Johnson, Texas A&M University, College Station, TX.)

The findings above may aid in making a diagnosis of liver disease but are not a substitute for histopathologic analysis, as cytologic specimens do not allow assessment of the hepatic architecture. Furthermore, only a tiny proportion of the liver is sampled when cytologic samples are examined. These limitations are reflected by the results of a retrospective study that found the overall agreement between the histopathologic and cytologic diagnosis of liver disease to be 30.3% for dogs and 51.2% for cats.[123]

Cytologic evaluation of bile can also be useful for the diagnosis of biliary disorders, particularly in cats. World Small Animal Veterinary Association (WSAVA) Standards for the Clinical and Histological Diagnosis of Canine and Feline Liver Disease suggest that the cytologic evaluation of bile forms part of the minimum diagnostic requirement for cats with extrahepatic cholestasis and for dogs

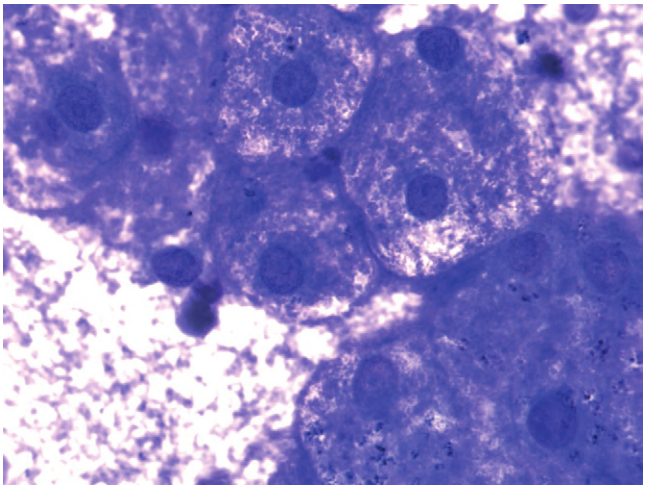

Figure 61-13 Fine-needle aspirate from the liver of a dog with glycogen deposition hepatopathy. Hepatocytes are distended and the cytoplasm is less dense than normal (cytoplasmic rarefaction) consistent with increased glycogen storage. Diff-Quik 100× objective. (Courtesy of Dr. Mark C. Johnson, Texas A&M University, College Station, TX.)

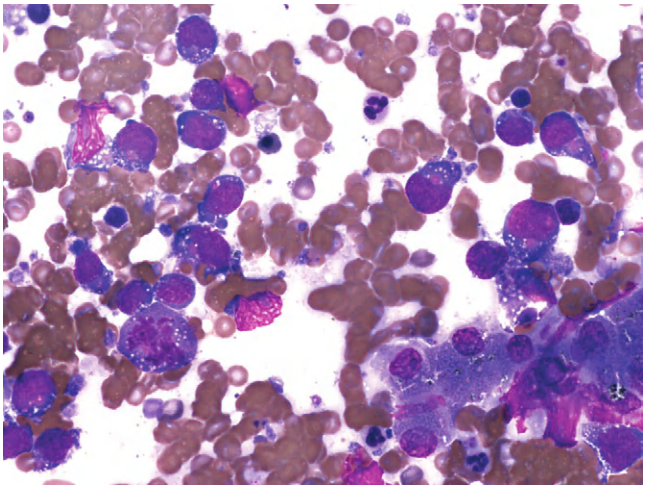

Figure 61-14 Fine-needle aspirate of the liver from a dog with T-Cell lymphoma (confirmed by immunohistochemistry. The predominant nucleated cell population consists of large atypical lymphoid cells. Hepatocytes (*lower right*) and occasional neutrophils are also present. Diff-Quik 60× objective. (Courtesy of Dr. Kathrin F. Burke, Texas A&M University, College Station, TX.)

and cats suspected to have cholangitis.[124] The finding of neutrophils and bacteria on bile cytology supports a diagnosis of feline neutrophilic cholangitis. Cytology is essential for the diagnosis of this disease, as cats with neutrophilic cholangitis may not have typical hepatic histopathologic changes and it can be difficult to distinguish these cats from those with lymphocytic cholangitis. Bile should also be submitted for aerobic and anaerobic bacteriologic culture.

Histopathologic Evaluation of the Liver

Histopathologic evaluation is required to make a definitive diagnosis of most liver diseases. Histopathologic evaluation of the liver allows a morphologic and sometimes an etiologic diagnosis to be made (see Chapter 29). In addition to routine staining with hematoxylin and eosin, a variety of other staining techniques can be employed to demonstrate hepatic pathology. To optimize the value of histopathologic evaluation of the liver, particular attention should be paid to specimen collection, specimen handling, and communication between the clinician and the pathologist.

Although liver biopsy is considered to be relatively safe, the patient should be assessed for bleeding disorders before this procedure. This assessment should include a platelet count, coagulation times, and a buccal mucosal bleeding time. Liver biopsies can be collected in a number of ways. Each method has advantages and disadvantages, and there is controversy in the veterinary literature as to which technique is optimal. Laparotomy allows collection of relatively large wedge biopsies, with direct visualization. This technique does not require specialized equipment or training, and excessive bleeding can be readily identified. However, laparotomy requires general anesthesia and is the most invasive biopsy technique. Percutaneous needle biopsy techniques have been described. These techniques may be possible under heavy sedation and are the least-invasive method for collecting liver biopsies. Ultrasound guidance is often used, allowing biopsy of focal lesions. It is also possible to biopsy tissue that is deeper within the hepatic parenchyma than is possible with other techniques. However, the specimens that are collected are relatively small and may be inadequate for accurate assessment in some patients. A prospective study showed that there was agreement between the histomorphologic diagnoses made upon examination of needle biopsies and those made on wedge biopsies collected during laparotomy or necropsy for only 48% of dogs and cats.[125] Excessive hemorrhage after biopsy may not be identified immediately. Laparoscopy allows collection of biopsies using forceps with laparoscopic guidance. This technique requires general anesthesia, but is less invasive than laparotomy. The biopsies collected are larger than needle biopsies and excessive bleeding can be visualized. However, laparoscopy requires specialized equipment and training. The use of biopsy forceps may result in crushing artifact and the tissue collected may be too superficial to identify lesions that lie deeper within the hepatic parenchyma.[126] Regardless of the technique used, a tiny proportion of the organ is sampled and, because liver disease can affect the hepatic parenchyma in a heterogeneous manner, sampling error is possible. To reduce the effect of sampling error, several biopsies from different areas of the liver should be collected and focal lesions should be specifically biopsied.

The clinician should provide the pathologist with all the pertinent information from the patient's history, physical examination findings, the results of laboratory testing, and the findings from diagnostic imaging. In turn the histomorphologic diagnosis that the pathologist makes should be interpreted by the clinician along with the other clinical data. When the histopathologic diagnosis does not fit the clinical picture, the pathologist should be consulted and when necessary a second opinion should be requested. Variation in the assessment of hepatic pathology between pathologists was highlighted by a study that found agreement between examiners for only 44% of needle biopsies and 65% of wedge biopsies examined.[125] Hopefully, the adoption of WSAVA Standards for the Clinical and Histological Diagnosis of Canine and Feline Liver Diseases since the aforementioned study will reduce this interobserver variation.

Quantification of hepatic metal concentrations requires submission of tissue for flame atomic absorption spectroscopy. Although zinc has a role as an antioxidant, hepatic copper and iron retention can lead to oxidative liver injury. Copper is the most frequently

measured of these metals and quantification is essential for the diagnosis of hepatic copper retention. These measurements are usually performed on freeze-dried pieces of liver. Specimens for metal measurement should not be stored in saline and should be kept in metal-free containers. Recently, it was shown that measurements of the concentration of copper and iron, but not zinc, can be ascertained from deparaffinized-archived liver tissue.[127]

BIOPSY TECHNIQUES

Keith Richter

Hepatobiliary diseases can be challenging to diagnose. Although diagnostic tests that employ biochemical, molecular biologic, serologic, functional, as well as imaging techniques are capable of establishing the etiology of some chronic or acute liver diseases, in most instances the gold standard for definitive diagnosis and the assessment of stage and severity of liver diseases is the histologic evaluation of a liver sample. Recent advances in imaging technology, the use of multiple imaging modalities, and newer biopsy methods have resulted in improvement in the ability to safely procure hepatic tissue for evaluation. There are several means of obtaining hepatic samples including fine-needle aspiration, ultrasound-guided biopsy, laparoscopy, and laparotomy. All techniques have both advantages and disadvantages, which should be carefully considered before choosing the appropriate sampling method.

Indications

Many biochemical tests are available to evaluate the anabolic and/or catabolic function of the liver and the hepatic circulation. These include measurement of concentrations of bile acids, ammonia, bilirubin, and the ability to excrete organic dyes. Other tests of hepatic function include measurement of serum albumin, glucose, urea nitrogen, and clotting factor analysis. Hepatic function can be markedly abnormal despite maintenance of the hepatocellular membrane and therefore normal serum activities of hepatic enzymes. Examples include PSSs, terminal cirrhosis, and metastatic hepatic neoplasia. Likewise, the liver can continue normal anabolic or catabolic function despite severe hepatocyte leakage of intracellular enzymes because of its marked reserve capacity. This can occur, for example, in certain cases of hepatocellular necrosis, blunt abdominal trauma, or primary hepatic neoplasia. Thus, the limitations of serum hepatic enzyme activities must be taken into consideration. Hepatocellular leakage enzyme activities include ALT and AST. Enzyme activities that increase with biliary tract obstruction include serum ALP and GGT.

No laboratory test identifies a specific problem, helps determine specific therapeutic management, or predicts an outcome. This is because different diseases produce similar alterations in hepatic function or in laboratory tests. Once biochemical tests identify the presence of hepatic disease, the diagnosis must be pursued further. In some instances, diagnostic imaging can reveal specific abnormalities (e.g., PSSs and extrahepatic bile duct obstruction). When results of imaging do not give a specific etiology, the next step is often to pursue a morphologic diagnosis obtained by analysis of a biopsy specimen. Often it is a judgment call as to when to pursue hepatic biopsy. In cases with severe clinical signs and/or severe biochemical abnormalities, biopsy is usually warranted early in the course of the evaluation. In patients that are asymptomatic and have abnormal biochemical testing, repeat evaluation is sometimes warranted. A general guideline is to obtain a liver biopsy in asymptomatic patients if there are moderate to severe elevations in serum hepatic enzyme activities that persist for at least 3 months, or if there are mild to moderate elevations in serum hepatic enzyme activities that persist for at least 6 months. If clinical signs of hepatic disease develop, then biopsy should not be unreasonably delayed. If there are concurrent elevations in serum bile acids, biopsy should also not be delayed.

Other indications for hepatic biopsy are ultrasound imaging abnormalities. If there are focal hepatic masses or diffuse echotextural changes, a biopsy may be warranted, depending on results of laboratory testing. In one study, abdominal ultrasound findings alone were not reliable for obtaining a diagnosis of infiltrative hepatic disease with diffuse changes in echogenicity (either hypoechoic or hyperechoic, uniform or mottled).[1] In another study, sonographic detection of a hepatic mass greater than or equal to 3 cm, ascites, abnormal hepatic lymph node(s), and abnormal spleen were predictive of liver neoplasia based on cytology.[2] Conversely, sonographic detection of hepatic nodules less than 3 cm was predictive of vacuolar hepatopathy on cytology. Thus several sonographic findings, alone or combined, may be predictive of liver ultrasound-guided fine-needle aspiration cytology results. In light of the fact that ultrasound-guided fine-needle aspiration cytology of the liver has limitations , the results of ultrasound and cytology should be adjuncts to other findings.

Another indication for hepatic biopsy is the need to assess response to therapy. In cases of chronic hepatitis in dogs, it is often difficult to determine if there is ongoing inflammation and resolution/progression of fibrosis during long-term therapy. This is particularly true when the patient is receiving glucocorticoid therapy as these medications cause variable increases in serum ALP and transaminase activities independent of the underlying disease. Repeat or serial hepatic biopsy analysis is often helpful to guide therapeutic decisions in these cases.

Prebiopsy Considerations

Among the most serious complications of liver biopsies are hemorrhage, infections, and injury to the adjacent viscera. Consequently the clinician must take into account the clinical question, the appropriate invasive biopsy method, and methods of managing postbiopsy complications. Postbiopsy hemorrhage is often the first concern, although it is unclear as to what the best predictor of hemorrhage is in patients about to undergo hepatic sampling. In one study of 200 human patients in which bleeding was evaluated laparoscopically, there was no correlation between any in vitro coagulation test and "liver bleeding time."[3] Other studies in man have used laparoscopy and ultrasonography to assess hepatic bleeding time following needle biopsy, and most have shown similar poor correlation between coagulopathies and hepatic bleeding times. Similar studies have not been reported in veterinary medicine. There also have been studies in human and veterinary medicine evaluating risk factors for bleeding complications (as opposed to "hepatic bleeding times").[4,5] Bigge et al. correlated coagulation profile findings and bleeding complications after ultrasound-guided biopsies in 310 dogs and 124 cats.[5] There was no apparent correlation between coagulation parameters and major complications following liver biopsy. Studies show that clotting times assessing proteins induced by vitamin K antagonism are more sensitive in detecting coagulopathies in patients with hepatic disease.[6,7] The

proteins-induced-by-vitamin-K-antagonism test is more than twice as sensitive in dogs and more than three times as sensitive in cats in detecting coagulopathies compared with prothrombin time (PT) and aPTT.[6,7] However, in a pilot study performed by me, hepatic bleeding times assessed via laparoscopy did not correlate with proteins induced by vitamin K antagonism times. Thus it appears that indices of coagulation in the peripheral blood are generally unreliable guides of the risk of bleeding after liver biopsy, and hence, are of limited value in determining contraindications to this procedure. This lack of correlation may be explained by the high concentration of clotting factors in the hepatic parenchyma and by mechanical compression of the needle tract by the elastic tissue within the liver. In most cases of significant hemorrhage, technical errors such as damaging a large vessel are the cause rather than persistent oozing from a needle biopsy site. Controlled studies in veterinary patients will be necessary to make final conclusions regarding postbiopsy hemorrhage in the patient with a coagulopathy.

In one study of normal dogs, biopsies taken from the left lateral hepatic lobe using a biopsy punch, biopsy needle, ligature method, laparoscopic biopsy forceps, and ultrasonically activated scalpel resulted in minimal hemorrhage (<2 mL).[8] However, this investigation did not assess the risk of hemorrhage in dogs or cats with hepatic disease. These risks will be discussed later under each sampling method. With the exception of fine-needle aspirations, each patient should have a prebiopsy packed cell volume and 3 and 6 hours postbiopsy packed cell volume for close monitoring of potential hemorrhage.

Fine-Needle Aspiration

Fine-needle aspiration involves obtaining a small amount of hepatic tissue for cytologic analysis, and is typically performed in conjunction with, and guided by, ultrasound. Ultrasound imaging helps determine if there is a diffuse abnormality (e.g., increased or decreased echogenicity, diffuse mottling) or if there are focal abnormalities (e.g., discrete nodules, cysts, masses, or focal areas of heterogenous mottling). An appropriate site to be sampled is chosen. Often multiple sites are chosen to represent different lobes, and in the case of focal lesions, to sample more than one area of abnormal tissue and sample seemingly normal tissue. The sites are also chosen based on accessibility. For example, a solitary nodule in the dorsocranial aspect of the liver in a large deep-chested dog would be impossible to reach with a 1.5-inch needle. A lesion adjacent to the gallbladder or caudal vena cava would involve considerable risk. The clinician would need to decide whether the relative risk of sampling such lesions is the appropriate decision, or whether other methods of sampling would be more appropriate such as laparoscopy or laparotomy. Figure 61-15 depicts a typical setup for fine-needle aspiration. Usually a 22-gauge, 1.5-inch needle is used. For most patients, the procedure is performed without sedation or local anesthetic. If it is determined that the animal is moving too much during the initial ultrasound examination, a sedative may be necessary (or an anesthetic in extreme cases). The needle is inserted without a syringe using ultrasound guidance. The needle is rapidly agitated in and out (sometimes referred to as mimicking the action of a sewing machine) and simultaneously twisted multiple times for a few seconds to obtain a sample. This method relies on capillary action rather than suction to get tissue into the needle, resulting in less hemodilution. After removing the needle from the liver, a syringe is attached and cells are expelled onto a glass slide for cytologic examination. Often three to five separate attempts are made to increase the sample size and diversity.

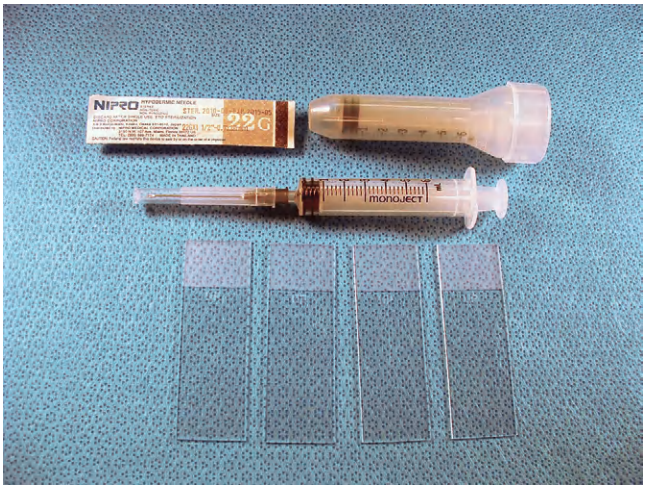

Figure 61-15 Fine-needle aspirate setup including 6-mL syringes, 1.5-gauge 22-inch needles, and glass slides.

Advantages and Disadvantages of Fine-Needle Aspiration

Fine-needle aspiration has several advantages. Little to no sedation is usually required. Because the size of the needle is so small, there is little risk of hemorrhage. Therefore multiple sites can easily be sampled. The procedure is rapid and can usually be performed on an outpatient basis. There is also less cost to the client.

The primary disadvantage of fine-needle aspiration is its questionable accuracy. The sample size often limits the number of available cells to obtain an accurate diagnosis, and hemodilution makes it difficult to assess whether inflammatory cells were present in the liver or peripheral blood. There are several important elements used to interpret pathologic information including lobular architecture, presence and location of inflammation within a lobule, presence and severity of fibrosis, metal accumulation, vascular abnormalities, and lobule heterogeneity. These criteria cannot be accurately determined using a cytologic sample obtained using FNA. Several studies have compared fine-needle aspiration cytology with biopsy with histopathology.[9-12] In one study with a total of 34 cases, there was good correlation in 35% of cases, partial correlation in 35% of cases, and no correlation in 30% of cases.[9] Poor correlation was found with a variety of histologic changes, including vacuolar change, lipidosis, cholestasis, inflammation, and neoplasia. In a similar study with 97 cases, complete agreement between fine-needle aspiration and histopathology was seen in only 30% of cases in dogs: 25% agreement with inflammation, 14% agreement with neoplasia (mainly carcinoma), and 64% agreement with vacuolar hepatopathy.[10] In cats, there was overall agreement in 51% of cases: 27% agreement with inflammation, 33% agreement with neoplasia (lymphoma), and 64% agreement with vacuolar hepatopathy. Although vacuolar hepatopathy was the most sensitive diagnosis, it was also the most common misdiagnosis using cytology. In another study, the best correlation between hepatic cytology and biopsy was seen with lipidosis, lymphoma, and carcinoma, whereas the worst performance was seen with inflammatory and fibrotic disorders.[11] Another study found high sensitivity and specificity with fine-needle aspiration in detecting inflammatory hepatic disease in dogs.[12] However, further information was not provided such as the severity of the inflammation or other histopathologic features. Additionally, for noninflammatory hepatic disease, cytology was inaccurate in 76% of cases.

Summary of Fine-Needle Aspiration

Although fine-needle aspiration is easy to perform, involves little risk, and little to no sedation, the information is of little value if it is inaccurate as often as it is accurate. There is institutional bias regarding its accuracy, which may relate to the experience and expertise of the cytologists. Given its clear limitations, fine-needle aspiration is best used as an adjunctive diagnostic modality in conjunction with other techniques or clinical findings, and does not replace histopathology. The clinician must be aware of its inherent inaccuracy before undertaking fine-needle aspiration and relying on the cytologic findings.

Ultrasound-Guided Biopsy

Ultrasound-guided hepatic biopsy uses a cutting-type needle as a sampling tool. Automated needles are preferred and should be either completely automated or semiautomated. These are spring-loaded needles similar in style to the manual Tru-Cut needle. Completely automated needles thrust the inner obturator (containing the biopsy tray or specimen notch) followed by the outer cutting sheath into the liver in a fraction of a second. These needles can be operated with one hand while the other hand operates an ultrasound transducer to allow precise placement of the biopsy instrument. There is minimal displacement of the liver, a shorter intraparenchymal phase, and a more reliable yield of tissue. This allows a smaller diameter needle to be used and a lighter degree of sedation in some cases. Using the rapid cutting action, the hepatic tissue tends to be less fragmented. Semiautomated needles require manual placement of the internal obturator into the liver, followed by an automatic thrusting of the outer cutting sheath by a spring-loaded mechanism. These needles have the additional advantage of control over the final needle position, as the tip of the needle can be precisely localized before the outer cutting sheath is deployed. I generally use a 16-gauge needle for ultrasound-guided hepatic biopsy. Figure 61-16 depicts a typical setup for ultrasound-guided biopsy.

In most dogs, the liver can be biopsied using local anesthesia and minimal sedation. Most cats require general anesthesia to safely obtain tissue. It must be emphasized that the degree of sedation must be tailored to each individual patient. A careful ultrasound examination is performed prior to biopsy. This allows planning of the procedure based on echo pattern, lesion size, proximity to other organs, proximity to blood vessels, determination of cystic or solid tissue, and optimal approach of the needle path. Care must be taken prior to taking samples to ensure that vessels and other organs are not within the path of the needle. For diffuse lesions, the transducer is typically placed caudal and to the left of the xiphoid, and aimed at the left medial or lateral lobes. In patients with a small liver, it may be difficult to adequately visualize the needle without gastric gas interference. Placing these animals in a 45-degree right lateral oblique position can reduce this interference. If the animal is under general anesthesia, an assistant can compress a rebreathing bag to hold the animal in deep inspiration, which serves to move the diaphragm and liver caudally to improve visualization. The area is surgically prepared. The ultrasound transducer is covered with sterile wrap and sterile lubricant is used to enhance skin contact. A small stab incision is made in the skin at the desired needle insertion site. While one hand maneuvers the transducer, the other hand advances the needle into the liver under direct ultrasound visualization. The image should be optimized to maximize the chance of recognizing the needle within the liver. To allow distinction of the needle from other echogenic structures, the needle can be gently moved in and out with minimal movements (attempting to move the liver within the abdominal cavity rather than the needle within the liver). Occasionally the needle cannot be seen, and indirect evidence of organ penetration must be used such as movement of the liver or visualization of movement at the liver border. The needle is then directed so the trajectory will avoid other structures when it is fired. The needle is then fired, and immediately removed. For most cases, four to five samples are obtained, and are submitted for aerobic/anaerobic culture, histopathologic evaluation, and metal (copper, zinc, and iron) quantification. In one study, liver tissues with high metal concentrations had significantly lower copper and iron in needle-core versus wedge biopsy specimens.[13] Consequently the value of needle-core biopsy specimens for measurement of metal concentrations is questionable. Careful examination for post-biopsy hemorrhage is then performed. External digital pressure may be used to help control hemorrhage in smaller patients. Usually an abdominal compression wrap is ineffective for controlling hemorrhage.

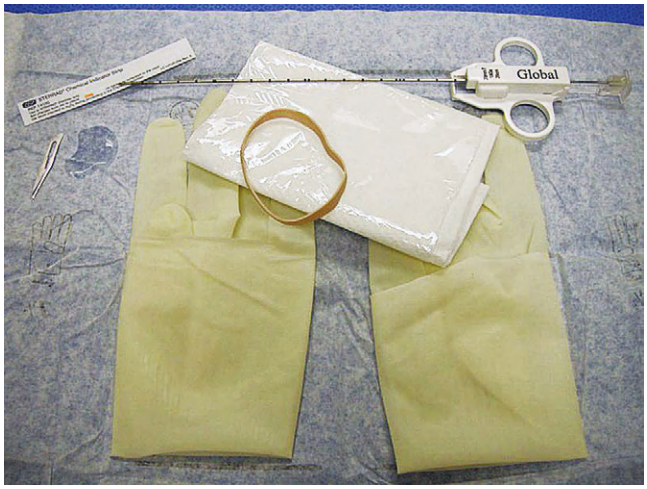

Figure 61-16 Ultrasound-guided biopsy setup including sterile gloves, sterile wrap and lubricant, number 11 surgical blade, and 16-gauge needle biopsy instrument.

Advantages and Disadvantages of Ultrasound-Guided Biopsy

Ultrasound-guided biopsy has many of the advantages of fine-needle aspiration, including the need for minimal sedation in some patients, the ability to sample multiple sites, and low to moderate cost to the client. Additionally, tissue is obtained for histopathology.

One disadvantage of ultrasound-guided biopsy is the risk of bleeding (especially when multiple sites are sampled and larger-gauge needles are used). In one study, 96 percutaneous transabdominal hepatic needle biopsy samples were obtained with no adverse consequences noted[14]; however, this study was performed in normal dogs, and still carries high risk. Additional disadvantages of ultrasound-guided biopsy include the needing sedation or anesthesia in some patients, difficulty of imaging small livers, difficulty of obtaining liver tissue in patients with fibrosis, and, most importantly, the obtaining of samples that have a questionable representation of the underlying hepatic pathology. The diagnostic accuracy of needle biopsy has been questioned by many clinicians, observing that results of needle biopsy analysis often do not adequately reflect the clinical and laboratory features of the patient. This questionable accuracy is in most part a result of potential for sampling error. This method still results in a relatively small sample size, possible

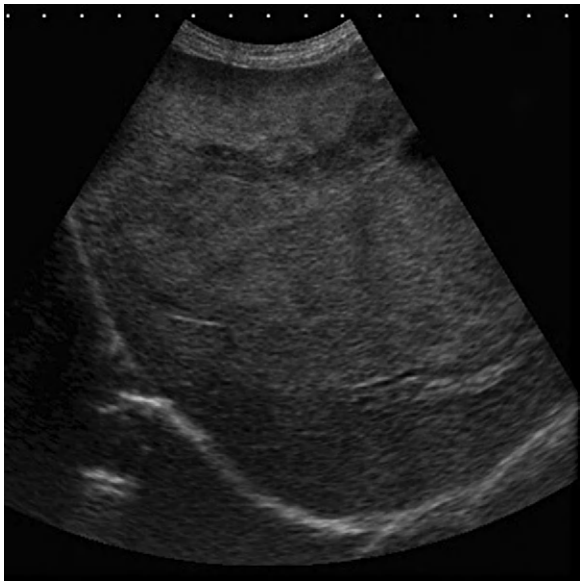

Figure 61-17 Ultrasound image of a focal hepatic mass (hepatocellular carcinoma) in a Pomeranian dog. This mass is amenable to ultrasound-guided biopsy.

fragmentation of fibrous tissue, and may not enable sampling of abnormalities located in other lobes (the left medial or lateral lobes are generally sampled because of their ease of imaging). In one study, percutaneous hepatic sampling using core biopsies resulted in 92% diagnostic quality samples, however these were not compared with large wedge biopsy to assess the accuracy of this method.[15] In another study, the diagnostic accuracy of the Tru-Cut–type needle biopsy was compared with the gold standard of surgical wedge biopsy of the liver in 124 patients.[16] The overall discordance between the two methods was 53% in dogs and 50% in cats, with a greater than 60% discrepancy occurring with chronic hepatitis or cirrhosis, cholangitis/cholangiohepatitis, portosystemic vascular anomalies, microvascular dysplasia, fibrosis, and miscellaneous disorders. These disorders are the most commonly seen among dogs and cats with hepatobiliary disease. The greatest accuracy was with neoplasia (80% concordance). Figure 61-17 is an example of a mass amenable to an ultrasound-guided needle biopsy. Use of a 14-gauge versus 18-gauge needle may reduce this discordance as it raises the number of portal triads sampled from an approximate mean of four to seven, though larger needles carry the risk of increased hemorrhage.

Summary of Ultrasound-Guided Biopsy

In summary, ultrasound-guided hepatic biopsy is relatively easy to perform, but involves more risk to the patient (primarily bleeding). Like fine-needle aspiration, ultrasound-guided biopsy has questionable accuracy. The accuracy may be increased by using a larger-gauge needle, but this carries a greater risk of postbiopsy hemorrhage. If the patient is suspected of having inflammatory disease, vascular abnormalities, or significant fibrosis, or is at risk for hemorrhage, laparoscopy or laparotomy should be considered.

Laparoscopic Biopsy

Chapter 28 provides a detailed description of laparoscopic liver biopsy. Briefly, laparoscopy is performed under general anesthesia with the patient in dorsal recumbency tilted 45 degrees to the left. A Veress needle is placed at the level of the umbilicus into the peritoneal space through a stab incision using a number 11 scalpel blade. After ensuring no obstruction and negative pressure using the infusion and aspiration of saline, the abdomen is insufflated with carbon dioxide gas and maintained at a pressure of approximately 12 mm Hg. A scope port (cannula) is then placed 4 cm right lateral to the Veress needle. The Veress needle is then removed and replaced with an instrument port. Hepatic sampling is achieved using a "spoon" or oval cup biopsy forceps. Multiple samples are obtained under direct visualization, and samples are submitted for aerobic/anaerobic culture, histopathologic evaluation, and metal (copper, zinc, and iron) quantification. Following procurement of all the biopsy specimens, the sites are inspected for hemorrhage. The abdomen is then decompressed, and lidocaine and bupivacaine are infused into the peritoneal cavity through either port. Both the instrument and scope ports are removed, and the port site incisions are closed using either a cruciate or simple interrupted pattern in the body wall, subcutaneous tissue, and skin.

Advantages and Disadvantages of Laparoscopy

This technique enables gross evaluation of the entire liver, extrahepatic biliary system, and surrounding structures while obtaining multiple large specimens of liver. The ability to obtain multiple samples decreases the risk for sampling artifact in cases of regional diversity within the liver. Additionally, by directly visualizing the hepatic parenchyma, the clinician can correlate the histopathologic findings and clinical data with the gross appearance of the liver to render the most accurate diagnosis. This method also enables the visualization of smaller masses and irregularities that may not be evident with ultrasonographic imaging. These masses can also be individually sampled. Laparoscopy also gives the clinician an excellent view of the liver regardless of the hepatic size or conformation of the patient, making it an easy method to sample the liver in patients that are difficult to image with ultrasound.

There is generally minimal bleeding during this procedure, even in patients with in vitro coagulopathies. Using a "spoon" or oval-cup biopsy forceps typically results in a marked decrease in the amount of hemorrhage when compared with needle biopsies. Any hemorrhage can be directly visualized for adequate clot formation. If hemorrhage persists, direct pressure using a blunt probe for 5 minutes can be used. If the site continues to bleed, electrocautery can be applied to the biopsy site or a topical hemostatic agent (Gelfoam) can be placed directly on the biopsy site using laparoscopic forceps.

Disadvantages of laparoscopy include the need for expensive equipment, the need for extensive training, the need for general anesthesia in most cases, and higher cost to the client.

Summary of Laparoscopy

Laparoscopy gives the clinician the advantages of a laparotomy (large sample size, ability to best direct sampling, and ability to take multiple samples, thus resulting in the highest diagnostic accuracy), though with a relatively minimally invasive procedure. The complication rate (especially hemorrhage) is far less than with ultrasound-guided biopsy in my practice. For these reasons, it is my method of choice for obtaining hepatic biopsy specimens in most cases.

Surgical Biopsy

Wedge biopsy via laparotomy is another potential method for obtaining hepatic biopsies. If a random liver biopsy is needed and a section of liver is protruding, a guillotine suture can be used. A preformed encircling ligature of 4-0 monofilament absorbable suture material is placed around the protruding section of liver.

The ligature is then tightened until it has crushed the hepatic parenchyma. After completing several throws in the knot, the sample is excised 1 to 2 mm distal to the ligature using Metzenbaum scissors or a scalpel blade. If a specific area of liver is needed, a sample can be obtained using the transfixation method or a biopsy punch. The transfixation method entails placing a ligature through the liver lobe approximately 8 to 10 mm from its edge. The ligature is tightened to crush through the hepatic parenchyma along one border of the desired biopsy specimen. An additional throw is made at a right angle to the first ligature, and this throw is tightened to crush the parenchyma of the second border of the specimen. The sample is removed 1 to 2 mm distal to the crushed area using a scalpel blade or Metzenbaum scissors. If the desired area does not lie near the edge of a liver lobe, a 6-mm biopsy punch can be used. The biopsy punch should be inserted into the hepatic parenchyma ensuring not to penetrate the opposite surface. If the biopsy site is close to the hilus, extra caution must be used so that no more than half of the thickness of the liver is penetrated. The biopsy sample is removed from the liver using scissors. Hemorrhage can be controlled by filling the defect with a topical hemostatic agent (Gel Foam) and applying digital pressure for 3 to 5 minutes, or by suturing the hepatic capsule with fine, absorbable monofilament suture in a cruciate pattern. Akin to laparoscopy, this method has similar advantages and disadvantages as listed previously. Although it is more invasive, it allows easier biopsy of other abdominal organs (such as intestine and mesenteric lymph node) and the ability to perform therapeutic maneuvers (such as hepatic mass removal or biliary diversion).

PARENCHYMAL DISORDERS

Susan E. Johnson

Inflammation and Necrosis

Acute Hepatitis and Acute Hepatic Necrosis

Etiology

Hepatocyte death (necrosis and apoptosis) in dogs and cats occurs secondary to a broad variety of insults, including infectious agents, drugs and toxins, hypoxia, immunologic events, and metabolic disorders. Hepatic necrosis and acute inflammation often occur together and the relationship between these two processes is complex. Acute inflammation may be the primary event, or necrosis of hepatocytes can be followed by a substantial inflammatory response, the "hallmark" of necrotic cell death.[1] The term *acute hepatitis* traditionally has been used when infectious agents cause hepatocellular necrosis, even though in the early stages, hepatic inflammation can be minimal or absent.[2] Controversy exists among veterinary pathologists regarding the preferred terminology (*acute hepatitis* versus *acute hepatic necrosis*), when necrosis predominates and is caused by noninfectious insults such as toxins or ischemia.[2] For the purposes of this discussion, lesions of acute hepatitis and acute hepatic necrosis are discussed together, recognizing that the primary contributions of each lesion may be variable, depending on the cause, host response, and passage of time. Acute hepatitis, a form of primary hepatitis, should be differentiated from "nonspecific reactive hepatitis," a response of the liver to a variety of extrahepatic disorders that is characterized by focal inflammation without necrosis.[2] Nonspecific reactive hepatitis is discussed in a later section of this chapter.

Acute hepatitis and necrosis are common morphologic hepatic lesions in dogs and cats presenting with acute liver disease caused by infectious, toxic, metabolic, and ischemic disorders (Box 61-1). However, acute liver disease can also be associated with other pathologic processes such as severe hepatic lipidosis (cats), granulomatous hepatitis (fungal infections), intrahepatic cholestasis (bacterial cholangitis, leptospirosis), and malignant infiltration (lymphoma, malignant histiocytosis). Canine adenovirus I, canine and feline herpesvirus in the neonate, *Clostridium piliforme*, and *Toxoplasma gondii* are specific examples of infectious agents that cause acute hepatic necrosis (with variable inflammation), often as part of a multisystemic disorder.[2] Although leptospirosis is a well-recognized infectious cause of acute liver disease in dogs, hepatic necrosis is an uncommon histologic feature and hepatic lesions are typically characterized by cholestasis, liver cell dissociation, and nonspecific reactive hepatitis.[3]

Despite the large number of potential causes of acute hepatitis and necrosis, a specific etiology is often not determined.[4,5] In a recent case series of 101 dogs with primary hepatitis (acute and chronic hepatitis) that were presented to a referral clinic, 21 dogs were diagnosed with morphologic features of acute hepatitis.[4] A cause could not be determined in the majority of these cases, although increased hepatic copper was detected in five dogs with acute hepatitis, suggesting that copper accumulation could be a significant contributing factor.[4]

Pathophysiology

Despite numerous potential causes of hepatocyte death, two general mechanisms are recognized: apoptosis and necrosis.[2] These two mechanisms have traditionally been considered to be distinct events. However, it now appears that apoptosis and necrosis are alternate outcomes of the same initiating causes and signaling pathways.[1] Apoptosis is adenosine triphosphate–dependent (caspase-dependent) programmed cell death that causes shrinkage of the cell (apoptotic bodies or acidophil bodies) with orderly resorption of cellular contents, minimal leakage of cellular components, and minimal secondary inflammation.[1,2] Necrosis occurs when depletion of adenosine triphosphate results in cellular swelling, loss of integrity of the cell membrane and cell lysis, with release of cell contents and secondary inflammation.[1,2]

Diffuse hepatic necrosis is the most consistent histological lesion detected in dogs and cats with acute liver failure.[5] Acute liver failure (ALF) is a rare clinical syndrome (usually fatal) that occurs when a sudden severe insult to the liver compromises at least 70% of functional hepatic mass. Liver cell death exceeds hepatic regenerative capacity, resulting in clinical signs of liver failure.[5] The clinical and laboratory features of ALF are not specific for the inciting cause but reflect disruption of one or more major hepatic functions.

Once hepatocellular injury has occurred (and assuming the patient survives), the morphologic hepatic response to injury may include parenchymal regeneration, fibrosis, and ductular proliferation.[2] Nearly complete hepatic regeneration is possible if hepatocyte injury is limited and the reticulin network remains intact.[2] With severe parenchymal destruction or extensive loss of hepatocytes, periportal ductular proliferation, hepatic fibrosis, postnecrotic scarring, and regenerative hepatic nodules are more likely.[2] Dogs with acute hepatitis may also progress to chronic hepatitis.[4]

Clinical Examination

The clinical presentation of dogs and cats with acute hepatitis and necrosis varies with the underlying cause and the extent and severity of the hepatic lesions. The spectrum of hepatic involvement may

include (a) subclinical (biochemical abnormalities only), (b) clinical signs of acute liver disease, or (c) the clinical syndrome of ALF. When liver injury is mild (focal necrosis and inflammation), clinical signs may be absent, mild, or related to an underlying cause in another organ system. In this setting, hepatic involvement may not be recognized until biochemical evaluation reveals increased liver enzyme activity or mild hyperbilirubinemia. It has been suggested that many dogs with acute hepatitis are not recognized clinically, because signs are mild and self-limiting, and dogs recover spontaneously regardless of treatment.[6] Clinical signs of acute hepatitis include acute onset of lethargy, anorexia, vomiting, diarrhea, PU, and PD, in a previously healthy animal. These are nonspecific findings of acute liver disease, which overlap those of other systemic disorders. The finding of icterus on the physical examination is a more specific indicator of hepatobiliary disease, especially in the absence of anemia.

Dogs and cats with acute diffuse hepatic necrosis often present with ALF. [5] In addition to the signs of acute liver disease described above, animals in ALF show signs of HE (depression, behavioral changes, dementia, ataxia, pacing, circling, blindness, hypersalivation, seizures, and coma) and clinical evidence of a bleeding tendency (melena, hematemesis, or cutaneous and mucosal hemorrhages), which suggest severe hepatic dysfunction.[5] Signs of ALF are rapidly progressive (over hours to days) and this clinical syndrome is often fatal, with reported mortality varying from 25% to 100%.[5]

With acute hepatic disease, the history typically reveals acute onset of signs in a previously healthy animal. However, liver failure that is recently recognized may not necessarily be recent in onset. With occult chronic liver disease, clinical signs may be vague and go unrecognized by the owner until a final phase of hepatic decompensation. The owner should be questioned about any subtle signs of chronic illness that would suggest the underlying liver disease may be chronic rather than acute, and that the current illness may be an exacerbation or decompensation of chronic liver disease. Dogs and cats with ALF are generally in good nutritional status compared with those with chronic hepatic disease. Findings of cachexia, emaciation, ascites, or edema suggest a more protracted illness and are characteristic of chronic rather than acute liver disease. It is important to make a distinction between acute and chronic liver disease as the intensive supportive care indicated in ALF might not be warranted in chronic end-stage liver disease. The long-term prognosis is better for acute hepatitis than chronic hepatitis.[4]

Diagnosis

An initial database consisting of complete blood cell count, serum chemistry, and urinalysis should be obtained in dogs and cats with acute liver disease. Liver enzyme elevations are a common finding in dogs and cats with acute hepatitis and necrosis. With mild hepatic injury or focal hepatic necrosis, increased ALT activity may be the only finding on an otherwise unremarkable biochemical profile. ALT and AST activities are moderately to markedly increased, because of enzyme leakage from damaged hepatocytes.[7] Although ALT activity increases with many hepatic diseases, the largest magnitude of increase is seen with acute hepatic necrosis and roughly correlates with the number of involved cells.[7] ALT activity may be increased as much as 100 times the upper range of normal, with increases in AST activity that parallel but are generally lower (30 times the upper limit of normal) than the ALT. It should be noted that some recognized hepatotoxins (aflatoxin and microcystin in blue-green algae) are not associated with severe or protracted increases in ALT activity because of toxin-suppressed transaminase synthesis.[7] Increased activity of the cholestatic liver enzymes, alkaline phosphatase, and GGT, also commonly occur with acute hepatitis and necrosis, but the magnitude of the increase is much less than for the ALT and AST.

Abnormalities in biochemical tests such as hyperbilirubinemia, increased SBAs, hypoglycemia, and hyperammonemia indicate compromised hepatic function. Hyperbilirubinemia and bilirubinuria support more significant hepatic injury once prehepatic (hemolytic) causes have been discounted. Primary biliary tract disorders including posthepatic mechanisms of hyperbilirubinemia should also be considered in the differential diagnosis. Other considerations for hypoglycemia in conjunction with acute liver disease include xylitol toxicity (excess insulin release) and sepsis. Hypoalbuminemia usually suggests chronic rather than acute liver disease, because of the long serum half-life of albumin. If azotemia is detected, dehydration, GI blood loss, and concurrent renal damage (e.g., leptospirosis, nonsteroidal antiinflammatory drugs [NSAIDs]) should be considered. Interpretation of azotemia is facilitated by concurrent urinalysis. Renal injury is supported by findings of cellular or granular casts, glucosuria, isosthenuria, and proteinuria. The complete blood cell count may reveal an inflammatory response suggesting underlying infectious or inflammatory disorders, and it is also useful for ruling out hemolytic anemia as cause of jaundice. Documentation of a coagulopathy is required for the clinical diagnosis of ALF. Laboratory findings indicative of a coagulopathy include prolonged PT and activated partial thromboplastin time (aPTT), decreased fibrinogen, increased fibrin degradation products, and thrombocytopenia.

Abdominal radiographs are often unremarkable in dogs and cats with acute hepatitis and necrosis. The liver may appear normal or increased in size. On abdominal ultrasound, the liver may appear normal or hypoechoic. Thoracic and abdominal imaging may be helpful to evaluate for other causes of acute hepatic disease (see Box 61-1), and biliary tract disorders.

Because dogs and cats with acute hepatitis and necrosis present with nonspecific signs of acute liver disease, the clinician should maintain a broad perspective regarding the many potential diseases and processes that can acutely affect the liver (see Box 61-1). Prior to obtaining a liver biopsy, ancillary testing (cytology or biopsy of more accessible lesions, infectious disease titers or molecular tests, diagnostic imaging) should be performed to evaluate for systemic disorders with secondary hepatic effects or multisystemic infections (see Box 61-1), thus providing a diagnosis of other causes of acute liver disease in a less-invasive manner.

When acute hepatitis or hepatic necrosis is suspected (or confirmed by liver biopsy), a thorough history is essential to identify exposure to potential hepatotoxins and infectious agents. The owner should be questioned regarding recent medications, including prescription and over-the-counter drugs, and alternative medicines such as herbal and dietary supplements. The potential for exposure to chemicals or hepatotoxins (*Amanita* mushrooms, blue-green algae, Sago palms, aflatoxins, or xylitol) should be assessed (for more details, see "Drug and Toxin-Induced Liver Injury" section). Other pertinent historical questions include current vaccination history (canine adenovirus, leptospirosis), travel history (fungal infections or tick-borne diseases), and exposure to other animals (infectious causes).

Liver biopsy is required to document the presence of acute hepatitis and necrosis; evaluate for specific causes; and differentiate acute from chronic disease. In patients with mild (or absent) clinical signs and liver enzyme elevations that correspond to recent medication administration, a liver biopsy may be postponed, the medication discontinued, and clinical signs and liver enzymes monitored for

improvement over a 2- to 3-week period. For patients with ALF and coagulopathy, the clinician must carefully weigh the benefits of histologic characterization versus the risk of excessive bleeding from the procedure.

Acute hepatitis is characterized histologically by a mononuclear or mixed inflammatory pattern, accompanied by hepatocellular apoptosis or necrosis.[2] Necrosis should be further characterized by the pathologist as to the morphologic pattern of injury (focal, multifocal, confluent, bridging, massive, or piecemeal) because the pattern of necrosis may provide insight into the pathogenesis of the lesion.[2] For example, because centrilobular hepatocytes have an abundance of cytochrome P450 enzymes, these hepatocytes are preferentially affected in drug-induced hepatotoxicity, when cytochrome P450 metabolism of the parent drug results in toxic metabolites.[8] Quantitative copper analysis and histochemical staining for copper are recommended, as copper accumulation may be an underappreciated cause of acute hepatitis in dogs.[4] Infectious causes of acute hepatitis may be diagnosed on liver biopsy, or by additional tests performed on liver tissue (culture, immunohistochemistry, polymerase chain reaction [PCR], virus isolation; Table 61-4).

Table 61-4 Infectious Diseases and the Liver

Classification/ Organism	Species	Hepatic Lesions	Tissue Tropism	Diagnosis
Viral				
Canine adenovirus I (infectious canine hepatitis)	D	Centrilobular necrosis; neutrophilic and mononuclear cell infiltrates; intranuclear inclusions in hepatocytes and Kupffer cells; gallbladder edema; chronic hepatitis?	Liver, vascular endothelial cells	Virus isolation, PCR, immunohistochemistry, histopathology
Herpesvirus (neonates)	D	Multifocal hemorrhagic necrosis; intranuclear inclusions	Kidneys, liver, lung, spleen, lymph node	Virus isolation, fluorescent antibody techniques; PCR, EM, histopathology
Canine acidophil cell hepatitis	D	Acute or chronic hepatitis; cirrhosis; acidophil cells characterized by angular shape, acidophilic cytoplasm and hyperchromatic nucleus	Liver	Histopathology
Coronavirus (feline infectious peritonitis)	C	Pyogranulomatous and granulomatous hepatitis; multifocal hepatic necrosis	Macrophages; vascular endothelium; peritoneum, liver, lymph nodes, kidneys, CNS, eyes	Immunohistochemistry on effusions or lesions with infected macrophages
Calicivirus (virulent form)	C	Massive or centrilobular hepatic necrosis; individualization of hepatocytes	Macrophages; vascular endothelium	Virus isolation, PCR
Bacterial				
Leptospira interrogans	D	Acute cholestasis, liver cell dissociation, and nonspecific reactive hepatitis; chronic hepatitis	Kidneys, liver, vascular endothelium	Serology, PCR on urine, histopathology
Clostridium piliforme (Tyzzer disease)	D, C	Multifocal periportal hepatic necrosis; intracellular filamentous organisms demonstrated on Giemsa or Warthin-Starry stain	Liver, ileum, colon	Histopathology
Sepsis and endotoxemia	D, C	Intrahepatic cholestasis, mild periportal lymphocytic infiltrate, scattered foci of macrophages or neutrophils, and occasional necrotic hepatocyte		Blood and extrahepatic tissue cultures; response to treatment of systemic infection
Mycobacterium spp.	D, C	Granulomatous hepatitis; acid-fast organisms demonstrated on special stains	Lungs, lymph nodes, GI tract; skin (varies with species)	Histopathology; cytology, culture; direct fluorescent antibody; PCR
Bartonella henselae and *clarridgeiae*	D	Granulomatous hepatitis and peliosis hepatis (*Bartonella henselae*); hepatic disease (*Bartonella clarridgeiae*)	Liver, lymph nodes, myocardium, joints	Serology, culture, PCR on liver tissue
Helicobacter spp. (enterohepatic)	D, C	Multifocal necrotizing hepatitis (dog); cholangitis (cats)	Liver and biliary tract	EM, PCR
Abscess (aerobic and anaerobic organisms)	D, C	Unifocal or multifocal hepatic abscesses	Primary liver or multisystemic infection	Aerobic and anaerobic cultures; histopathology

Continued

Table 61-4 Infectious Diseases and the Liver—cont'd

Classification/ Organism	Species	Hepatic Lesions	Tissue Tropism	Diagnosis
Fungal				
Histoplasma capsulatum, Coccidioides immitis, Blastomyces dermatitidis, others	D, C	Granulomatous or pyogranulomatous hepatitis; fungal organisms seen on Grocott or Gridley silver stains	Varies with organism	Serology, cytology, histopathology, urine antigen testing (*Blastomyces*)
Protozoan				
Toxoplasma gondii	D, C	Hepatic necrosis; cholangitis (cats)	Lungs, CNS, liver, pancreas, heart, eyes	Serology, histopathology, PCR
Neospora caninum	D	Hepatic necrosis, neutrophils, hemorrhage	CNS, muscle, nerves, liver	Serology, histopathology, PCR
Cytauxzoon felis	C	Schizont-laden macrophages in the lumen of small vessels in liver; granulomatous hepatitis	Liver, spleen, bone marrow	Organism seen on blood smears; histopathology
Leishmania infantum	D	Multifocal, mild to moderate, granulomatous to pyogranulomatous inflammation; chronic hepatitis: lymphocytic plasmacytic portal inflammation with mild fibrosis	Skin, hemolymphatics; spleen, liver, kidneys	Organisms seen on cytology or histopathology; serology, culture, PCR
Babesia canis, Babesia gibsoni	D	Hepatitis, focal necrosis, bile stasis	Red blood cells	Cytology, serology, PCR
Hepatozoon canis	D	Hepatitis; mononuclear and neutrophil infiltration; meronts	Lymph nodes, marrow, liver, spleen, lungs	Serology, histopathology
Sarcocystis canis	D	Necrosuppurative and eosinophilic hepatitis; vasculitis; schizonts	CNS, liver, skin	Histopathology, EM
Rickettsial				
Ehrlichia canis	D	Portal hepatitis; lymphocytes, plasma cells, macrophages; morulae in mononuclear cells	Monocytes; macrophages	Serology, PCR, immunohistochemistry
Rickettsia rickettsiae	D	Focal hepatic necrosis	Endothelial cells; skin, CNS, heart, kidney	Serology, direct fluorescent antibody staining of tissues
Parasitic				
Visceral larval migrans (*Toxocara* migration)	D	Subcapsular and parenchymal granulomas with fragments of parasitic larvae; portal areas with eosinophils; lymphocytes	GI tract	Histopathology, fecal examination
Heterobilharzia americana (schistosomiasis)	D	Granulomas and schistosome ova; portal fibrosis	Liver, GI tract, lymph nodes	Histopathology, fecal examination, fecal PCR, serology
Dirofilaria immitis (Caval syndrome)	D, C	Passive congestion, cavernomatous change of hepatic veins, centrilobular necrosis and fibrosis, microfilaria in sinusoids with occasional small nodular aggregates; microthrombi	Heart, lungs, liver	Serology, microfilaria identification in blood; thoracic radiographs, echocardiography
Liver flukes: *Platynosomum concinnum, Amphimerus pseudofelineus; Opisthorchis, Metorchis*; others	D, C	Chronic cholangitis (eosinophils; lymphocytes, plasma cells, neutrophils); dilated bile ducts; periductal and portal fibrosis	Biliary tract; pancreas	Identification of ova on fecal exam or cytology of bile; direct visualization at surgery or necropsy
Alveolar echinococcosis (*Echinococcus multilocularis*)	D	Cystic hepatic masses containing amorphous debris; granulomatous inflammation	Intestine	Serology, fecal examination, histopathology
Algae				
Prototheca zopfii	D	Granulomatous hepatitis; organisms stained by periodic acid-Schiff or methenamine silver stain	Eyes, colon, CNS, kidneys, liver	Cytology or histopathology of affected tissues; culture

C, cat; CNS, central nervous system; D, dog; EM, electron microscopy; MAT, microscopic agglutination test; PCR, polymerase chain reaction.

Unfortunately, in most cases, routine liver biopsy is unlikely to reveal a specific cause of acute hepatitis.[2,4] Findings of inflammation and necrosis/apoptosis accompanied by nodular regeneration and fibrosis suggests chronic rather than acute hepatitis. The long-term prognosis is better for acute hepatitis than for chronic hepatitis.[4]

Treatment

If a probable cause of acute hepatitis and hepatic necrosis can be determined, then specific treatment is directed at the primary etiology (e.g., discontinuing potentially hepatotoxic medications, treating for leptospirosis with doxycycline, or chelating hepatic copper with penicillamine). In most cases specific therapy is unavailable and treatment is directed at more general supportive and symptomatic treatment of liver disease. Glucocorticoid therapy is not typically indicated in the treatment of acute hepatitis.[4] Empirical treatment with antioxidants such as *S*-adenosylmethionine (SAMe; 20 mg/ kg PO q24h), milk thistle (Siliphos; 3 to 6 mg/kg PO q24h), or vitamin E (10 to 15 IU/kg q24h) may be warranted, as oxidative stress is believed to play a role in drug (carprofen, potentiated sulfonamides, diazepam, methimazole, lomustine, others), and toxin (aflatoxin, organic solvents, and heavy metal toxicity) induced hepatic injury.[9] SAMe and milk thistle have additional cytoprotective properties that could be beneficial in necroinflammatory hepatopathies and hepatotoxicity. Antioxidants and cytoprotective agents are discussed in more detail in Chapters 40 and 46, respectively. Liver biochemistries should be monitored to assess patient response to therapy. Repeat liver biopsy performed 6 to 8 weeks after the initial diagnosis has been recommended, to confirm that acute hepatitis has improved or resolved, or to document a progression toward chronic hepatitis.[4,6] It has been suggested that most dogs with mild idiopathic acute hepatitis (not in ALF) recover after several days, regardless of treatment.[6]

For patients with ALF, aggressive supportive treatment is required. Goals of therapy are to treat the underlying cause when possible, allow adequate time for hepatic regeneration and repair, and prevent or control complications of liver failure, such as hypoglycemia, coagulopathy and anemia, HE, GI ulcers, and septicemia. Intravenous *N*-acetylcysteine (NAC), a glutathione source/ antioxidant, is the antidote of choice for treatment of acetaminophen toxicity. NAC also appears to have additional potential benefits (improved systemic hemodynamics and tissue oxygen delivery), and should be considered for use in any dog or cat with ALF.[9] The optimal dose regimen when NAC is used for this purpose has not been determined. Treatment of complications of liver failure are discussed in "Complications of Liver Disease" section.

Prognosis

The prognosis for recovery in dogs with acute hepatitis is good, as most dogs recover uneventfully.[4] However, there is a potential for dogs with acute hepatitis to develop chronic disease.[4] If animals present with signs of advanced liver failure (e.g., HE, coagulopathy, hypoglycemia), the prognosis is guarded. If the animal survives, hepatic lesions such as periportal ductular proliferation, hepatic fibrosis, postnecrotic scarring, and regenerative hepatic nodules are likely.[2] If a hepatic drug reaction is suspected, reexposure of the patient to the suspect drug should be avoided.

Hepatic Abscesses

Etiology

Hepatic abscesses from bacterial infection of the liver occur uncommonly in dogs and cats.[10-13] Abscesses may form as solitary or multiple macroscopic masses or microabscesses. In newborn animals, Gram-positive and Gram-negative bacteria cause hepatic abscesses, presumably related to postpartum umbilical infections.[14] In adult animals, Gram-negative enteric bacteria (especially *Escherichia coli*) and anaerobes (especially *Clostridia* spp.) are most commonly identified; multiagent infections are frequent.[10,12] Other organisms such as *Yersinia* spp., *Actinomyces* spp., *Nocardia asteroides* can also cause hepatic abscesses as part of a systemic infection.[14]

Pathophysiology

The pathogenesis of hepatic abscesses in dogs and cats is unclear. Hepatic abscesses are usually associated with extrahepatic infections or regional hepatic parenchymal damage. Small numbers of bacteria, including *Clostridium* spp., can be cultured from liver tissue of healthy dogs. Hypoxia of hepatic tissue caused by hepatic neoplasia, liver lobe torsion, or trauma may predispose to abscess formation, because small numbers of existing anaerobes (e.g., *Clostridium* spp.) can proliferate under these conditions.

Other potential sources of bacteria include hematogenous spread (via the umbilical vein, hepatic artery, or translocation of intestinal bacteria into the portal blood), ascension via bile ducts, penetrating abdominal and caudal thoracic wounds, and direct extension from local suppurative diseases. Concurrent diseases or potential predisposing factors in dogs include systemic infections (pneumonia, pyelonephritis, prostatitis, pyometra, endocarditis), gallbladder rupture, pancreatitis, diabetes mellitus, liver lobe torsion, coexisting hepatic disease such as hepatic neoplasia (infected necrosis), long-term phenobarbital administration, long-term corticosteroid administration, and previous surgical biopsy.[10,11] Concurrent diseases in cats include cholecystitis, pyothorax, and hepatic neoplasia.[12] Solitary abscesses are more common in dogs, whereas cats are more likely to be septic and have multiple hepatic abscesses.[11,12] No association with feline leukemia virus or feline immunodeficiency virus infection has been made.[12] Solitary liver abscesses are more likely to involve the right liver lobe in cats and the left liver lobe in dogs.[11,12]

Clinical Examination

When adult dogs and cats are diagnosed with hepatic abscesses, they are usually older than 8 years of age.[10-12] Clinical signs are nonspecific and can be attributed to sepsis, inflammation, and hepatic dysfunction. The most common signs are anorexia, lethargy, vomiting, and diarrhea.[10,11] Clinical signs of hepatic involvement may be overshadowed by signs of the associated disease process (e.g., neoplasia, pyelonephritis, pancreatitis). Dogs with hepatic abscess may have a history of failure to respond to antibiotics or improvement that relapsed when antibiotics are discontinued.[10]

Physical examination findings are often vague and include depression, dehydration, fever, abdominal pain, hepatomegaly, abdominal mass, and abdominal effusion.[10-12] Hypothermia is a more common finding than fever in cats with hepatic abscesses.[12] Because the clinical findings are vague and nonspecific, hepatic abscesses often go undetected until an abdominal ultrasound is performed or they rupture and are discovered during laparotomy. Rupture of a hepatic abscess leads rapidly to peritonitis, septic shock, and death.

Diagnosis

Clinicopathologic abnormalities are consistent with an inflammatory hepatic disease. Potential findings on the complete blood count include neutrophilia with a left shift (or neutropenia and degenerative left shift if rupture occurs), mild anemia, and thrombocytopenia.[10,12] Increased ALT and ALP activity are common findings although the ALT may be in the normal range.[10] Liver enzyme elevations are a less-consistent finding in cats with hepatic abscesses

(increased ALT and ALP activity occurred in less than 50% of cats).[12] Other potential biochemical findings include hyperglobulinemia, mild hyperbilirubinemia, and hypoglycemia (sepsis). Laboratory abnormalities may also reflect the associated disease processes (e.g., hyperglycemia with diabetes mellitus, increased pancreatic lipase immunoreactivity with acute pancreatitis). If an abscess ruptures, cytology of the abdominal infusion reveals septic suppurative inflammation.

Abdominal radiographs may be normal or reveal hepatomegaly, hepatic mass lesion, or decreased abdominal detail or effusion associated with secondary peritonitis. With proliferation of gas-producing organisms, radiolucent areas may be seen in the liver. Ultrasonographic examination permits earlier detection of hepatic abscesses.[11] Ultrasonographically, a liver abscess appears as a hypoechoic or anechoic structure with irregular, hyperechoic margins.[11,13] The ultrasonographic pattern is similar to that seen with hepatic hematomas, cysts, neoplasia, and biliary cystadenoma. Gas may be seen within the abscess.[11] If abscess rupture has occurred, concurrent abdominal effusion may be detected. Additional ultrasonographic findings may reflect associated disorders such as pancreatitis, cholecystitis, or pyelonephritis. Ultrasound-guided fine-needle aspiration of a suspected liver abscess can be safely performed to obtain samples for cytology and culture to confirm the diagnosis.[11] If ultrasonography is not available, the diagnosis of hepatic abscesses is usually established during exploratory laparotomy (or at necropsy).

An attempt should be made to isolate and identify the organism(s) associated with abscessation so that appropriate antibiotic therapy can be instituted based on sensitivity testing. Aerobic and anaerobic cultures can be performed on abscess contents (by fine-needle aspiration), abdominal exudate, blood or hepatic tissues.

Treatment

Treatment of hepatic abscesses consists of surgical resection or drainage of focal lesions, administration of appropriate antibiotics, correction of associated fluid, electrolyte, and acid–base imbalances, and identification and treatment of any underlying disease process. Treatment of large unifocal hepatic abscesses has typically involved surgical resection of affected tissue, which may necessitate partial or full lobectomy.[10,12] If perforation and peritonitis are present, surgical abdominal drainage and lavage are indicated. Ultrasound-guided percutaneous drainage of a solitary abscess may resolve the abscess or allow stabilization until surgical resection can be performed.[11] The successful management of focal hepatic abscesses (up to 8 cm in diameter) by ultrasound-guided percutaneous drainage and alcoholization has been described in five dogs and one cat.[13]

Broad-spectrum combination antibiotic therapy (directed toward both aerobic and anaerobic bacteria) should be initiated as soon as cultures have been obtained. Results of a Gram stain on the exudate may provide preliminary information as to type of organism and guide the empirical choice of potentially effective antibiotics. Recommendations for broad-spectrum antimicrobial coverage of hepatobiliary infections include either a fluoroquinolone combined with amoxicillin/clavulanate or a fluoroquinolone combined with penicillin and metronidazole, until culture results are available. The dose of metronidazole should be adjusted in animals with hepatic dysfunction (7.5 mg/kg PO q8-12h). Antibiotic therapy should be continued for at least 6 to 8 weeks. Response to treatment can be monitored with serial ultrasound examinations and repeated blood work.

Prognosis

Historically, hepatic abscesses have carried a grave prognosis, with an overall reported mortality rate of approximately 50% in dogs[10] and 79% in cats.[12] The survival rate appears to be better when solitary abscesses are detected.[12,13]

Granulomatous Hepatitis

Granulomatous hepatitis is characterized histologically by focal or multifocal aggregates of activated macrophages with an epithelioid appearance, usually accompanied by lymphocytes and plasma cells.[14] This inflammatory response is distinct from that encountered in canine chronic hepatitis. Systemic infectious diseases are an important cause of granulomatous hepatitis and this lesion has been described with fungal infections (histoplasmosis, coccidioidomycosis, many others), bacterial infections (*Mycobacteria, Bartonella, Nocardia, Actinomyces, Rhodococcus*), protozoal diseases (cytauxzoonosis, leishmaniasis); parasitic diseases (visceral larval migrans, schistosomiasis, alveolar echinococcus, *Hepatozoon americana*), and disseminated protothecosis (see Table 61-4).[15,16] In cats, feline infectious peritonitis (coronavirus) is an important cause of multisystemic granulomatous or pyogranulomatous inflammation.

Other causes of granulomatous inflammation include a local response to foreign material (crystalline material, sutures, plant material) or a drug reaction. In humans, granulomatous liver lesions have been associated with administration of diltiazem, sulfonamides, quinidine, allopurinol, interferon-α, and phenytoin.[17,18] However, drug therapy as a cause of granulomatous hepatitis in dogs and cats has not been specifically reported. Granulomatous lesions in the liver has been described in a small number of dogs with lymphangiectasia, lymphosarcoma, and histiocytosis.[19] Many cases of granulomatous hepatitis are idiopathic.[16] Hepatic lipogranulomas ("fatty cysts"), which are often found in dogs with congenital portosystemic shunt, are aggregates of pigment-laden foamy macrophages and should not be confused with granulomatous hepatitis.

Clinical findings with granulomatous hepatitis are highly variable, depending on the underlying cause. When granulomatous hepatitis is identified on liver biopsy, special stains for fungal and mycobacterial organisms should be performed. Other diagnostics to either identify an organism (cytology, culture, fecal exam, PCR) or detect antibodies against the organism (serology) vary widely with the underlying agent (see Table 61-4). If a cause cannot be found after a thorough diagnostic evaluation, consideration should be given to presumptive treatment for undiscovered infectious agents such as atypical mycobacteria, *Bartonella* spp., or systemic fungal infection. Corticosteroids or other immunosuppressant agents should only be used when diagnostic testing and empirical treatment have been unsuccessful, as steroid-induced immunosuppression may exacerbate an underlying infection.[19]

Eosinophilic Hepatitis

Eosinophilic hepatitis occurs rarely in dogs and cats.[2] Potential causes include visceral larval migrans (*Toxocara)*, schistosomiasis, liver fluke infections, *Sarcocystis canis*, and possibly, fungal infections (see Table 61-4).[2] With parasitic causes, eosinophils are often located at or near the site of the parasitic lesion in the liver. Dogs and cats with systemic allergic, parasitic (heartworms), or hypereosinophilic syndromes, may also have scattered eosinophils in the liver, a variant of nonspecific reactive hepatitis.[2] Hepatic drug-induced liver injury should also be considered. Phenytoin and minocycline are associated with eosinophilic infiltrates in humans with drug-induced liver injury.[18,20] Potentiated sulfonamides have been suggested to cause drug-induced eosinophilic hepatitis in dogs,[2] although a more typical pattern is acute hepatocellular necrosis or a cholestatic hepatopathy.[21] When eosinophilic infiltrates are identified, efforts should be directed at diagnosing parasitic causes (fecal,

heartworm test; see Table 61-4), systemic eosinophilia, and hypersensitivity reactions. If no specific cause can be determined, empirical treatment with fenbendazole should be considered, followed by corticosteroid therapy as described for idiopathic chronic hepatitis.

Nonspecific Reactive Hepatitis

The term *nonspecific reactive hepatitis* is used to describe the slight to moderate widespread inflammatory infiltrates of the liver that occur secondary to a spectrum of extrahepatic disease processes.[2] Lesions of nonspecific reactive hepatitis are associated with febrile and inflammatory disorders, especially those involving the GI tract and pancreas, or they may represent residual evidence of a previous intrahepatic inflammatory disorder.[2] Inflammation occurs in portal or parenchymal areas and necrosis is absent. Neutrophils predominate with acute extrahepatic disorders, whereas mononuclear inflammation occurs with chronic extrahepatic disorders or residual hepatic inflammation. The liver may be secondarily affected by systemic disorders because of changes in liver blood flow, portal blood delivery of bacteria, drugs, hormones, cytokines, or other substances from the GI tract, or activation of intrahepatic Kupffer cells (monocyte-macrophage system) involved in the hepatic immune response. It may be challenging to differentiate nonspecific reactive hepatitis from resolving acute hepatitis or mild chronic hepatitis, without supportive clinical information.

Clinical signs in dogs and cats with nonspecific reactive hepatitis are usually referable to the extrahepatic disorder. Liver enzyme elevations (ALT—two times the upper limit of normal; ALP—three- to fourfold increases) are common, thus mimicking primary hepatic disease. However, tests that reflect liver function, including serum bile acids, are usually normal. It is important to consider extrahepatic disorders that can secondary affect the liver, prior to focusing on primary hepatic disease. Treatment is directed at the underlying extrahepatic disorder.

Canine Chronic Hepatitis

Chronic hepatitis, a heterogeneous group of inflammatory-necrotizing diseases of the liver, occurs commonly in dogs, but is rare in cats. Cholangitis, which is inflammatory liver disease that targets the biliary tract, rather than hepatocytes, is more common in cats but also occurs in dogs.The term *chronic hepatitis*, rather than *chronic active hepatitis* or *chronic persistent hepatitis*, is recommended.[2,15] If the etiology is known, it should be included as an adjective, such as "drug-induced chronic hepatitis," or "copper-associated chronic hepatitis"; otherwise, it is considered "idiopathic chronic hepatitis."

Chronic hepatitis in dogs is defined based on histopathologic features of hepatocellular necrosis or apoptosis associated with inflammation and evidence of regeneration and fibrosis.[2] Lymphoplasmacytic inflammation is characteristic, but a neutrophilic component may be present.[2] The histopathologic features of chronic hepatitis are similar, regardless of the underlying cause. Chronic hepatitis has the potential to progress to cirrhosis.[15,16] Recommendations have been made to include a clinical component to the definition of chronic hepatitis, such as documenting an increase in ALT activity along with histologic evidence of hepatic inflammation for a minimum of 4 months. However, many dogs with chronic liver disease are not clinically apparent until the advanced stages, so duration can be difficult to evaluate. The early stages may not be recognized unless biochemistries are monitored for hepatic injury.

A familial predisposition to develop chronic hepatitis has been suggested by demographic studies, pathologic surveys, and clinical case series (see Chapter 62). Breeds of dogs at increased risk for chronic hepatitis include the Bedlington Terrier,[22,23] West Highland White Terrier,[24,25] Doberman Pinscher,[26-28] American and English Cocker Spaniel,[29-33] Skye Terrier,[34] Dalmatian,[35] Labrador Retriever,[36-38] and English Springer Spaniel.[39] Unfortunately, with the exception of hereditary copper-associated liver disease in Bedlington Terriers, information is lacking for most of the breed-related disorders. Female dogs appear to be at increased risk in some studies,[4,40] while others report that male and female dogs are equally affected.[41,42] Within particular breeds, sex differences have been noted (female Doberman Pinschers, Labrador Retrievers, and English Springer Spaniels; male Cocker Spaniels).[26,29,36,38,39] Dogs diagnosed with chronic hepatitis are generally 4 to 7 years of age, but adult dogs of any age (or breed) can be affected.[4,29,41]

Etiology and Pathogenesis

Ideally, canine chronic hepatitis should be classified on an etiologic basis. However, with the exception of copper-associated liver disease in Bedlington Terriers, the cause, pathogenesis, natural history, optimal treatment, and prognosis of these disorders are unknown (Table 61-5). Idiopathic chronic hepatitis is the most common clinical diagnosis.[4,32,40,41]

Infectious Causes. Viral infections are a common cause of chronic hepatitis in humans, but are not currently recognized as an important etiology in dogs. In humans, viruses have the potential

Table 61-5 Causes of Canine Chronic Hepatitis

Category	Cause	Breed Predisposition
Infectious	CAV-1	
	Acidophil cell hepatitis	
	Leptospira spp.	
	Leishmania infantum	
Metabolic	Copper associated	Bedlington Terrier
		West Highland White Terrier
		Skye Terrier
		Doberman Pinscher
		Dalmatian
		Labrador Retriever
		Other breeds?
	α_1-Antitrypsin deficiency?	English (and American?) Cocker Spaniel
Toxic	Phenobarbital, primidone, phenytoin	
	Oxibendazole-diethylcarbamazine	Doberman Pinscher
	Lomustine	
	Carprofen?	
	Aflatoxicosis	
	Transient protoporphyria	German Shepherd
Autoimmune		Doberman Pinscher?
Idiopathic		Any breed
		Cocker Spaniel
		West Highland White Terrier
		Labrador Retriever
		English Springer Spaniel
		German Shepherd

to cause hepatitis either because of a persistent hepatic infection or as a transient infection that triggers an immune response because of a cross-reaction between the virus and liver antigens.[43] In an attempt to identify infectious causes of canine hepatitis, PCR screening of liver tissue was performed in 98 dogs with various stages of hepatitis to look for canine adenovirus type 1, *Hepadnaviridae*, hepatitis A virus, hepatitis C virus, hepatitis E virus, *Helicobacter* spp., *Leptospira* spp., and *Borrelia* spp.[44] Based on negative results, the authors concluded that canine hepatitis is not typically caused by these infectious agents.[44] However, dogs that are experimentally infected with canine adenovirus type I, but are partially immune, can develop chronic hepatitis that progresses to cirrhosis.[45] The virus could not be detected beyond the first week postinfection, although the disease progressed over a period of months.[45] Canine adenovirus antigen has been demonstrated by immunohistochemical techniques in formalin-fixed liver sections from five of 53 dogs with various hepatic inflammatory lesions, suggesting that canine adenovirus 1 (CAV-1) may play a role in spontaneous chronic hepatitis.[46] In contrast, PCR and immunohistochemistry failed to detect canine adenovirus in liver tissue of 45 dogs with chronic liver disease.[47] Whether CAV-1 is a significant cause of chronic hepatitis under natural conditions is unknown.

Another proposed viral cause of chronic hepatitis and cirrhosis is the "canine acidophil cell hepatitis virus," reported from Great Britain in the 1980s.[48,49] This transmissible agent, most likely a virus, is distinct from CAV-1. It was transmitted experimentally by subcutaneous injection of serum or liver extracts from affected dogs, resulting in experimentally induced acute and chronic hepatitis. No further studies have been published to clarify the nature of this infectious agent or the associated hepatitis.

Canine leptospirosis is typically associated with acute cholestatic hepatic disease and acute renal failure. However, persistent infection can cause chronic hepatitis in the absence of azotemia.[50,51] *Leptospira* serovar *grippotyphosa* was incriminated as a cause of chronic hepatitis in a kennel of American Foxhounds, based on serologic evidence and demonstration of spirochetes in the liver.[50] *Leptospira* serogroup *australis* (serovars *australis*, *bratislava*, and *muenchen*) infection was suspected to cause chronic hepatitis in 16 young Beagle dogs in a breeding colony routinely vaccinated against leptospirosis serogroups *canicola* and *icterohaemorrhagica*.[51]

Canine leishmaniasis has been associated with histologic evidence of chronic hepatitis,[52] but clinical features suggestive of hepatic involvement (hepatomegaly, ascites, or icterus) were absent. Histologic findings revealed granulomatous hepatitis in most dogs, but some dogs had marked portal infiltration with lymphocytes and plasma cells, and mild portal fibrosis. *Leishmania* amastigotes were routinely identified in macrophages in liver or other affected tissues. *Bartonella clarridgeiae* DNA was amplified from a liver biopsy of a Doberman Pinscher with copper-associated chronic hepatitis, although the significance of this finding is unclear.[53]

Copper Accumulation. Copper is an essential trace element in diets and is required for a number of physiologically important enzymes. Cells have highly specialized and complex systems for maintaining intracellular copper concentrations. At toxic concentrations, free intracellular copper initiates oxidative damage causing hepatocellular necrosis and inflammation.[54,55] Normal copper metabolism has been reviewed in detail elsewhere.[54,56]

Copper accumulation in the liver can be associated with significant hepatic injury resulting in acute hepatitis, chronic hepatitis, and cirrhosis (Figure 61-18).[4,54,57] It is one of the few well-documented causes of canine chronic hepatitis. In one study, copper-associated

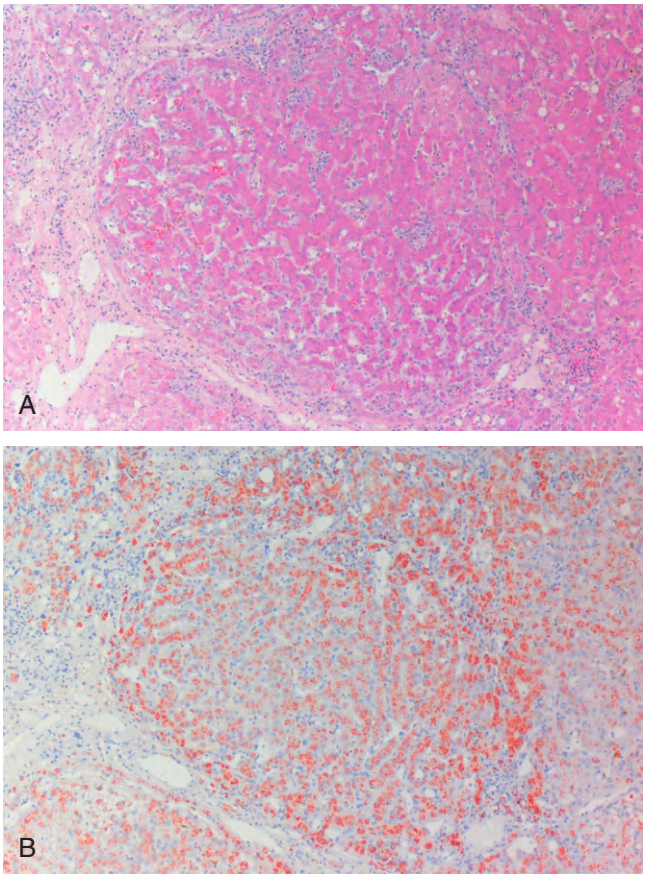

Figure 61-18 Liver biopsy from a 12-year-old Dalmatian/mixed breed dog with copper-associated chronic hepatitis and a quantitative hepatic copper of 8264 µg/g dry weight (normal <400 µg/g). **A,** Periportal hepatitis with portal fibrosis and nodular hepatic regeneration (H&E, 10×). **B,** Rhodanine stain of liver tissue was markedly positive for copper (orange granules, 10×). (Courtesy of Dr. Paul Stromberg.)

hepatitis (acute and chronic) accounted for one-third of all dogs with primary hepatitis.[4] Hepatic copper accumulation and hepatopathy have been described in cats but appears to be rare.[58,59] The severity of hepatic injury correlates with the amount of hepatic copper, but subcellular localization of molecules and the molecular association also plays a role.[54] Serum copper levels do not accurately reflect hepatic copper content and quantitative analysis of copper in the liver is required.[56] Hepatic copper concentration in normal dogs is between 150 and 400 µg/g dry weight (parts per million).[28,57] Inflammatory hepatic injury does not consistently occur until copper concentrations exceed 2000 µg/g dry weight.[60,61] However, there may be breed variations; for example, in Doberman Pinschers hepatic inflammation is present with copper concentrations of less than 2000 µg/g.[27,57] Transient acquired Fanconi syndrome has been described in dogs with excess hepatic copper accumulation.[62,63] Copper granules were demonstrated on renal biopsy in some but not all dogs.

Potential mechanisms for hepatic copper accumulation include primary metabolic defects in hepatic copper metabolism, cholestasis causing impaired biliary excretion of copper, and excess copper absorption.[54,56] A primary defect in hepatic copper metabolism occurs in Bedlington Terriers with a genetic mutation in the gene encoding the copper transport protein, COMMD1 (formerly MURR1), resulting in a defect in biliary copper excretion.[64,65] In

the early stages, copper is sequestered in hepatic lysosomes and hepatic damage is minimal. However, with progressive accumulation of copper, hepatic injury becomes significant. The average copper concentration in Bedlington Terriers with chronic hepatitis is approximately 6000 µg/g dry weight and values up to 12,000 µg/g dry weight have been reported.[23,57] Inherited copper-associated liver disease is also described in the West Highland White Terrier, Skye Terrier, Doberman Pinscher, Dalmatian, and Labrador Retriever, but with the possible exception of Dalmatians, the hepatic copper levels are much lower than in Bedlington Terriers.[25-27,34,35,38] The pathogenesis of copper accumulation and the relationship to chronic liver disease in these breeds is poorly understood. It seems likely that these breeds have a hereditary disorder of copper handling, but it is unlikely to be the same as described for the Bedlington Terrier.

Hepatic copper accumulation in the liver may also be a consequence rather than the cause of chronic hepatitis. Because copper is normally excreted in the bile, chronic cholestasis and impaired bile flow can result in secondary copper accumulation.[57,66] Secondary copper accumulation is predominantly periportal and is usually less than 2000 µg/g dry weight.[57,66] The effect of cholestasis on hepatic copper content was evaluated in three groups of dogs: Bedlington Terriers with copper toxicity, dogs with extrahepatic biliary obstruction (the prototype example of a cholestatic disorder) and chronic hepatitis in breeds not known to be at risk for copper-associated liver disease.[66] Hepatic copper content was evaluated by a semiquantitative method based on copper staining of liver tissue with rubeanic acid, using a scale of 0 (no copper) to 5.[67] Copper staining revealed absent to mild increases (scores of 0 to 2+) in dogs with biliary obstruction and chronic hepatitis when compared with Bedlington Terriers (scores of 5+). It was concluded that copper scores of 3+ or higher were suggestive of a primary copper storage disease.[66] Unfortunately, quantitative copper analysis was not evaluated. Markers of oxidative injury and altered defense mechanisms were similar in the three groups, consistent with the concept that copper, inflammation, and cholestasis can all contribute to oxidative injury.[66]

High dietary copper intake appears to be an unlikely explanation for hepatic copper accumulation and liver disease in dogs.[56] However, the copper content of commercial dog foods ranges from 12 to 16 mg/kg dry matter, which is relatively high compared with recommended minimum daily copper requirements in dogs.[56] There is speculation that the recent increase in pathologically elevated hepatic copper concentrations (specifically evaluated in Labrador Retrievers), may coincide with a pet food industry recommendation to replace cupric/cuprous oxide in feed formulations because of its low bioavailability.[68]

Many dogs with copper-associated chronic hepatitis also have increased hepatic iron concentrations.[69] Hepatic iron accumulation usually correlates with degree of inflammation.[40,69] Whether iron, as an oxidant, interacts with copper to contribute to lesions seen in copper-associated hepatitis remains to be determined.

α_1-Antitrypsin Deficiency. Inherited α_1-antitrypsin deficiency is a well-recognized cause of chronic hepatitis and cirrhosis in humans, and may play a role in the pathogenesis of chronic hepatitis in some dogs.[31] α_1-Antitrypsin is a circulating protease inhibitor that is synthesized and secreted by the liver. α_1-Antitrypsin deficiency in affected humans results in defective formation and impaired hepatic secretion of α_1-antitrypsin, resulting in hepatic accumulation of α_1-antitrypsin and hepatic injury. Serum levels of α_1-antitrypsin are typically low. In a study of 57 dogs with chronic liver disease, α_1-antitrypsin was detected by immunohistochemical staining in the liver of 37 dogs but was not identified in any control samples from healthy livers. None of the dogs had decreased serum levels of α_1-antitrypsin. Positive α_1-antitrypsin staining was a more consistent finding in English and American Cocker Spaniels with chronic liver disease, than in other breeds. The authors concluded that accumulation of α_1-antitrypsin might play a role, but it could not be determined if it was the cause or a result of chronic liver disease.[31]

Drugs and Toxins. Drug or toxin exposure is a potential cause of canine chronic hepatic disease. Drugs that have been incriminated include anticonvulsants (phenobarbital, primidone, phenytoin), oxibendazole-diethylcarbamazine, lomustine, and possibly carprofen.[70-73] Chronic hepatitis and cirrhosis from long-term phenobarbital therapy is most widely recognized.[70,71] Exposure to aflatoxin from contaminated commercial dog food is usually associated with ALF, but low-level long-term exposure in dogs can result in chronic hepatic injury (biliary hyperplasia, fibrosis, nodular regeneration). A breeding colony of German Shepherd dogs developed chronic hepatitis and cirrhosis that was suspected (but never confirmed) to be a result of exposure to a porphyrinogenic substance, based on the finding of aggregates of crystalline pigments with orange birefringence with polarized light.[74] Early recognition of drug- or toxin-induced chronic hepatic injury requires biochemical monitoring of liver enzymes, as dogs are clinically asymptomatic in the early stages.

Autoimmune/Immune Mechanisms. Autoimmune hepatitis has not been documented in dogs. However, some dogs with chronic hepatitis appear to respond to corticosteroid therapy and thus may correspond to autoimmune hepatitis in humans.[41] Autoimmune hepatitis in humans is a progressive chronic hepatitis of unknown cause that is believed to occur when an environmental agent (viruses, medications) triggers a cascade of T-cell–mediated events directed at liver antigens, in a genetically predisposed individual.[43] Women are more commonly affected than men. Hyperglobulinemia is a common finding. An infectious cause is difficult to document, as exposure may have occurred many years prior to the overt autoimmune disease.[43] Certain drugs may induce or unmask an autoimmune hepatitis, or simply cause hepatocellular injury that mimics autoimmune hepatitis.[43] An autoimmune component to Doberman Pinscher hepatitis has been speculated, because of the breed's predisposition, high female predominance, and the finding that expression of MHC class II antigens on hepatocytes of affected dogs correlates with degree of inflammation and decreases after treatment with prednisolone.[75] Dogs with chronic hepatitis may have concurrent disorders associated with immune aberrations (immune hemolytic anemia, hypothyroidism, atopy, glomerulonephritis), but whether this is coincidental or indicative of the presence of multiple immune disorders as seen with autoimmune hepatitis in humans is unknown.[37,76,77]

Autoimmune hepatitis in humans is diagnosed when other causes of acute or chronic hepatitis have been excluded and serum autoantibodies (antinuclear, antismooth muscle, antibody to liver/kidney microsomes type 1, antibody to liver cytosol type 1) are detected.[43] A number of studies have evaluated the role of liver-associated antibodies and cell-mediated response in dogs with chronic hepatitis, but none answers the question of whether the immune response is the primary cause of the hepatitis or a secondary phenomenon. Twenty-four dogs with chronic hepatitis were evaluated for circulating autoantibodies (against cell nuclei, smooth muscle, liver membrane, and mitochondria) by indirect immunofluorescence.[77] Antibodies to cell nuclei and liver membranes were

detected, but were also found in dogs with other types of hepatic disease, suggesting a nonspecific secondary response. Patterns of circulating autoantibodies found in dogs differed significantly from those found in humans with chronic liver disease.[77] In another study, serum anti–liver-membrane-protein antibody-positive dogs (1:40 to >1:1600) had higher ALT activity, total bilirubin concentration, and more severe hepatic lesions than did anti–liver-membrane-protein antibody-negative dogs, but it was not determined whether autoantibodies were primary or secondary.[78] CD3+ lymphocytes are the most common hepatic lymphoid cells in dogs with chronic hepatitis and are associated with hepatic necrosis,[79-81] but also account for 54% of hepatic lymphocytes in normal dogs.[82]

Clinical Examination

Historical and physical examination findings in dogs with chronic hepatitis are indicative of chronic hepatic disease, and are similar regardless of the underlying cause. Signs are often initially vague and nonspecific, such as anorexia, lethargy, vomiting, diarrhea, weight loss, PU, and PD.[4,32] With increased severity of hepatic dysfunction, signs of overt liver failure develop, such as ascites, jaundice, and HE. The presence of ascites and HE suggest that chronic hepatitis has progressed to cirrhosis, and ascites is a negative prognostic indicator.[4,42] Melena associated with gastroduodenal ulceration or coagulopathy is also more likely with advanced liver disease.[32] Because of the large functional reserve capacity of the liver, the onset of signs may appear very recent, initially suggesting an acute rather than chronic hepatic disorder. Clinicopathologic features that support chronicity include poor body condition, ascites, microhepatia, hypoalbuminemia, and histologic evidence of fibrosis.

Diagnosis

In the early (subclinical) stages, dogs are asymptomatic and only identified by biochemical screening for liver enzyme elevations. Increased serum ALT activity, reflecting ongoing hepatic injury, is reported in 75% to 95% of dogs with chronic hepatitis.[4,7] Serum ALT activity may exceed 10 times the upper normal limit.[7] Periods of normal ALT activity may reflect cyclic disease activity and the varying severity of necrosis.[7] Serum ALP activity is also commonly increased, but the magnitude of the increase is generally lower than seen with ALT activity. When chronic hepatitis advances to cirrhosis, liver enzyme activity may be normal, indicating decreased viable parenchymal mass.[7] Abnormalities in biochemical tests such as hyperbilirubinemia, hypoalbuminemia, decreased blood urea nitrogen (BUN), hypoglycemia, and increased SBA indicate hepatic dysfunction and a more advanced stage of disease.[32] Hyperglobulinemia can be seen in dogs with cirrhosis, but it remains to be determined whether this corresponds with increased autoantibodies as occurs in humans with autoimmune hepatitis, or whether it reflects nonspecific systemic antibody production in response to antigens from the portal blood which bypass the liver through acquired PSSs.[83] Mild nonregenerative anemia may be a reflection of chronic disease. Regenerative anemia can occur from blood loss secondary to a coagulopathy or bleeding GI ulcers. Copper-associated hemolytic anemia has only been documented in Bedlington Terriers. Abnormal hemostatic parameters (prolonged aPTT and PT) are indicative of severe hepatic dysfunction or DIC. A prolonged PT and thrombocytopenia may be negative prognostic indicators.[16,37] Analysis of ascitic fluid reveals a transudate or modified transudate.[32,42]

Abdominal radiographs are unremarkable except when advanced stages of disease are accompanied by microhepatia or ascites. In the early stages of chronic hepatitis, ultrasonography of the liver may be normal or reveal nonspecific changes in echogenicity. When chronic hepatitis has advanced to cirrhosis, potential ultrasonographic findings include microhepatia, irregular hepatic margins, focal lesions representing regenerative nodules, increased parenchymal echogenicity associated with increased fibrous tissue, and ascites. Splenomegaly and acquired PSSs may also be detected.

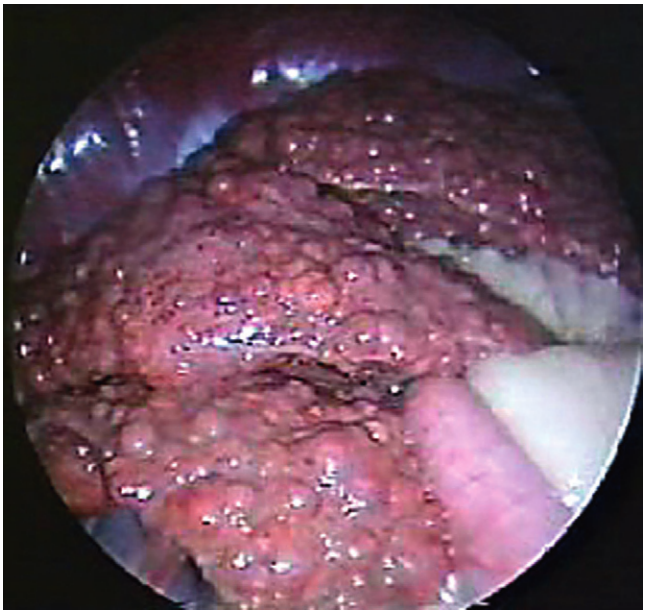

Figure 61-19 Laparoscopic appearance of a cirrhotic liver in a dog with idiopathic epilepsy treated with long-term phenobarbital therapy.

A liver biopsy is essential for the diagnosis of chronic hepatitis. Wedge biopsies are preferred over needle biopsies because they provide more tissue and are more likely to represent pathologic process(es) in the liver. When cirrhosis is present, laparotomy or laparoscopy often provide a better appreciation for the gross nodularity of the liver than can be ascertained from blind percutaneous needle biopsy (Figure 61-19). Chronic hepatitis is characterized histologically by moderate to severe inflammation (usually combinations of lymphocytes and plasma cells) associated with piecemeal necrosis. Piecemeal necrosis, also referred to as interface hepatitis, is necrosis involving the layer of hepatocytes adjacent to the portal tract or "limiting plate."[2] The term *bridging necrosis* is used when necrosis and inflammation dissect across the hepatic lobule from portal areas to central veins or to adjacent hepatic lobules and suggests a severe form of chronic hepatitis.[2] Histopathologic evaluation of the liver should not only consider etiology, but the pathologist should also comment on the activity (amount of inflammation, extent of apoptosis and necrosis) and the stage of disease (extent and pattern of fibrosis; architectural distortion suggestive of cirrhosis).[2]

Biopsies from dogs with chronic hepatitis should routinely be evaluated for copper accumulation. On hematoxylin and eosin staining, excess copper appears as golden brown refractile granules.[28] Histochemical stains, such as rhodanine or rubeanic acid, can be used to semiquantitatively evaluate for copper in the liver (see Figure 61-19). These stains consistently detect copper when amounts exceed 400 μg/g dry weight.[60] Values obtained by quantitative copper analysis have a strong correlation with the number and size of granules seen with histochemical stains within the range of 400 to 1000 μg/g of liver tissue.[60] Zonal distribution of copper

accumulation should be noted, as copper accumulation starting in the centrilobular area is more likely with a primary metabolic defect in copper metabolism.[54] Copper granules can also be detected on cytology of hepatic aspirates or impression smears stained with rhodanine or rubeanic acid. Quantitative analysis for copper, by atomic absorption analysis on fresh hepatic tissue, is the definitive method to document increased hepatic copper content. Needle core biopsy specimens may not be reliable for metal analysis, as copper and iron values are consistently lower in needle core versus wedge biopsy samples.[84] Formalin-fixed tissues should be avoided, because formalin may contain copper or leach copper from the tissue.[57] Hepatic copper can be reliably determined retrospectively on deparaffinized-archived liver biopsy specimens.[84]

Once chronic hepatitis has been confirmed, a careful consideration of known causes of chronic hepatitis is essential (see Table 61-5). Findings that would support a primary metabolic defect in copper metabolism include a previously recognized breed predisposition, copper accumulation that precedes cholestasis or inflammation, centrilobular (zone 3) distribution of copper, histochemical score for copper of 3+ or greater, or quantitative copper measurements that exceed 2000 µg/g dry weight.[54,57,66] Special stains of the liver should be requested to evaluate for infectious agents such as leptospirosis; serum antibody titers for leptospirosis may be indicated. A history of chronic drug therapy should be sought, especially long-term anticonvulsant therapy or other drugs listed in Table 61-5.

Treatment

Recommendations for treatment of chronic hepatitis are empirical at best, because of the lack of controlled therapeutic studies on a well-defined population of dogs with this disorder. If a probable cause or category of injury can be determined, then specific treatment is directed at the primary etiology, for example, discontinuation of phenobarbital, treatment of leptospirosis, or chelation of hepatic copper with penicillamine. In most cases, specific therapy will be unavailable.

Treatment of chronic hepatitis in dogs has traditionally centered on the use of corticosteroids, presuming that, as in humans with the autoimmune form of hepatitis, immunologic mechanisms (inflammatory cells and mediators, local cytokines), contribute to hepatic inflammation and progression to cirrhosis. Corticosteroids have antiinflammatory, immune-modulating, and antifibrotic effects, which may be beneficial in chronic hepatitis. A large retrospective study suggested that corticosteroid therapy at initial immunosuppressive doses (2.2 mg/kg/day; eventually tapered to 0.6 mg/kg/day) improved survival in dogs with chronic hepatitis.[41] However, many concurrent drugs were given and, undoubtedly, a heterogeneous group of disorders were included under the diagnosis of "chronic hepatitis." Corticosteroid therapy appears warranted in dogs with histologic features of active inflammation and persistent increases in serum liver enzyme activity, for which known causes of chronic hepatitis (including infectious causes) have been excluded.[41,85] Glucocorticoid therapy is not indicated for treatment of chronic hepatitis caused by drug therapy, infectious agents, or primary hepatic copper accumulation.

The optimal dose and duration of corticosteroid therapy for treatment of canine chronic hepatitis is unknown, including whether immunosuppressive doses are required, or whether lower, anti-inflammatory levels would suffice.[76] Even in humans with autoimmune hepatitis, immunosuppressive doses of corticosteroids may not be required.[43] Prednisone (or prednisolone) at an initial dose of 1 to 2 mg/kg/day PO and then gradually tapered to 0.5 to 1.0 mg/kg every 48 hours is most often recommended for treatment of canine chronic hepatitis. Complications of corticosteroid therapy include GI bleeding (which may precipitate HE), secondary infections, iatrogenic Cushing disease, and worsening of ascites. Dexamethasone (0.2 mg/kg PO q24h) may be preferred in dogs with ascites or edema, because it lacks mineralocorticoid activity, which could exacerbate these signs.

Prednisone is often used in combination with azathioprine, especially if side effects of prednisone become objectionable. Azathioprine is an antimetabolite with antiinflammatory and immune-modulating effects, and is commonly used in combination with prednisone in humans with autoimmune hepatitis.[43] The dose of azathioprine in dogs is 1 to 2 mg/kg/day PO every 24 hours for 1 to 2 weeks, then tapered to every 48 hours for maintenance therapy. Prednisone (0.5 to 1.0 mg/kg/day) is given on the alternate days. Because azathioprine may cause bone marrow suppression and acute hepatotoxicity, the complete blood count and biochemical profile should be monitored. Antiinflammatory agents and immunosuppressive drugs are discussed in more detail in Chapters 38 and 49, respectively. Because glucocorticoids increase liver enzyme activity (especially serum ALP activity), response to therapy is best evaluated by a followup liver biopsy performed 3 to 6 months after starting therapy. If glucocorticoid therapy is eventually discontinued, clinical and biochemical parameters should be periodically monitored to detect a relapse.

Dogs with hepatic copper concentrations greater than 1500 µg/g, should be treated with the copper chelator penicillamine at a dose of 10 to 15 mg/kg PO every 12 hours.[57] Treatment usually requires months to years to produce significant decreases in hepatic copper. A mean decrease in copper of approximately 1500 µg/g was achieved in Bedlington Terriers treated for 6 months.[86] Dogs with secondary copper accumulation appear to respond more rapidly, possibly because hepatic copper content is lower in these breeds.[86] Doberman Pinschers with subclinical hepatitis treated with penicillamine for 4 months had a mean decrease in copper from 1036 µg/g to 407 µg/g.[87] Penicillamine has additional effects beyond copper chelation, which may be beneficial in dogs with chronic hepatitis, including inhibition of collagen deposition, stimulation of collagenase activity, immunosuppression, and immunomodulation.[54] Common side effects of penicillamine therapy include anorexia, nausea, and vomiting, which can be minimized by giving the medication with a small amount of food. The copper chelator, trientine (10 to 15 mg/kg PO q12h), is also effective for reducing hepatic copper concentrations.[86] It has fewer side effects than penicillamine and is effective in dogs with hemolytic anemia caused by copper release from necrotic hepatocytes. Iatrogenic copper deficiency (microcytosis and hepatic dysfunction) has been described in a dog treated with long-term copper chelation therapy (trientine) and a copper-restricted diet.[88] Decisions on duration of chelator therapy are based on followup liver biopsies with periodic monitoring of quantitative hepatic copper content.

Oral zinc salts can be used for maintenance therapy after copper chelation, or as initial therapy in dogs with hepatic copper concentrations between 400 µg/g dry weight and 1500 µg/g dry weight. Zinc supplementation is typically used in conjunction with dietary copper restriction. Zinc decreases intestinal copper absorption by inducing the intestinal copper-binding protein, metallothionein, within intestinal epithelial cells, which preferentially binds dietary copper and prevents its absorption. Zinc acetate is given at a dose of 100 mg PO BID for 2 to 3 months, then at a maintenance dose of 50 mg PO BID.[89] A minimum of 3 months of zinc therapy is required before copper uptake from the intestinal tract is blocked.[89]

Zinc administration should be separated from meals by at least 1 hour and should theoretically not be prescribed at the same time as a copper chelator.[54] Serum zinc concentrations should be monitored to achieve a level of 200 to 400 µg/dL. Zinc concentrations greater than 500 µg/dL may be toxic (hemolytic anemia).

Low-copper diets are most beneficial for managing early (subclinical) copper accumulation in dogs affected with primary metabolic defects in hepatic copper metabolism.

Feeding a low-copper diet decreases hepatic copper content in Labrador Retrievers with subclinical copper-associated liver disease.[90] Additional treatment with zinc does not appear to increase the copper-lowering effect of dietary management.[90] Foods containing large amounts of copper (liver, other organ meats, shellfish, eggs, bean/legumes, chocolate, nuts, cereals, and copper-containing vitamin supplements) should be avoided.

Because oxidative stress is a significant mechanism for hepatic damage associated with copper accumulation and necroinflammatory hepatic disorders,[66,91] antioxidant therapy with vitamin E (10 to 15 IU/kg/day), or SAMe (20 mg/kg/day) has been advocated.[9] Other cytoprotective agents such as silymarin (milk thistle) and ursodeoxycholic acid may also be beneficial.[9] Chapters 40 and 46 discuss cytoprotective agents used in the treatment of hepatobiliary disease in detail. When end-stage cirrhosis is diagnosed, treatment is mainly supportive, as cirrhosis itself is essentially irreversible. Measures should also be instituted to control the complications of chronic liver failure, such as ascites, HE, gastroduodenal ulcers, and coagulopathy, which are discussed in more detail in "Complications of Liver Disease" section.

Prognosis

The response to treatment of chronic hepatitis is variable, which is not unexpected as it is likely a heterogeneous group of diseases. Some dogs can eventually be taken off medication and remain in remission, but more often, therapy must be continued indefinitely. Other dogs fail to respond, especially those that have advanced disease with cirrhosis.[4,32] In one study, the estimated median survival time in 42 dogs with idiopathic chronic hepatitis was 18 months (range: 0 to 49 months) and in 23 dogs with copper-associated chronic hepatitis it was 17 months (range: 7 to 27 months).[4] Mean survival time in 20 dogs with cirrhosis was 1 week.[32]

Chronic Hepatitis in Specific Breeds

Bedlington Terrier

Bedlington Terriers develop chronic hepatitis and cirrhosis from copper toxicity, as a consequence of an inherited metabolic defect resulting in impaired biliary copper excretion.[23,57,76] The disorder is transmitted by autosomal recessive inheritance. The gene responsible for this metabolic disorder is COMMD1, which is different than that described for copper toxicity (Wilson disease) in humans, in which the gene involved is ATP7B.[64] There is no gender predilection. At one time, it was speculated that as many as 60% of the breed might be affected.[57] Hepatic copper concentration in normal Bedlington Terriers ranges from 91 to 358 µg/g with a mean of 206 ± 56 µg/g dry weight.[23] Bedlington Terrier copper-associated liver disease is associated with progressive, hepatic copper accumulation (copper levels of up to 12,000 µg/g) unless treatment is instituted. The lowest hepatic concentrations of copper are found in the youngest dogs and concentrations increase with age, peaking at around 6 years. Copper content usually declines thereafter in affected dogs, but not to normal. This decline may be a result of replacement of copper-containing hepatocytes by fibrous tissue or regenerative nodules that do not contain copper. The severity of hepatic disease is correlated with the amount of hepatic copper. Hepatic injury is believed to occur when progressive copper accumulation exceeds the storage capacity of the lysosomes; copper is released to the cytoplasm, damaging mitochondria, initiating lipid membrane peroxidation, and eventually causing cell death.

Affected dogs can be asymptomatic (in the early stages) or show signs of acute hepatic necrosis, chronic hepatitis, or cirrhosis.[54] In young dogs, copper accumulates in centrilobular (zone 3) hepatocytes and is sequestered in hepatic lysosomes. During this first stage, copper concentrations are between 400 and 1500 µg/g, dogs are asymptomatic, biochemical testing is within normal limits, and liver biopsy findings are unremarkable. In the second stage, when hepatic copper concentrations are between 1500 and 2000 µg/g, copper granules are also found in midzonal (zone 2) and periportal (zone 1) hepatocytes. Although dogs are still asymptomatic, focal hepatic inflammation (centrilobular mixed cell foci, with necrotic hepatocytes, lymphoplasmacytic inflammation, and copper-laden macrophages) is seen on biopsy, and increased serum ALT activity reflects hepatocellular injury. In the most advanced stage, when hepatic copper concentration exceeds 2000 µg/g, morphologic changes reveal chronic hepatitis that may progress to cirrhosis, and clinical and biochemical evidence of liver disease become apparent. Clinical signs include anorexia, lethargy vomiting, and weight loss. With progression to cirrhosis, findings of jaundice, ascites, and HE may develop. Biochemical findings vary with the stage of disease. Increased serum ALT activity is the most sensitive laboratory indicator, although findings will be normal in young dogs in stage I, because of the lack of hepatic inflammation. Other serum biochemical abnormalities typical of chronic hepatic dysfunction eventually develop. In some cases, acute hepatic necrosis and ALF occur. Hepatocellular necrosis may be associated with release of copper from necrotic hepatocytes, resulting in hemolytic anemia. During episodes of hemolysis, plasma copper levels are increased; other findings include low packed cell volume, hemoglobinemia, and hemoglobinuria. Liver biopsy and quantitative analysis of hepatic copper concentrations is required for definitive diagnosis and staging of the disease. Serum copper or ceruloplasmin concentrations are not helpful to make a diagnosis.[57]

Liver biopsies should be performed in all Bedlington Terriers considered for breeding, in order to identify and remove affected dogs from breeding programs. Screening of asymptomatic dogs with a liver biopsy at 6 months and 15 months of age can determine if an affected dog is homozygous or heterozygous (a carrier).[15] Affected dogs (both homozygous and heterozygous) typically have increased hepatic copper by 6 months of age. However, copper concentrations in dogs who are carriers (heterozygous) return to normal by 1 year of age, whereas copper concentrations in homozygous dogs continues to increase.[57] Selective breeding programs in the Netherlands has decreased the prevalence of Bedlington Terrier copper-associated liver disease from 46% (1976-1986) to 11% (1990-1997).[92]

DNA testing of Bedlington Terriers is available from VetGen (www.vetgen.com). This assay evaluates a linkage-based DNA marker (CO4107, allele 2) that is located in the chromosome close to the gene for copper toxicity.[93] The test can identify normal, affected, and carrier dogs with 90% accuracy. However, the marker can only be relied on for diagnosis of the genetic status of an individual dog when supported by a pedigree study.[93,94] Significant discrepancies were reported in 22 Bedlington Terriers, when comparing results of liver biopsy and the DNA marker.[94] This may be attributed to different subpopulations of Bedlington Terriers with variations in the disease-causing mutation of the COMMD1 gene or a second mutant copper gene could play a role.[94] Liver biopsy for quantitative

copper and morphologic examination remain the best option for diagnosis in the individual dog.[94] A database for certification of Bedlington Terriers is maintained on the Web site (www.caninehealthinfo.org) of the Canine Health Information Center, which is sponsored by the AKC/Canine Health Foundation and the Orthopedic Foundation for Animals.

Affected Bedlington Terriers who are asymptomatic (copper >400 μg/g dry weight but less than 1500 μg/g dry weight) should have dietary copper restriction and zinc supplementation. Bedlington Terriers with copper accumulation (copper >1500 μg/g dry weight) and chronic hepatitis should be treated with a copper chelator such as penicillamine or trientine.[57] Early diagnosis and treatment with either zinc or copper chelators will allow most dogs to lead a normal life.[57] Treatment of hemolytic anemia may require a blood transfusion. Trientine dihydrochloride (but not penicillamine) may be effective in chelating circulating copper during a hemolytic episode. Chapter 43 discusses copper-chelating agents in more detail.

Doberman Pinscher

Doberman Pinschers are at increased risk for the development of severe chronic hepatitis and cirrhosis.[26,28,81,95] Doberman hepatitis accounted for 4% of all deaths in a Dutch population of 340 Dobermans.[96] Middle-aged (4 to 7 years) female dogs are at increased risk, but males also may be affected. Although a hereditary mechanism is suspected, the pathogenesis of this disorder is unclear.[28] Copper accumulation appears to be associated with hepatic damage, but the pathogenesis is different from the Bedlington Terrier disorder.[27] Immune mechanisms may also play a role.[75,81]

Many Doberman Pinschers are diagnosed in the advanced stages of hepatic failure.[26] Evidence of excessive bleeding (gingival bleeding, epistaxis, and melena) are common. Signs of HE often predominate in the terminal stages. Common physical examination findings include ascites, jaundice, and weight loss. Splenomegaly (associated with portal hypertension) is common. Laboratory findings included increased ALT and ALP activity, hyperbilirubinemia, hypoalbuminemia, hyperammonemia, coagulopathy, and thrombocytopenia.[26] Typical histologic lesions include portal inflammation (lymphocytes, plasma cells, and macrophages), piecemeal necrosis, bridging necrosis, bile duct proliferation, and portal fibrosis.

Hepatic copper concentrations are increased in most affected dogs and are typically between 1000 and 2000 μg/g dry weight, although values as high as 4700 μg/g have been reported.[28,81] The significance of the increased hepatic copper concentration in this breed remains controversial. Copper accumulation was originally attributed to secondary mechanisms, as Doberman Pinschers with advanced disease (chronic hepatitis and cirrhosis) have biochemical and histologic evidence of cholestasis. However, evaluation of affected dogs in the early (subclinical) stage, reveals that copper accumulation precedes cholestasis,[27,95] and decreased biliary excretion of radiolabeled copper has been documented.[97] The hepatic distribution of copper and location of inflammation varies with the stage of disease. In the early stages, the copper (and focal inflammation) is centrilobular.[27,81,95] As the disorder progresses, copper accumulation and inflammation are more pronounced in periportal regions and areas of bridging necrosis.[95] Although copper appears to be related to the hepatic inflammatory reaction, copper levels are typically less than 2000 μg/g dry weight, the minimum amount of copper that is believed to cause hepatocellular injury in Bedlington Terriers and West Highland White Terriers.[60,61] A primary copper retention disorder has been proposed,[28] but the genes associated with Bedlington copper toxicity (COMMD1) and Wilson disease in humans (ATP7B) have been excluded.[98]

Recent efforts have focused on identification of affected Doberman Pinschers prior to advanced hepatic disease. In Finland, a survey of 626 randomly selected, clinically healthy Doberman Pinschers, revealed that 8.8% of dogs had increased ALT activity, and 3.4% had hepatitis (parenchymal and portal mononuclear inflammation and positive stains for copper).[99,100] The mean age of dogs with subclinical hepatitis was 3.8 years, compared with clinically affected dogs (5.5 years). The asymptomatic period lasted an average of 19 months. The prevalence of subclinical Doberman hepatitis was investigated in 106 randomly selected 3 year old Doberman Pinschers in the Netherlands.[27] Subclinical hepatitis was identified in 22 dogs (19 females and three males); hepatic copper concentration was higher in dogs with hepatitis (419 ± 414 μg/g dry weight) than those without liver disease (197 ±113 μg/g).[27] Serial liver biopsies over at least a 2-year period, revealed that hepatitis persisted only in dogs with copper levels greater than 400 μg/g dry weight, and copper levels continued to increase in these dogs (939 ± 299 μg/g), supporting a relationship between copper, inflammation and hepatitis.[27]

It has also been proposed that hepatic copper is incidental to chronic hepatitis in this breed, based on the findings that five of 35 Doberman Pinschers with chronic hepatitis had normal copper levels, and histologic changes were similar regardless of copper status.[81,26,75] An immune-mediated mechanism has been suggested, based on the finding that expression of MHC class II antigens on hepatocytes of dogs with Doberman hepatitis was correlated with degree of inflammation.[75] Aberrant MHC class II molecule expression on nonlymphoid cells could be a result of toxins, drugs, viral infection, or autoimmunity, and hepatocytes with MHC class II expression might become a target as an antigen-presenting cell for CD4+ T cells.[75] Dogs treated with low-dose prednisolone (0.1 to 0.5 mg/kg/day) for 4 to 5 months had significantly decreased expression of MHC class II antigens.[75]

Chronic hepatitis should be suspected in any Doberman Pinscher (especially females) with clinical or biochemical evidence of hepatic disease. Definitive diagnosis requires liver biopsy. Other causes of chronic hepatitis should also be considered, since Doberman Pinschers appear to be at risk for drug-induced hepatitis.[71] Early detection of chronic hepatitis provides the best opportunity for treatment. It has been recommended that all Doberman Pinschers older than 1 year of age be screened for ALT activity.[99] Persistent increases in ALT activity suggest further evaluation including liver biopsy is warranted. The magnitude of increased ALT activity is not different between subclinical and clinically affected dogs. Hyperbilirubinemia is suggestive of more advanced disease.[28,99]

Effective treatment for Doberman Pinschers with chronic hepatitis has not been established. However, a preliminary study showed that if diagnosed in the subclinical stage, treatment with penicillamine (200 mg total dose PO BID for 4 months) lowered hepatic copper content and improved hepatic histopathology.[87] Traditionally, antiinflammatory or immunosuppressive drugs such as prednisone with or without azathioprine have been instituted. The efficacy of this treatment remains to be determined but generally, the response is poor if dogs are presented in advanced stages of liver failure. The use of ursodeoxycholic acid (15 mg/kg PO BID) deserves special consideration in this chronic cholestatic disorder, but has not yet been objectively evaluated. Treatment of copper-associated hepatitis in Doberman Pinschers with advanced disease is usually unsuccessful. Most dogs die within weeks to months. The prognosis appears more favorable if the disease is detected in the early stages, but the optimal therapeutic regimen remains to be determined.

West Highland White terrier

West Highland White Terriers are at increased risk to develop chronic hepatitis and cirrhosis.[25,76,101] Males and females are equally affected. The mode of inheritance for the familial copper-associated disorder has not been established.[24] Decreased biliary excretion of radiolabeled copper occurs in affected dogs.[89] Centrilobular (zone 3) copper accumulation occurs during the first year of life, but rarely exceeds 2000 μg/g dry weight.[24] In contrast to the Bedlington Terrier, West Highland White Terriers do not continuously accumulate copper over their lifetime; in fact, copper content may actually decrease with time.[56] In one report of 395 clinically normal West Highland White Terriers, most dogs had hepatic copper levels between 100 and 1500 μg/g dry weight with normal liver biopsies.[25]

In West Highland White Terriers with chronic hepatitis, histologic lesions include multifocal hepatitis, subacute bridging necrosis, massive necrosis, and cirrhosis.[25] The relationship of hepatic copper to chronic hepatitis in the West Highland White Terriers is unclear. There appears to be at least two types of chronic hepatitis.[25] Some dogs have copper-associated hepatitis with elevated copper content (>2000 μg/g) and multifocal centrilobular hepatitis. Copper concentrations do not usually exceed 3500 μg/g dry weight. Lesions of chronic hepatitis can also be seen in the absence of substantial copper accumulation, and have been described as "idiopathic chronic hepatitis."[25] Quantitative copper analysis is necessary to determine if copper accumulation is a significant (>2000 μg/g dry weight) contributing factor.

If chronic hepatitis and cirrhosis are associated with increased hepatic copper content (>2000 μg/g dry weight), treatment for hepatic copper accumulation should be instituted. Mature West Highland White Terriers with chronic hepatitis and less than 2000 μg/g dry weight of copper may not require chelation therapy, as hepatic copper accumulation is not continuous throughout life. Other therapeutic options for treatment of idiopathic chronic hepatitis, such as glucocorticoids, should be considered in these dogs.

Labrador Retriever

Labrador Retrievers are at increased risk for chronic hepatitis.[29,37] Age at presentation ranges from 2.5 to 14 years, with an average age of 7 to 9 years.[36-38] A female predisposition was noted in two studies,[36,38] whereas in another study, males and females were equally affected.[37]

Most affected dogs have increased hepatic copper, which has been described as centrilobular (zone 3) or diffuse.[36-38] Copper concentrations exceeded 2000 μg/g dry weight in 10 of 12 dogs (mean copper: 3369 μg/g; range: 2375 to 4972; reference interval: 120 to 400 μg/g).[38] Most dogs also had elevated iron levels with a mean of 4117 μg/g (reference interval: 350 to 1750).[38] A genetic basis is suspected, based on the finding of increased copper concentrations in asymptomatic related dogs, but the genetic defect remains to be determined.[36] A retrospective survey of hepatic copper content in Labrador Retrievers during two time periods (1980-1997 and 1998-2008), revealed significantly higher copper concentrations in the more recent period both in dogs with chronic hepatitis and in control dogs; no difference in age or gender was noted.[68] It was speculated that increased hepatic copper might reflect increased dietary copper bioavailability, because of pet food industry recommendations to replace cupric/cuprous oxide in feed formulations.[68]

Treatment with penicillamine (15 mg/kg PO q12h) appears to be effective in decreasing hepatic copper content and inflammation.[36,90] However, some dogs appear to respond to immunosuppressive (prednisone, azathioprine), supportive (ursodeoxycholic acid, SAMe, milk thistle), and symptomatic therapies that are not designed to lower hepatic copper.[37] Feeding a low-copper diet to 20 Labrador Retrievers with hepatic copper accumulation (seven of 20 dogs had varying degrees of hepatitis) was effective in decreasing hepatic copper concentrations, but severity of inflammation remained unchanged.[90] Additional treatment with zinc did not appear to increase the copper-lowering effect of dietary management.[90] Long-term survival appears variable.[36,37] Dogs who died within 2 months of diagnosis were more likely to have a prolonged PT and thrombocytopenia.[37]

Dalmatian

Dalmatians are reported to have acute hepatic necrosis, chronic hepatitis, and cirrhosis associated with increased hepatic copper concentrations.[35,102] Cholestasis is not a prominent biochemical or histologic feature until later in the disease, suggesting that hepatic copper accumulation is more likely to be caused by a familial metabolic disorder rather than secondary to altered hepatic biliary copper excretion. Most dogs presented initially with acute GI signs (anorexia, vomiting, and diarrhea). Biochemical findings revealed markedly increased ALT activity with lesser increases in ALP activity. Hyperbilirubinemia and hypoalbuminemia were seen with advanced disease. Glucosuria (in the absence of hyperglycemia) and proteinuria were identified in some dogs. Ultrasound findings were usually unremarkable. Liver biopsy revealed piecemeal necrosis, bridging fibrosis, and inflammation (predominantly lymphocytes or neutrophils). The mean hepatic copper level was 3197 μg/g dry weight (normal <400 μg/g dry weight) with a range of 754 to 8390 μg/g dry weight. In five of nine dogs, copper exceeded 2000 μg/g. Rapid progression of the disease was characteristic. Copper chelation therapy may be beneficial if diagnosed before advanced liver disease occurs.

Skye Terrier

Chronic hepatitis and cirrhosis associated with hepatic copper accumulation (800 to 2200 μg/g dry weight) in genetically related Skye Terriers has been described.[34] In the early stages, copper accumulation is absent, and biopsy findings indicate hepatocellular degeneration with cholestasis and mild inflammation. Chronic lesions are associated with intracanalicular cholestasis, chronic hepatitis, and cirrhosis. Skye Terrier hepatitis is speculated to be a disorder of disturbed bile secretion with subsequent accumulation of copper.

Cocker Spaniel

American and English Cocker Spaniels have an increased incidence of chronic hepatitis and cirrhosis.[29,30] The cause is unknown. Hepatic copper accumulation does not appear to be a consistent feature. It is unclear whether accumulation of α_1-antitrypsin in hepatocytes, a well-recognized cause of cirrhosis in humans, is important in the pathogenesis.[31] Male Cocker Spaniels (average age: 5 years) are at increased risk.[29,30] Despite the chronicity and severity of the underlying hepatic lesions, most affected dogs have a short duration of clinical illness, usually less than 2 weeks. Ascites is the most consistent presenting complaint. Profound hypoalbuminemia (mean: 1.7 g/dL) is a consistent laboratory finding. Total serum bilirubin concentration is normal or only mildly increased, supporting that cholestasis is not a key feature of the disorder. Ascitic fluid analysis is consistent with a transudate or modified transudate. On liver biopsy, hepatic lesions are consistent with chronic hepatitis and cirrhosis. Treatment of Cocker Spaniels with chronic hepatitis consists of general supportive therapy for the complications of liver failure. Corticosteroid therapy prior to progression to cirrhosis may

be beneficial. The prognosis is poor and most dogs die within a month of diagnosis.

A recent report described seven American Cocker Spaniels with histologic features resembling lobular dissecting hepatitis.[33] Males and females were equally affected. In contrast to previous reports of hepatitis in Cocker Spaniels, most dogs in this study improved with corticosteroid therapy.[33]

English Springer Spaniel

A preliminary report has described chronic hepatitis in 34 English Springer Spaniels from Norway and the United Kingdom.[39] Female dogs were overrepresented. Copper does not appear to play a role. The prognosis appears to be poor, with most dogs dying 4 to 7 months after diagnosis.[39]

Hepatic Cirrhosis and Fibrosis

Hepatic cirrhosis (end-stage liver disease), is characterized by fibrosis, regenerative nodules that alter liver architecture and intrahepatic (microscopic) PSSs (see Figure 61-19).[2] Hepatic fibrosis is not synonymous with cirrhosis. Cirrhosis is common in dogs but less so in cats.[2] Cirrhosis can result from postnecrotic scarring after acute massive necrosis or from chronic hepatic injury caused by a variety of insults such as infection (e.g., leptospirosis, CAV-1), hepatotoxins (e.g., copper, phenobarbital, aflatoxin), inflammation (chronic hepatitis), or hypoxia. The common denominator is hepatocyte death, which leads to repair by fibrosis and nodular regeneration. When cirrhosis is fully developed, the histologic features of the original inciting injury often are obscured by the cirrhotic changes.

Substantial hepatic fibrosis (without "cirrhosis") can be seen with long-standing extrahepatic biliary obstruction, noninflammatory fibrosis, congenital hepatic fibrosis (a disorder of biliary system development), and congenital portal vein hypoplasia.[2,103-105] A unique form of macronodular cirrhosis, characterized by noninflammatory regenerative hyperplastic nodules and diffuse vacuolar hepatopathy, is seen in dogs with hepatocutaneous syndrome (superficial necrolytic dermatitis).

Hepatic fibrosis was once considered irreversible, but is now recognized to be a dynamic process, which exists in a balance between synthesis and degradation. A better understanding of the underlying mechanisms may provide potential therapeutic targets.[106] The major fibrogenic cell in the liver is the activated HSC (Ito cell, vitamin A–storing cell), which is normally present in the perisinusoidal space.[106,107] Under the influence of fibrogenic stimuli (inflammation and the immune response, oxidative stress, apoptosis, hypoxia, steatosis), the HSC is activated to a myofibroblast, which produces collagen and other extracellular matrix (ECM) constituents.[106] The cytokine, TGF-β, appears to play a central role in fibrogenesis in humans and dogs.[106,108] Perisinusoidal fibrosis decreases the permeability of normal sinusoids, impairing metabolic exchange between hepatocytes and sinusoidal blood further compromising hepatic function.[106] Excess fibrous tissue also limits the ability of vessels and sinusoids to distend, resulting in increased resistance to hepatic blood flow and portal hypertension. When fibrotic septae become vascularized, these microscopic communications (between portal vein or arterial artery and hepatic vein) lead to portosystemic shunting of blood. Reversal of hepatic fibrosis and improvement in liver function can occur, especially if the underlying cause of injury is treated or removed.[106] Examples in human medicine include antiviral drugs for hepatitis B and hepatitis C and prednisone for autoimmune hepatitis. Although fibrosis is potentially reversible, cirrhosis for all practical purposes is not, because of the accompanying architectural changes and PSSs.[109]

Clinical features of cirrhosis in dogs include ascites (portal hypertension, hypoalbuminemia), HE (intrahepatic and extrahepatic portosystemic shunting of blood), and evidence of decreased hepatic function (hypoalbuminemia, increased SBA, coagulopathy, hyperbilirubinemia). Findings on hepatic ultrasonography (small nodular liver, splenomegaly, and acquired PSSs) are suggestive for cirrhosis, but liver biopsy is required for confirmation. Because cirrhosis is essentially irreversible, treatment is mainly supportive, emphasizing measures that control complications of severe generalized liver failure, such as ascites, encephalopathy, gastric ulcers, coagulopathy, and infection (see "Complications of Liver Disease" section). If clinical signs of liver failure are already present, the prognosis is poor.

Prevention of fibrosis, an important long-term goal, is best achieved by early specific treatment directed at the probable cause of injury (e.g., discontinuing a suspect drug, penicillamine for copper-associated liver disease, antiinflammatory drugs for idiopathic chronic hepatitis, surgical relief of extrahepatic biliary obstruction). Many therapeutic agents used for treatment of liver disease, such as penicillamine, prednisone, azathioprine, milk thistle, ursodeoxycholic acid, and zinc, have potential antifibrotic properties,[9] and are discussed in more detail in other chapters. Colchicine, a microtubule assembly inhibitor which increases collagenase activity, has been recommended for treatment of hepatic fibrosis, but its effectiveness in dogs has not been critically evaluated. The recommended dose in dogs is 0.025 to 0.03 mg/kg/day PO. Reported side effects include nausea, vomiting, and diarrhea. Bone marrow toxicity and myoneuropathy have been reported in humans.

Lobular Dissecting Hepatitis

Lobular dissecting hepatitis is a specific histologic form of cirrhosis seen in neonatal or young adult dogs.[2,4,110-112] It is suggested to be a nonspecific response to a variety of hepatic insults.[111] The age at presentation is younger than for dogs with either acute or chronic hepatitis.[4] In 21 affected dogs, the median age was 11 months, with 12 dogs (54%) being 7 months or younger.[4,110] Females appear to be at increased risk.[4,111] Lobular dissecting hepatitis may occur in an isolated dog or in groups of dogs from the same litter or kennel.[111] Standard Poodles may be at increased risk.[110,112] Clinical features are those of advanced hepatic failure and portal hypertension.[111] The most consistent clinical finding is ascites. Liver enzymes are typically increased and hypoalbuminemia and increased SBA concentrations are common.[4,111]

Liver biopsy is required for diagnosis and to differentiate it from other types of chronic hepatitis and cirrhosis. The lesion is characterized histologically by lobular hepatitis: inflammatory cells (lymphocytes, plasma cells, macrophages, and neutrophils) are scattered throughout the hepatic lobule rather than concentrated in periportal regions. Bands of collagen and reticulin fibers dissect around single or small groups of hepatocytes and disrupt hepatic lobular architecture.[111] Copper stains are negative or moderately positive, consistent with secondary copper accumulation.

Specific treatment has not been reported, but general measures for management of chronic liver failure are appropriate.[4] In a small group of dogs with lobular dissecting hepatitis, the mean survival time was approximately 3 months, which was significantly shorter than for dogs with acute or chronic hepatitis.[4]

Hepatic Infections

Infection of the liver is an important cause of hepatic disease in dogs and cats.[113] The liver may be the primary target of infection (e.g., infectious canine hepatitis, bacterial cholangitis, hepatic abscess) or

it may be one of several organ systems involved in a multisystemic disease process such as feline infectious peritonitis (coronavirus), toxoplasmosis, or histoplasmosis (see Table 61-4). Infectious agents can be associated with widespread invasion of organs with a large mononuclear phagocytic component, including the liver, spleen, lymph nodes, and bone marrow, although clinically significant liver disease is uncommon. Liver biopsy can be diagnostically useful for identification of these organisms in infected animals.

Canine Adenovirus 1

Etiology

Infectious canine hepatitis (ICH) caused by CAV-1 has long been recognized as a cause of acute hepatic necrosis in dogs.[114] This virus is genetically and antigenically distinct from CAV-2, a cause of infectious canine respiratory disease. The incidence of clinical disease caused by CAV-1 is now very low because of effective vaccination procedures. Neutralizing antibodies to CAV-1 are also found in mature, unvaccinated dogs, suggesting that natural exposure to the virus is widespread.

Pathophysiology

CAV-1 has a special tropism for vascular endothelial cells and hepatocytes.[114] Dogs with sufficient immunity (neutralizing antibodies >1:500) do not develop clinical signs of disease. Susceptible dogs (titer <1:4) develop widespread centrilobular to panlobular hepatic necrosis, which is often fatal. Distinctive intranuclear inclusions are present in hepatocytes and the endothelium of other tissues. Experimentally, dogs with an intermediate titer (between 1:16 and 1:500) develop chronic hepatitis that can progress to cirrhosis.[115] Whether CAV-1 is a significant cause of chronic hepatitis under natural conditions is unknown. CAV-1 antigen was demonstrated in formalin-fixed liver sections from five of 53 dogs with various naturally occurring hepatic inflammatory lesions, suggesting that CAV-1 may play a role in spontaneous chronic hepatitis.[46] Other attempts to identify CAV-1 in dogs with chronic hepatitis have been negative.[44,47]

Clinical Examination

ICH is seen most commonly in unvaccinated dogs younger than 1 year of age. Clinical signs vary with the stage of disease. Dogs that are peracutely ill do not have clinical evidence of hepatic disease but simply become depressed and moribund, and die within a few hours. Dogs with a more extended clinical course (5 to 7 days) have signs associated with acute hepatic necrosis that include vomiting, diarrhea, and abdominal pain. A hemorrhagic diathesis may occur during the viremic phase and is manifested by epistaxis, petechial or ecchymotic hemorrhages of the skin, or excessive bleeding from venipunctures. Failure of the liver to clear activated clotting factors and impaired hepatic synthesis of clotting factors probably also contributes to development of DIC. Signs of central nervous system (CNS) dysfunction include depression, disorientation, seizures, and coma and have been attributed to HE or nonsuppurative encephalitis.

Common physical examination findings include fever, enlarged tonsils, pharyngitis, laryngitis, cervical lymphadenopathy, and subcutaneous edema of the head, neck, and trunk. Hepatomegaly, abdominal pain, and abdominal effusion can occur. Jaundice is rare but can develop in dogs that survive the acute fulminant stage of ICH. An uncomplicated clinical course lasts approximately 5 to 7 days before recovery begins. Unilateral or, less frequently, bilateral corneal edema and anterior uveitis ("hepatitis blue eye") are complications that may become evident during the recovery period. These ocular complications occur in approximately 20% of naturally infected dogs, and are caused by corneal endothelial damage and antigen–antibody complexes.

Diagnosis

ICH should be suspected in any young, unvaccinated dog with evidence of ALF. ICH must be differentiated from diseases with similar clinical signs, such as canine distemper, parvoviral enteritis, and hepatotoxicity. Abnormalities on the leukogram are common and vary with the clinical stage of infection. During viremia, neutropenia and lymphopenia are often present. Neutropenia is also a common a feature of canine parvovirus, a much more prevalent disease of puppies. Rebound lymphocytosis and neutrophilia occur in the recovery stages of ICH (7 days after infection). Biochemical findings are characteristic of acute hepatic necrosis and include increased serum ALT and ALP activity, and abnormal liver function tests. Hyperbilirubinemia is a less-consistent finding. Hypoglycemia may complicate the terminal stages of the disease. Coagulation parameters are consistent with DIC. Other potential findings include proteinuria secondary to glomerular damage, abdominal fluid consistent with an exudate, and an increase in protein and mononuclear cells in the cerebrospinal fluid.

The clinical diagnosis of ICH is usually suspected on the basis of age, vaccination history, clinical signs, and laboratory findings, and is confirmed by liver biopsy or necropsy findings. Additional diagnostic tests that are used less frequently include serologic testing, virus isolation, and direct immunofluorescence.

Treatment and Prognosis

Therapy for ALF caused by ICH is primarily supportive care and control of complications that frequently occur such as DIC, HE, and hypoglycemia. The prognosis in dogs with ICH depends on the severity of hepatic necrosis and the incidence of serious complications such as DIC. Hepatic regeneration and recovery is possible unless widespread coagulation necrosis destroys entire lobules. ICH can be effectively prevented by vaccination.

Canine Herpesvirus

Canine herpesvirus causes an acute, afebrile, rapidly fatal disease in neonatal puppies (1 to 3 weeks of age).[116] Hepatic necrosis is one manifestation of the widespread multiorgan necrosis and hemorrhage that occurs in this systemic viral infection. Clinical signs include acute onset of depression, diarrhea, failure to suckle, crying, and abdominal pain in previously healthy puppies. Other findings include petechial hemorrhages and vesicles of the mucous membranes. Jaundice is rare. Seizures and loss of consciousness may be present in the terminal stages, and most pups die within 24 hours of onset of clinical signs. Typical gross pathologic findings include focal areas of necrosis and hemorrhage in the liver, kidneys, lungs, and serosal surfaces of the intestines. Microscopically, these areas are characterized by foci of necrosis with occasional intranuclear inclusions.

Neonates are infected by oronasal exposure to the virus in utero or by secretions from an infected bitch or littermates. Neonates are particularly susceptible, possibly because of their low body temperature and immature mechanisms for temperature regulation. The diagnosis of canine herpesvirus is primarily based on the history, physical examination, and pathologic findings. Laboratory findings are inconsistent but include neutrophilia or neutropenia, and increased serum ALT activity.

Treatment of affected puppies is generally unsuccessful because of the acute fulminant nature of the disease. Maintenance of body

temperature (36.7°C to 37.8°C [98°F to 100°F]) may be helpful. Intraperitoneal infusion of 1 to 2 mL of hyperimmune serum obtained from bitches with previously infected litters may reduce mortality rates. Vaccination for herpesvirus infection is not routinely performed because of the low incidence of disease.

Canine Acidophil Cell Hepatitis

Canine acidophil cell hepatitis, which encompasses a spectrum of hepatic lesions ranging from acute and chronic hepatitis to cirrhosis and liver failure, has been reported in Great Britain.[48,114] It is caused by a transmissible agent, suspected to be a virus that is distinct from CAV-1, although a specific virus has never been identified. The disease is experimentally transmissible by serum or liver extracts from affected dogs. In the experimentally induced disease, acute hepatitis can progress to chronic hepatitis in the absence of clinical signs. Episodic increases in serum ALT activity and fever spikes correspond with histologic evidence of acute hepatitis.

The liver is enlarged and friable in the acute stages, and becomes progressively smaller and nodular with chronicity. The most notable histologic feature, regardless of the stage of disease, is the acidophil cell. Acidophil cells are dying hepatocytes with an angular shape, reduced volume, hyperchromatic nucleus, and strongly acidophilic cytoplasm caused by small acidophilic coalescing granules. End-stage hepatic disease is accompanied by typical findings of cirrhosis.

Most dogs with spontaneous disease are presented with signs of chronic hepatic failure. The duration of clinical signs can exceed 1 year. Based on experimental studies, it is speculated that the early mild stages may go unrecognized until advanced hepatic disease and failure is present. Biochemical findings are consistent with hepatic inflammation and necrosis, evidenced as increased serum ALT activity. With advanced disease, severe hepatic dysfunction is noted. The diagnosis requires liver biopsy. Recommendations for specific therapy of acidophil cell hepatitis await further information on the causative agent. Supportive measures should be instituted as needed.

Feline Infectious Peritonitis (Coronavirus)

Feline infectious peritonitis (FIP) is a highly fatal coronaviral infection of both domestic and wild cats. The liver is one of many organs (kidneys, spleen, pancreas, mesenteric lymph nodes, CNS, uveal tract, omentum, serosal surfaces) that can be affected by widespread immune complex vasculitis and granulomatous or pyogranulomatous inflammation (see Table 61-5).[117]

Clinical findings in cats with hepatic involvement are nonspecific and include lethargy, depression, anorexia, dehydration, weight loss, and fever. Jaundice is a common finding. Extrahepatic findings include nodular renomegaly, abdominal mass (lymph node), and ascites or dyspnea (pleural effusion). Ophthalmoscopic examination may detect chorioretinitis or anterior uveitis, which must be differentiated from similar ocular changes seen with the other systemic disorders that involve the liver such as lymphosarcoma, toxoplasmosis, and the systemic mycoses.

Serum hepatic enzyme (ALP and ALT) activities are usually normal or only mildly increased. Mild to moderate increase in serum bilirubin concentration is common. Other findings indicating hepatic dysfunction include bilirubinuria and increased SBA concentrations. Hyperglobulinemia, neutrophilia, and mild to moderate nonregenerative anemia are other laboratory features of FIP. Abdominal and pleural effusions, when present, are usually pyogranulomatous exudates with greater than 3 g/dL protein. Serologic detection of a high coronaviral antibody titer may support a diagnosis of FIP, but is not definitive because of its lack of specificity. Diagnosis of FIP should be supported by cytologic or histologic evidence of pyogranulomatous inflammation. The currently recommended "gold standard" for FIP diagnosis is immunohistochemistry performed on effusions or lesions containing infected macrophages.[117] The prognosis for recovery is poor.

Leptospirosis

Etiology

Canine leptospirosis is caused by *Leptospira interrogans sensu lato*, with at least 10 serovars appearing to have clinical significance in dogs.[118] Serovars *canicola* and *icterohemorrhagica* have been included in vaccines for more than 30 years and the incidence of clinical disease from these serovars has decreased accordingly. An epidemiologic shift in serovars causing clinical disease has since occurred, with increasing reports of disease associated with serovars *grippotyphosa, pomona*, and *bratislava*.[118] It has been suggested that serovars *icterohemorrhagica* and *pomona* are more likely to be associated with hepatic damage.[118] However, other reports have been unable to correlate serogroups with specific clinical features.[119,120] Chronic hepatitis has been associated with serovar *grippotyphosa*[50] and serogroup *australis*.[51] Reports of clinical leptospirosis in cats are rare, although antibodies to several serovars have been demonstrated.[118]

Pathophysiology

Acute renal failure is the most common clinical disease syndrome in dogs with leptospirosis.[121] The liver can also be a target organ and ALF may occur concurrently in 10% to 20% of dogs with acute renal failure or independent from renal involvement.[121] With acute hepatic involvement, the liver is enlarged, friable, and yellow-brown. Tissues are often markedly jaundiced. Microscopic changes in the liver include intrahepatic cholestasis, liver cell dissociation, and nonspecific reactive hepatitis.[3,122] Hepatic necrosis is an uncommon histologic feature. The liver may not show striking changes, presumably because hepatic dysfunction can be caused by a toxin that produces mainly subcellular damage. Organisms can be identified in tissues with a Warthin-Starry stain.

Clinical Examination

Common clinical signs include anorexia, depression, and vomiting. Hepatocellular involvement is suggested by jaundice. Other findings may include arthralgia or myalgia, PU, PD, fever, and dehydration. Widespread petechial and ecchymotic hemorrhages of the mucous membranes, sclera, and skin are caused by thrombocytopenia and DIC. The terminal stages include signs of cardiovascular collapse, shock, coma, and death.

Diagnosis

A diagnosis of leptospirosis should be considered in dogs with acute cholestatic liver disease, especially when accompanied by acute renal failure. Hematologic findings vary with the stage and severity of disease. Leukocytosis and left shift are frequent, but in the early stages of leptospiremia, leukopenia is more likely. Thrombocytopenia can also be seen. Coagulation parameters are normal unless complicated by DIC. Routine serum chemistry and urinalysis findings reflect involvement of the liver or kidney. Serum liver enzyme activity is usually increased with hepatic involvement, and the magnitude of the increase in serum ALP activity is usually greater than that of serum ALT activity owing to intrahepatic cholestasis. Other findings include hyperbilirubinemia, bilirubinuria, and abnormal liver function tests. An increase in BUN or creatinine may result from renal failure or prerenal uremia. The urinalysis is often compatible with acute nephritis with findings of proteinuria and increased

leukocytes, erythrocytes, and granular casts. Increased serum creatine kinase activity may indicate leptospiral-induced muscle damage. Leptospirosis is most easily diagnosed in the clinical setting by demonstration of a fourfold rise in serum antibody titer (microscopic agglutination test) in paired samples taken at initial presentation and 2 to 4 weeks later. The rise in titer indicates recent or active infection and differentiates a titer from previous exposure or previous vaccination.

Treatment and Prognosis

The optimum treatment regimen for leptospirosis is unknown. Traditionally, intravenous ampicillin, 25 mg/kg every 6 hours (with dose reduction in dogs with renal failure), or penicillin G (25,000 to 40,000 units/kg IV q12h), has been used for initial treatment of leptospirosis.[121] Doxycycline (5 mg/kg PO q12h for 2 to 4 weeks), was recommended as followup therapy to eliminate organisms from renal tubules. However, doxycycline, 5 mg/kg orally or intravenously every 12 hours for 2 weeks, appears to be effective in clearing all phases of leptospiral infection and may be the most effective treatment strategy.[121] Management of fluid, electrolyte, and acid–base imbalances is important supportive therapy. The prognosis generally depends on the degree of renal dysfunction and is poor when oliguria develops.

Clostridium piliforme (Tyzzer Disease)

C. *piliforme* (formerly known as *Bacillus piliformis*), a spore-forming Gram-negative bacteria, is a rare cause of multifocal hepatic necrosis and necrotizing ileitis in dogs and cats.[123] The infection is mainly opportunistic in stressed or immunocompromised animals with a predisposing disorder (e.g., canine distemper, feline panleukopenia, feline leukemia) or familial hyperlipoproteinemia in kittens.[123] Clinical signs include an acute onset of anorexia, lethargy, depression, and abdominal discomfort. Jaundice may be observed, especially in cats. These signs rapidly progress to a moribund state; death occurs within 24 to 48 hours. Marked increases in ALT activity may be detected. Histopathology reveals multifocal periportal hepatic necrosis and necrotic ileitis or colitis. Bacilli are best seen with special staining techniques (Warthin-Starry or Giemsa), or methylene blue–stained impression smears of fresh tissue. Organisms appear as large, slender, intracellular filamentous organisms within hepatocytes surrounding areas of necrosis and in intestinal epithelial cells. Routine culture techniques are ineffective for isolation of this organism. The disease is rapidly fatal, and successful therapy has not been reported.[123]

Sepsis and Endotoxemia

Extrahepatic bacterial infection associated with sepsis and endotoxemia is an important cause of acute functional cholestatic hepatopathy. However, morbidity is generally related to the underlying infection and not overt hepatic failure.[113,124] Studies in humans and experimentally in dogs, suggest that endotoxemia and the subsequent release of cytokines induces functional changes that interrupt the transport and excretion of conjugated bilirubin.[113,125] Microscopically, hepatic lesions are often mild and nonspecific. Intrahepatic cholestasis, characterized by bile canalicular plugs and bile pigment accumulation in hepatocytes, is the most consistent finding.[124] A mild periportal lymphocytic infiltrate can be seen, with scattered foci of macrophages or neutrophils, and occasional individual necrotic hepatocytes. Total serum bilirubin concentrations as high as 30 mg/dL can be seen and are disproportionately high compared to the mild to moderate increases in serum ALP activity. Increased serum ALT activity is a less consistent finding. The serum bile acid concentration can be markedly increased (>200 μmol/L).[124]

Extrahepatic bacterial infection–induced hepatic damage should be considered when evidence of cholestatic hepatopathy is found concurrently with extensive bacterial infection in other organ systems (e.g., pyometra, peritonitis) or with extrahepatic disorders likely to be associated with endotoxemia (e.g., parvoviral enteritis). Associated clinical findings that would be compatible with endotoxemic crisis include shock, fever or hypothermia, hypoglycemia, neutrophilia or neutropenia with left shift, toxic changes of the neutrophils, and hyperbilirubinemia that is disproportionately increased in comparison to serum ALP activity.[124] It is important to recognize that jaundice can occur secondary to extrahepatic infection from a diagnostic standpoint, so that the clinician is not misled into considering that the cause is a primary hepatic or biliary disease. In jaundiced patients with evidence of an inflammatory process, key differential diagnoses include acute pancreatitis, extrahepatic bacterial infections, and primary hepatobiliary disorders such as leptospirosis (dogs only), cholangiohepatitis, cholecystitis, ruptured gallbladder mucocele, and hepatic abscesses. Specific therapy for hepatic disease is not usually required, and hepatic damage is reversible with control of sepsis. Morbidity is related to the underlying disease process and not overt hepatic failure.

Hepatotoxicity

Drug and Toxin-Induced Liver Injury

Etiology

Hepatotoxicity can be caused by a variety of drugs (prescription or over-the-counter), herbal and dietary supplements, or biologic toxins or chemicals (see Box 61-1).[17,126,127] The liver is uniquely susceptible to xenobiotic substances because it is directly exposed to them following absorption from the GI tract. The liver is also vulnerable to toxic injury because it plays a central role in the metabolism of many substances. Hepatic metabolism renders lipophilic substances more hydrophilic, which promotes excretion via the urine or bile.[17] The process is controlled by phase I and phase II reactions. Phase I reactions are catalyzed by the cytochrome P450 enzyme systems, which activate or detoxify (oxidize, reduce, or hydrolyze) a drug or toxin. Phase I reactions may lead to generation of unstable chemically reactive intermediates, which can be toxic. Phase II reactions conjugate drugs or metabolites and produce products that are nontoxic. During biotransformation, the liver can either reduce or enhance the toxicity of the parent compound. For example, after carbon tetrachloride ingestion, the liver converts the nontoxic parent compound into toxic metabolites, which subsequently cause severe hepatocellular damage. Genetic polymorphisms of phases I and II enzymes have the potential to influence drug metabolism in the individual animal.

There has been an increased awareness and recognition that drug-induced liver injury can be a significant cause of liver disease in dogs and cats (see Box 61-1). This information has been gained from isolated case reports, retrospective clinical studies, and experimental studies. Unfortunately, for many of these drug reactions, characterization of the clinical and pathologic features are lacking because only small numbers of affected animals have been described, and liver biopsies are not typically obtained when drug withdrawal results in clinical and biochemical improvement. It is possible that drug-induced liver injury is underrecognized in dogs and cats, as in humans, drug-induced hepatic injury accounts for more than 50% of the cases of ALF in the United States, and is the most frequent reason cited for withdrawal of an approved drug from the market.[17]

The Center for Veterinary Medicine of the Food and Drug Administration, Washington, DC, maintains a registry (http://www.fda.gov/AnimalVeterinary/default.htm) for reporting adverse drug reactions in animals. This service has been useful to accumulate data and to alert veterinarians to suspected drug effects, including hepatotoxicity. However, because reporting of adverse drug reactions is voluntary and the information obtained may be incomplete, only subjective trends can be identified. Furthermore, because mild hepatic injury may not be associated with clinical signs, these cases will not be detected unless biochemical testing is performed while the animal is receiving the drug. Evaluating the incidence of drug-induced liver injury in dogs and cats is further clouded by the fact that there are no pathognomonic clinical, laboratory, or biopsy findings to distinguish drug-induced liver injury from other causes of liver disease. Specific drugs that have been reported to cause drug-induced liver injury are listed in Box 61-1.

Herbal and dietary supplements (herbs or other botanicals, nutraceuticals, vitamins, minerals) have the potential to cause hepatotoxicity, similar to drug-induced injury.[127-129] In humans, herbal and dietary supplements are reported to account for 10% of patients with "drug-induced" liver injury.[127] The incidence of hepatotoxicity may be underrecognized, as only a third of humans taking herbal and dietary supplements reported their use of these products to their health care provider.[127] Causality is difficult to prove, because herbal and dietary supplements are often dispensed without medical supervision, FDA oversight of product quality is minimal, multiple active ingredients contribute to product variability, and product contamination with hepatotoxic substances (toxic herbs or heavy metals) may occur.[127-129] Drug interactions between herbal and dietary supplements and prescription medications may also occur, because medicinal plants can have effects on hepatic P450 enzyme systems.[129] The rate of dietary supplement use in dogs and cats appears to be lower than that reported for humans.[130] However, because these products are often marketed as "all natural," pet owners may assume they are safe and underreport their use to the veterinarian. Reports of herbal and dietary supplement hepatic injury in animals are rare. Pennyroyal oil, a volatile oil derived from plants of the Labiatae family (pennyroyal, squaw mint, or mosquito plant) was associated with fatal acute hepatic necrosis in a dog after topical application for use as a flea repellent. Clinical signs occurred within 1 hour after application and included vomiting, diarrhea, hemorrhage, seizures, and death. Other reports include the finding of increased liver enzyme activity in dogs consuming St. John's wort, and increased ALT activity and hypoglycemia after accidental ingestion of high doses of α-lipoic acid in two dogs.[129,131] The paucity of reported hepatic reactions does not necessarily mean herbal and dietary supplements are safe, and the clinician should maintain a high level of suspicion regarding their potential toxicity. Box 61-1 lists the herbal and dietary supplements that have been incriminated as causing hepatic injury in humans with potential relevance to dogs and cats. For more detailed information on hepatic injury and herbal and dietary supplements, additional sources should be consulted.[127-129]

Hepatic injury may also occur after exposure to a wide variety of industrial chemicals, organic solvents, pesticides, heavy metals, and biologic toxins. Most information on chemical hepatotoxins is derived from experimental studies in dogs or extrapolated from information in other species. Very few clinical case reports are available in the veterinary literature. Isolated reports and case series of clinical liver disease in dogs associated with exposure to biologic toxins, such as aflatoxin, *Amanita* mushrooms, blue-green algae, and Cycads (Sago palms) have been published. Selected hepatotoxins are listed in Box 61-1.

Pathophysiology

Hepatic injury caused by drugs, herbal and dietary supplements, biologic toxins, or chemicals can occur via a number of mechanisms, which influence the histologic pattern of disease.[17,20] Although hepatic necrosis is the most common histologic response, drug- and toxin-induced liver injury can also potentially mimic the full spectrum of acquired hepatic disorders, including acute and chronic hepatitis, granulomatous hepatitis, cholestatic hepatopathy, vacuolar hepatopathy (lipid or glycogen accumulation), hepatic fibrosis and cirrhosis, and venoocclusive disease. Hepatic necrosis occurs when covalent binding of a drug or toxin to intracellular proteins disrupts cellular functions, or formation of drug–enzyme adducts stimulates an immunologic response (antibody- or T-cell–mediated cytotoxicity). Hepatic inflammation (typically lymphoplasmacytic, but may be granulomatous or eosinophilic), suggests an underlying immunoallergic mechanism. Intrahepatic cholestasis occurs when drugs or toxins interfere with hepatic transport proteins at the canalicular membrane, which interrupts bile flow. Hepatic lipid accumulation results when direct damage to mitochondria disrupts fatty acid oxidation and energy production, and is the predominant hepatic lesion seen with stanozolol hepatotoxicity in cats,[132] and tetracycline in dogs and cats.[126] Hepatic vacuolation caused by glycogen accumulation occurs in dogs treated with corticosteroids, and typically does not cause significant clinical evidence of hepatic dysfunction. Damage to the sinusoidal epithelium can result in peliosis hepatic or venoocclusive disease.

Mechanisms of drug-induced liver injury (and also injury from herbal and dietary supplements) can be characterized as either intrinsic (predictable) or idiosyncratic (unpredictable) reactions.[126] Intrinsic hepatotoxic reactions are dose-related and occur shortly after a consistent threshold of toxicity is reached. Because intrinsic hepatotoxins predictably damage the liver in an exposed population, they can be experimentally reproduced and studied. Hepatic injury is caused by a direct toxic effect of the parent compound (or a reliably generated toxic metabolite) on vital cell targets. Acetaminophen is an intrinsic hepatotoxin in dogs and cats and is discussed in more detail later in this section. With intrinsic hepatotoxins, lowering the dose, rather than stopping the drug can be tried. In many cases, most such drugs or chemicals, (e.g., carbon tetrachloride, phosphorus, and chloroform), are no longer used for therapeutic purposes once their intrinsic hepatotoxicity is recognized, but accidental exposures could still occur.

In contrast, idiosyncratic hepatotoxic reactions occur at therapeutic doses in only a small number of individuals in the exposed population. These reactions are unpredictable and infrequent; most individuals treated with the drug do not have a reaction, even at high doses. However, toxicity may be more pronounced at higher doses in susceptible individuals.[72,133] Examples of drugs causing idiosyncratic drug-induced liver injury in dogs and cats that have a dose-related effect are phenobarbital, itraconazole, amiodarone, and lomustine (CCNU).[134] Idiosyncratic reactions are characterized by a variable latency period (5 to 90 days, but may be longer for some drugs, such as phenobarbital, CCNU, amiodarone) from initial drug ingestion to recognition of hepatic injury. Because of the infrequent occurrence (approximately 1 in 100,000), the potential for hepatotoxicity may not be recognized in preclinical screening of a new drug, and cannot usually be reproduced in an experimental setting. Individual differences in susceptibility to idiosyncratic drug-induced liver injury may reflect genetic differences in either (a) alternate metabolic pathways by which a drug is converted to different (potentially hepatotoxic) metabolites, (b) the ability of the individual to detoxify the toxic intermediates, (c) an underlying

immunologic or allergic reaction, or (d) an individual's tolerance or ability to "adapt" to hepatocellular injury (mechanisms unknown) with resolution of injury despite continued medication administration.[20,135] Oral medications with substantial hepatic metabolism are more likely to be associated with adverse hepatic events in humans, presumably because of hepatic generation of reactive toxic metabolites.[136] Because of the unpredictability of an idiosyncratic reaction and the low incidence of occurrence, a cause-and-effect relationship is difficult to establish. If an idiosyncratic reaction occurs, the drug must be discontinued or it could result in death of the patient. An idiosyncratic mechanism is suspected for most of the drugs that cause hepatic injury in dogs and cats.

Susceptibility to hepatotoxicity in humans is influenced by a number of factors such as age, sex, nutritional status, and concurrent drugs.[20] The most important factor may be the effect of genetic polymorphisms on hepatic drug metabolism.[20] In humans, preexisting liver disease does not appear to enhance susceptibility to drug-induced liver injury, but impacts the patient's ability to recover.[20] This may be because drug-metabolizing enzyme systems are remarkably preserved in hepatic disease. Similar information on risk factors for hepatotoxicity in dogs and cats has not been determined. However, because many toxic metabolites are normally detoxified by glutathione, some metabolites may become more toxic when hepatic glutathione stores are depleted (e.g., animals with preexisting chronic necroinflammatory and cholestatic liver disease).[126] A breed predisposition has been suggested for Doberman Pinschers (sulfonamides, amiodarone, diethylcarbamazine/oxibendazole) and Labrador Retrievers (carprofen), which may be a reflection of a genetic predisposition.[21,71,73,134,137]

Clinical Examination

The spectrum of drug- and toxin-induced liver injury and, thus, the associated clinical presentation, can vary from subclinical hepatic injury with only increased serum liver enzyme activity, to severe liver damage manifested as ALF, or chronic end-stage liver disease. Acute rather than chronic liver injury is more likely for most of the drugs and toxins listed in Box 61-1. Clinical features often include acute onset of lethargy, anorexia, vomiting, diarrhea, PU, PD, or jaundice in a previously healthy animal, which corresponds to hepatotoxin exposure. ALF (signs of acute liver disease plus HE and coagulopathy) is most likely with drugs or toxins that cause diffuse hepatic necrosis. Drug- and toxin-induced injury is an important diagnostic consideration in dogs and cats presenting for acute hepatitis and hepatic necrosis.

Drugs or toxins also have the potential to cause chronic hepatic disease, if the initial hepatic injury is mild and goes unrecognized, and exposure to the drug or toxin is continued. For example, phenobarbital, CCNU, or chronic aflatoxicosis can cause chronic liver injury in dogs.[70,72,138]

Diagnosis

There are no pathognomonic clinical, laboratory, or biopsy findings that distinguish drug- or toxin-induced liver injury from other causes of liver disease. The diagnosis of drug-induced liver injury often relies on the clinician maintaining a high level of suspicion, and obtaining an accurate and thorough medication history (including prescription and over-the-counter drugs, and herbal and dietary supplements), in every animal with unexplained increases in liver enzyme activity or clinical liver disease. A definitive diagnosis of hepatic injury caused by biologic toxins or chemicals is rarely possible in a clinical setting, unless the owner specifically observes ingestion of a substance that is a known hepatotoxin.

Increased liver enzyme activity is a common finding with hepatotoxicity. Increased ALT activity (more than three times the upper limit of normal, but can be as high as 100 times the upper limit), suggests hepatocellular injury (often necrosis), and is of more concern than an isolated increase in ALP activity (reflecting cholestasis), although mixed patterns commonly occur. Progressive increases in ALT activity or those accompanied by evidence of hepatic dysfunction (hyperbilirubinemia, increased serum bile acids, coagulopathy, hypoglycemia, hyperammonemia, hypoalbuminemia) are more likely to represent serious hepatic injury.

When drug-induced liver injury is suspected, the diagnostic approach is determined by the clinical presentation. If clinical signs are absent or mild, a minimum database consisting of complete history and physical examination, complete blood cell count, serum chemistry, and urinalysis should be performed. If the only abnormality detected is increased liver enzyme activity, and these increases correspond to the recent administration of a drug (especially those listed in Box 61-1), the drug should be discontinued and serum biochemistries should be repeated in 10 to 14 days. In many instances, clinical and biochemical abnormalities resolve after the suspected hepatotoxic drug is discontinued and a liver biopsy is not performed. Further evaluation of the liver, including SBA concentrations, abdominal radiographs, ultrasonography, and liver biopsy, may be warranted if biochemical abnormalities persist, or if initial clinical and biochemical findings suggest hepatic dysfunction.

With suspected drug- or toxin-induced liver disease, a liver biopsy can be helpful to (a) characterize the histologic changes (are they consistent with previously described lesions caused by this particular drug or toxin?), (b) determine the severity (focal or diffuse necrosis?) or reversibility (is cirrhosis present?) of the lesions for prognostic purposes, and (c) rule out known causes of liver disease. Histologic changes secondary to drug- and toxin-induced hepatic injury are nonspecific and similar to those seen with other non–drug-related causes of acute and chronic liver disease.[126] The most common pathophysiologic response is necrosis without inflammation.[126] Hepatic necrosis may be centrilobular (zone 3) or panlobular (Figure 61-20). Centrilobular hepatocytes have an abundance of P450 enzymes, and are preferentially affected in drug-induced hepatotoxicity when P450 metabolism of the parent drug results in toxic metabolites.[8] Drugs or toxins can also cause a variety of other hepatic lesions, such as cholestasis, lipidosis, or mild inflammation. A chronic response to injury is reflected by findings of biliary

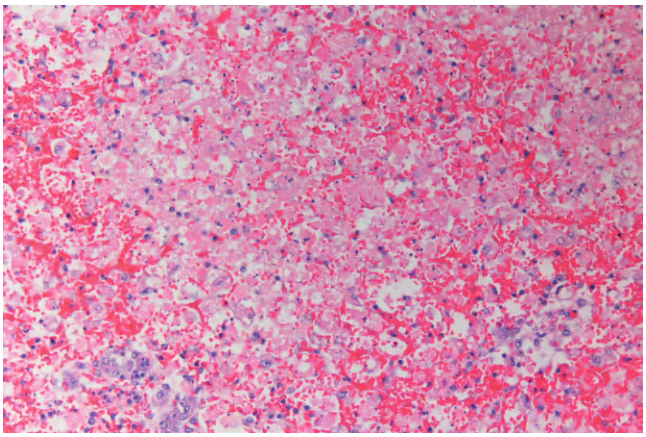

Figure 61-20 Severe panlobular acute hepatic necrosis in a dog with fatal acute liver failure caused by ingestion of *Amanita* mushrooms (20×). (Courtesy of Dr. Paul Stromberg.)

hyperplasia, fibrosis, and cirrhosis. Although individual drugs and drug classes may follow the same pattern, there is often not a consistent reaction for any given drug. For example, hepatic injury in dogs secondary to potentiated sulfonamides may cause hepatic necrosis, primary cholestasis, or marked inflammation.[21] For many of the potentially hepatotoxic drugs listed in Box 61-1, histologic features have not been fully characterized.

It should be emphasized that for most drug-induced disorders, the diagnosis is presumptive and cannot be proved. It can be especially difficult to pinpoint the causative agent when the patient is receiving a combination of drugs. A clinical diagnosis of drug-induced hepatic injury is easier to establish when the hepatotoxicity of the drug has been previously described and the associated clinical and pathologic features have been characterized (see discussion of specific drugs). The diagnosis may be less convincing when the suspected drug has not been previously incriminated as causing liver damage. However, a drug reaction should still be considered, since an idiosyncratic reaction could occur *with any drug*. The clinician should also maintain a level of suspicion regarding the potential for hepatotoxicity in newly marketed drugs that have not yet been used widely in the population, where idiosyncratic reactions are often first detected. The suspected hepatotoxic drug should be discontinued while a complete diagnostic evaluation is pursued for other causes of liver disease, for which a specific treatment might be available.

A diagnosis of drug-induced injury is supported by the following: (a) evidence of liver injury that occurred within the first 3 months of drug therapy (especially if predrug liver enzyme activity was within normal limits); (b) clinical and biochemical improvement when the drug is discontinued; (c) exclusion of other causes of liver disease; (d) reccurrence of hepatic damage after a challenge dose of the same drug (or inadvertent reexposure). It should be emphasized that rechallenge with a suspected hepatotoxic drug is not recommended as a diagnostic consideration, because it is potentially dangerous, especially with a drug that causes acute hepatic necrosis. Rechallenge should only be considered if the association of the drug with hepatic injury is highly questionable and there is no alternative drug available for a significant medical condition. With hypersensitivity or immunologic reactions, the hepatic reaction is more rapid and severe with repeated exposure.[20]

Hepatic injury because of a biologic toxin or chemical is suspected when exposure to a potential hepatotoxin has been documented. A clinical diagnosis of "toxic" hepatic injury is often made when an episode of acute hepatic injury occurs, hepatic biopsy indicates diffuse hepatic degeneration and necrosis, and no other cause for liver disease can be identified. In selected cases, tissues, blood, or food (aflatoxin) samples can be submitted to a toxicology lab to confirm a suspected toxin. Toxin-induced injury should also be considered in the absence of known exposure to toxins, because potential hepatotoxins can be present in contaminated dog food or garbage (aflatoxins), pond water (blue-green algae), and many other unobserved sources.

Treatment

When ingestion of a potential hepatotoxin (e.g., toxic mushrooms, Sago palms) has occurred within the preceding 8 hours, general procedures for GI decontamination are recommended, including induction of emesis or gastric lavage (within first 3 hours), followed by administration of activated charcoal (1 to 3 g/kg).[126,139] Induction of vomiting is contraindicated if the patient is comatose or debilitated in such a way that the gag reflex is diminished, which could predispose to aspiration pneumonia. Whenever possible, the source of toxin exposure should be identified and further exposure prevented. Treatment of drug-induced hepatic disease consists of discontinuing the suspect drug. After a drug is discontinued, clinical (and biochemical) improvement usually occurs within a few weeks, even with chronic drug administration. However, exceptions can occur. For example, in dogs with amiodarone toxicity, liver enzyme elevations can transiently progress despite discontinuation of the drug, and biochemical abnormalities may not resolve for 6 to 8 weeks.[137]

With the exception of NAC for acetaminophen, and silymarin for *Amanita* mushroom toxicity, no specific antidotes are available, and treatment of drug- and toxin-induced liver injury is primarily supportive and symptomatic. However, nonspecific hepatoprotective therapy with antioxidants (vitamin E), glutathione replacement (NAC, SAMe), or milk thistle (silymarin) may be helpful and are discussed in more detail in Chapter 46. Use of NAC (or SAMe) may be beneficial, as glutathione depletion may predispose to hepatotoxicity (e.g., methimazole) or impair metabolism of toxic metabolites to a nontoxic form. NAC has been suggested to be beneficial for treatment of ALF associated with toxicities such as diazepam, methimazole, carprofen, and trimethoprim-sulfa.[9] In addition to treating *Amanita* mushroom hepatotoxicity, silymarin may be beneficial in the treatment of carbon tetrachloride and acetaminophen toxicity.[9,140,141] Corticosteroids are not typically indicated for treatment of drug- and toxin-induced hepatotoxicity.

Prognosis

It is important to consider a drug-induced cause of liver injury because rapid recognition and prompt discontinuation of an hepatotoxic drug can lead to improvement or complete resolution of hepatic disease, depending on the specific drug and the stage of the lesion. When drug- or toxin-induced hepatic injury causes severe or widespread hepatic necrosis, rapid deterioration and death in 3 to 4 days often occur. With less-severe hepatic injury, complete recovery is possible.

Selected Hepatotoxic Drugs

Acetaminophen

Acetaminophen is well known as an intrinsic hepatotoxin in dogs and cats.[142,143] Although acetaminophen is occasionally used as an analgesic in dogs (therapeutic doses up to 15 mg/kg TID), most toxicity occurs because of accidental ingestion of improperly stored medication (dogs) or owner administration without veterinary supervision (dogs and cats).[142] Toxic metabolites of acetaminophen cause oxidative injury to erythrocytes and hepatocytes, resulting in methemoglobinemia, anemia, and hepatic necrosis. In therapeutic doses, acetaminophen is detoxified by a combination of hepatic glucuronidation and sulfation and renal excretion.[144] After acetaminophen overdosage, these pathways become saturated and a greater proportion of acetaminophen is metabolized through the P450 system, leading to production of the toxic metabolite, *N*-acetyl-*p*-benzoquinoneimine (NAPQI). Glutathione detoxifies NAPQI and thus protects hepatic cellular constituents from its direct toxic effect. However, once glutathione levels are depleted by large amounts of NAPQI, centrilobular necrosis occurs. Toxicity occurs in a dose-dependent manner.

There are substantial species differences in both the metabolism of acetaminophen and the toxic manifestations.[142] Cats are uniquely sensitive to acetaminophen because of a deficiency of glucuronyl transferase and limited sulfation capabilities. Clinical signs in cats may develop after administration of as little as 162.5 mg (½ tablet). Signs of methemoglobinemia usually dominate the clinical picture, such as cyanosis, dyspnea, facial edema, depression, hypothermia,

and vomiting. Although increases in serum ALT activity may be detected, centrilobular hepatic necrosis appears to be uncommon. Clinical signs in dogs are more likely when doses exceed 200 mg/kg and can be indicative of methemoglobinemia and/or centrilobular necrosis.[142] Laboratory features include methemoglobinemia, anemia, increased serum ALT activity, and hyperbilirubinemia.

Intravenous NAC is the treatment of choice for acetaminophen toxicity in dogs and cats.[142] NAC increases the synthesis and availability of glutathione, which when conjugated to NAPQI, decreases toxicity. For maximum effectiveness, NAC should be given within 12 hours of acetaminophen exposure; however, there may still be a benefit if given 36 to 80 hours after exposure. NAC (10% solution) is diluted 1:2 or more with saline and given intravenously through a nonpyrogenic 0.25 µm filter at an initial dose of 140 mg/kg over a 20- to 30-minute period. A maintenance dose of 70 mg/kg is given IV or orally every 6 hours for seven treatments. SAMe also serves as a glutathione source and has been shown to have protective effects against acetaminophen-induced oxidative stress on the erythrocytes in cats and dogs.[143,145] In an experimental study in cats, silymarin (30 mg/kg PO) was as effective as NAC for treatment of acetaminophen toxicity when given up to 4 hours after exposure.[140] Vitamin C (30 mg/kg IV q6h) may be helpful in the treatment of acetaminophen toxicity because of its antioxidant effects. Cimetidine (5 mg/kg IV q8h) is also recommended as adjunctive therapy in the early stages (first 16 hours) because it inhibits hepatic P450 enzymes and decreases NAPQI formation.

Amiodarone

The antiarrhythmic drug amiodarone is associated with a reversible hepatotoxicity in dogs.[134,137] Doberman Pinschers may be at increased risk.[134] Toxicity, which appears to be at least partially dose related (doses of 400 mg/day), was identified in 45% of Doberman Pinschers treated with amiodarone in one clinical series.[134] Clinical signs (anorexia, lethargy, vomiting, diarrhea) and biochemical abnormalities (increased ALT and ALP activity ± hyperbilirubinemia) developed 6 days to 8 months after initiation of therapy. Liver biopsy in one dog revealed multifocal hepatocellular necrosis with mild lipidosis and lymphoplasmacytic inflammation.[137] Clinical improvement usually occurs within a few days of stopping the drug, but liver enzyme elevations may not return to normal for 3 months.[134] Transient progression of enzyme abnormalities despite discontinuing the drug has also been noted, which may reflect the long half-life of amiodarone causing a delay in systemic elimination.[137] Biochemical changes precede clinical signs, so monitoring of liver enzymes at least monthly is recommended.

Azole Antifungals

The azole antifungal drugs ketoconazole and itraconazole (and rarely fluconazole) are associated with increased liver enzyme activity and icterus in dogs and cats.[146] Hepatotoxicity is more likely with ketoconazole than with itraconazole. Cats are more sensitive to the hepatotoxic effects than are dogs, but considerable individual variation occurs. Histologic findings are poorly characterized but include bile duct proliferation and infiltration of mononuclear cells. Transient mild subclinical elevations of liver enzymes (ALT and ALP activity) are common, and do not necessarily require a change in therapy. A clinically significant hepatic reaction is suggested by ALT activity that exceeds two to three times the upper limit of normal, especially when accompanied by clinical signs of anorexia and vomiting. Drug therapy should be stopped for 1 to 2 weeks until appetite and liver enzymes return to normal. A rapid recovery usually occurs, and treatment can be restarted at a lower dose (50% of previous dose or given as alternate-day therapy), with careful monitoring of liver parameters every 2 weeks.[146] Hepatotoxicity appears to be at least partly dose related, as dogs receiving higher daily doses of itraconazole (10 mg/kg) are more likely to be affected. Icterus and evidence of hepatic dysfunction suggests a more serious, potentially fatal hepatopathy, requiring discontinuation of medication and symptomatic and supportive care. It is recommended that liver enzymes be monitored on a monthly basis in all animals receiving ketoconazole or itraconazole.

Azathioprine

Azathioprine, a purine analogue commonly used for treatment of immune-mediated disorders in dogs, is commonly listed as a potential hepatotoxin.[126] However, few clinical details regarding the hepatotoxic reaction are available. In a clinical study of 12 dogs with atopic dermatitis treated with azathioprine (2.2 mg/kg daily for 8 weeks) as a single agent, an increase in ALT or ALP activity was noted in the first 2 weeks in 10 (83%) of the dogs.[147] Three dogs had clinical signs suggestive of liver disease, which resolved uneventfully when azathioprine was discontinued. In an experimental study of dogs given azathioprine at a dose of 2 to 4 mg/kg PO daily for 40 days, all dogs had increased liver enzyme activity (ALT >> ALP) within 2 to 7 days of initiating therapy.[148] Values peaked within the first 2 weeks and then declined, but not to normal, despite continued medication administration. Hyperbilirubinemia was absent. Liver biopsies in most dogs revealed centrilobular degeneration and necrosis, with intrahepatic cholestasis but no inflammation.[148] These findings raise the possibility that azathioprine may be an intrinsic (dose related) hepatotoxin in dogs, with possible adaptive tolerance to liver injury. It should be noted that doses used in this study exceeded current clinical recommendations of 1 to 2 mg/kg daily or every other day for maintenance therapy.

Carprofen and Other Nonsteroidal Antiinflammatory Drugs

Hepatotoxicity is considered a class characteristic of NSAIDs, despite the fact that there are many different chemical classes of NSAIDs, and no consistent mechanism of liver injury.[149] With the exception of aspirin, which is an intrinsic (dose-related) hepatotoxin, the mechanism with other NSAIDs is believed to be idiosyncratic (either immune or as a consequence of toxic metabolites).[149,150] Toxicity does not appear to be related to prostaglandin inhibition like the renal or GI side effects.[149] Preexisting hepatic disease has not been shown to be a risk factor for NSAID-induced liver injury.[150] All NSAIDs have the potential to cause idiosyncratic hepatotoxicity in dogs, but hepatic reactions appear to be rare.[150] Carprofen has specifically been reported as a cause of drug-induced liver injury in dogs.[73] Labrador Retrievers were overrepresented in the series, but it is not clear whether this is a true breed predisposition.[150] Clinical signs (anorexia, lethargy, vomiting, PU/PD) occurred within the first 4 weeks of therapy and icterus was a common finding on physical examination. Biochemical evaluation revealed marked increases in liver enzymes (ALT activity usually exceeded ALP activity) and hyperbilirubinemia. Hepatic biopsy findings revealed multifocal to diffuse hepatic necrosis, mild to moderate lymphocytic–plasmacytic inflammation, secondary cholestasis, and variable biliary hyperplasia and bridging fibrosis.[73] Concurrent renal toxicity (glucosuria without hyperglycemia, proteinuria, granular casts) also was noted in some dogs. Most dogs recovered with discontinuation of carprofen and appropriate supportive care, although some dogs died of ALF. General hepatoprotective therapy with SAMe or Silybin has been recommended, although the benefits are unproven. NAC has been suggested for ancillary treatment when carprofen causes ALF.[128]

Early recognition of hepatotoxicity (including periodic monitoring of liver enzymes during the first 3 months) and discontinuation of drug therapy provides the best opportunity for full recovery. Whether dogs with previous carprofen hepatotoxicity can be safely switched to another NSAID without experiencing a hepatic reaction is unknown.

Diazepam

Oral diazepam has been incriminated as a cause of acute idiosyncratic fatal hepatic necrosis in cats.[151,152] Intravenous diazepam, and oral oxazepam, clonazepam, and zolazepam also have been implicated.[126,152] Onset of signs occurs within 5 to 13 days of initiating therapy. Clinical signs and biochemical evaluation are consistent with acute hepatic necrosis and liver failure. Most cats die within 15 days of initial administration of the drug. If treatment of a cat with oral diazepam is unavoidable, liver enzymes should be checked before and within 5 days after starting therapy. If liver enzymes are increased, the drug should be discontinued and symptomatic therapy should be started. Ancillary treatment of ALF with NAC may be beneficial.[9]

Glucocorticoids

Glucocorticoid therapy in dogs is commonly associated with increased serum ALP activity and development of a reversible vacuolar ("steroid") hepatopathy as a result of hepatic glycogen accumulation. These hepatic effects can be seen with virtually any glucocorticoid preparation (including topical ophthalmic and otic preparations) and are influenced by drug preparation (e.g., repositol versus short-acting), dose, duration of therapy, and individual dog susceptibility. In contrast, cats are quite resistant to the hepatic effects of glucocorticoids and only rarely develop these hepatic changes.[153] Increased serum ALP activity can occur within 3 days after initiating glucocorticoid therapy in dogs and is often striking (up to 64 times normal). Glucocorticoids are associated with the induction of a specific corticosteroid-induced isoenzyme of ALP, which may account for 60% to 100% of the total ALP activity.[154] In contrast, serum ALT activity is often normal or only mildly increased. In most dogs, glucocorticoids do not cause significant hepatic dysfunction or clinically relevant hepatic disease and biochemical tests reflecting hepatic function (serum bilirubin, albumin, glucose, blood ammonia concentration, and coagulation tests) are typically normal. Serum bile acid concentrations are normal or only mildly increased (<60 mmol/L). Hepatic glycogen accumulation causes hepatomegaly (which can be detected on abdominal radiographs), and diffuse or multifocal increases in hepatic echogenicity (detected on ultrasonography). The hepatic effects of glucocorticoids are reversible after drug withdrawal. The length of time required for complete resolution is unpredictable, varying from weeks to months.

Lomustine

CCNU [1-(2-chloroethyl)-3-cyclohexyl-1-nitrosourea] is an oral nitrosourea alkylating agent that is used for chemotherapy of lymphoma, mast cell tumor, histiocytic sarcoma, and brain tumors in dogs. Idiosyncratic dose-related hepatotoxicity was described in 11 of 179 (6.1%) dogs given an oral dose of CCNU (50 to 110 mg/m^2), with a dosing interval of 3 to 6 weeks.[72] The median time to detection of hepatic disease (from the last dose of CCNU) was 11 weeks and ranged from 2 to 49 weeks. Delay in onset was noted, with an inverse relationship between the size of dose, and length of time before abnormal serum ALT was detected.[72] A cumulative dose effect was suspected. Clinical findings of hepatotoxicity included decreased appetite, weight loss, PU/PD, vomiting, ascites, and pleural effusion. Ascites was due to a combination of hypoalbuminemia and portal hypertension. Common biochemical abnormalities included increased liver enzyme activity (ALT, AST, ALP, GGT) and hypoalbuminemia. Other less-consistent findings included hyperbilirubinemia, hypercholesterolemia, and increased serum bile acid concentrations. Glucosuria (without hyperglycemia) and renal failure were noted in some dogs, possibly attributable to CCNU renal toxicity.[72] Liver biopsy findings were nonspecific (hemosiderin-laden Kupffer cells, hepatocellular vacuolization, mild to moderate periportal inflammation, and fibrosis) but suggested chronicity. The majority of affected dogs died from progressive chronic liver disease.

In a recent study, routine monitoring of ALT activity prior to each subsequent dose of CCNU suggested that subclinical elevations of ALT activity (greater than five times the upper limit of normal) are common.[155] Thirty-two of 109 dogs (29%) had increased ALT activity, which developed most commonly after one to three doses of CCNU.[155] Increases in ALT activity were not associated with cumulative dose. The lower incidence of clinical hepatotoxicity in this study (3 of 109 or 2.8%) versus the Kristal study (11 of 179 or 6.1%), was attributed to prompt cessation of CCNU treatment in dogs with significant increases in ALT activity.[155] However, it was noted that chronic administration of CCNU could be associated with chronic irreversible hepatopathy, in the absence of a significant ALT elevation. The mechanism of hepatotoxicity is suspected to be a result of generation of toxic intermediate metabolites (e.g., isocyanates, diazonium hydroxide), and depletion of glutathione may play a role.[126] Preliminary results of a clinical study using Denamarin (SAMe and sylibin; Nutramax Labs, Lancaster, SC) for prevention of CCNU hepatotoxicity, suggested that dogs receiving Denamarin had less-severe liver enzyme elevations.[156]

Methimazole

Methimazole, an antithyroid drug, is associated with hepatic injury in cats with hyperthyroidism. Clinical findings include anorexia, vomiting, lethargy, jaundice, markedly increased serum liver enzyme activity, and hyperbilirubinemia that usually occurs within the first month of therapy.[126] Histologic lesions have not been fully characterized, although biopsy findings in one cat revealed hepatic degeneration and necrosis. Clinical signs resolve within a week of discontinuing therapy but biochemical resolution may take up to 45 days. Reduced hepatic glutathione concentrations, which have been documented in other species with hyperthyroidism, may predispose to hepatic injury.[126] Treatment with SAMe may be beneficial.

Phenobarbital, Primidone, Phenytoin

Phenobarbital is associated with chronic hepatic disease and cirrhosis in dogs.[70] Most dogs have been treated with phenobarbital for more than a year before the liver disease is apparent. The mechanism of hepatic injury is not known but higher doses, higher blood levels (>40 μg/mL), and long duration appear to be important risk factors.[70] Clinical signs in dogs reflect chronic liver disease and include sedation, ataxia, anorexia, weight loss, weakness, ascites, jaundice, coagulopathy, and encephalopathy. Phenobarbital-induced hepatic injury should be suspected in any dog with a history of chronic phenobarbital therapy and clinical and biochemical evidence of hepatic dysfunction.

Routine biochemical screening (every 4 to 6 months) of dogs on long-term phenobarbital therapy is recommended for early detection of hepatic injury. However, mild liver enzyme elevations (especially ALP) are commonly seen in dogs treated with phenobarbital, who do not have clinical or histologic evidence of significant liver

disease.[157] Potential indicators of clinically significant liver injury include increases in ALT and ALP activity that exceed five times the upper limit of normal; ALT activity that exceeds ALP activity; any elevation in AST activity; or enzyme elevations accompanied by evidence of hepatic dysfunction (hyperbilirubinemia, hypoalbuminemia, hypocholesterolemia, increased SBA). Hepatic cirrhosis associated with chronic phenobarbital therapy is characterized grossly by a small, nodular liver and histologically by bridging portal fibrosis, nodular regeneration, biliary hyperplasia, and mild inflammation (see Figure 61-19).[70] These lesions are by no means pathognomonic for phenobarbital-induced hepatic damage; however, in the absence of other known causes of hepatic damage, circumstantial evidence would support drug therapy as a likely cause. Chronic phenobarbital therapy also is associated with superficial necrolytic dermatitis (hepatocutaneous syndrome) in dogs.[158] Liver biopsy changes were typical of those seen with hepatocutaneous syndrome (marked vacuolar change and parenchymal collapse), which are distinct from the characteristic chronic hepatitis and cirrhosis as described above.[158]

Phenobarbital should be decreased or discontinued if possible in dogs with biochemical and histologic evidence of hepatic disease. In dogs with phenobarbital-associated toxicosis, clinical, biochemical, and histologic improvement can occur if the drug is discontinued or used at a reduced dosage prior to severe, end-stage liver disease. Improvement in clinical signs can be noted within days to weeks of decreasing serum phenobarbital levels. Primidone also is associated with chronic liver disease in dogs, likely as a consequence of metabolism of primidone to phenobarbital. Phenytoin can cause acute or chronic hepatitis in dogs, as well as jaundice and death. The risk of hepatotoxicity is increased with combination therapy of phenobarbital, primidone, and phenytoin.[126]

Sulfonamides

Potentiated sulfonamides (trimethoprim-sulfadiazine, trimethoprim-sulfamethoxazole, and ormetoprim-sulfadimethoxine) are associated with the acute idiosyncratic drug-induced liver injury in dogs.[21] Trimethoprim-sulfadiazine was implicated in over 20% of hepatic drug reactions in dogs that were reported to the Center for Veterinary Medicine between 1988 and 1990.[71] Doberman Pinschers are suggested to be at risk for development of polyarthropathy from sulfonamide hypersensitivity, but not necessarily the idiosyncratic hepatic reaction.[159] Onset of clinical signs occurs within 5 to 36 days (mean: 12 days) from starting the drug.[159] Previous exposure to sulfonamides is not required. Doses of potentiated sulfonamides are generally higher in dogs who develop the idiosyncratic hepatic reaction, as compared with other systemic manifestations of sulfonamide hypersensitivity (thrombocytopenia, fever, polyarthropathy, other).[159] Biochemical findings include increased liver enzyme activity (ALT > ALP) and hyperbilirubinemia. Liver biopsy usually reveals marked hepatic necrosis; however, cholestasis and marked lymphocytic–plasmacytic inflammation also have been described.[21] The pathogenesis of the idiosyncratic hepatic reaction is unclear. Dogs in general may be at increased risk for sulfonamide reactions because they lack genes that express the *N*-acetylation enzymes, which is a major metabolic pathway of detoxification of sulfonamides in humans.[21] However, this does not explain individual risks among dogs. Hepatotoxicity may be a result of P450 oxidation of sulfonamides to reactive metabolites, such as hydroxylamine and a nitroso metabolite, which may be associated with hapten formation, T-cell proliferation, or direct cytotoxicity.[21] Impaired detoxification of reactive metabolites via a deficiency in glutathione, cysteine, and ascorbate, may play a role, and theoretically supports the use of glutathione precursors (NAC, SAMe) and vitamin C in treatment.[21] Dogs with hepatopathy are less likely to recover (46%) than are dogs with nonhepatic manifestations of sulfonamide hypersensitivity (89%).[159]

Tetracycline and Doxycycline

Tetracycline can predispose to hepatic lipid accumulation because it inhibits protein synthesis and interferes with hepatic secretion of triglyceride-rich lipoproteins.[126] However, it does not appear that these hepatic effects are clinically significant in most dogs and cats, although clinically significant idiosyncratic hepatic injury has been reported. Increased liver enzyme activity was a common finding in dogs treated with doxycycline (increased ALT activity in 39.4%; increased ALP activity in 36.4%), but the clinical significance remains to be determined.[160]

Other Hepatotoxins

Aflatoxicosis

Aflatoxins are metabolites, produced primarily from strains of the saprophytic fungus, *Aspergillus*, which cause toxic hepatitis in dogs and many other species.[138,161] Exposure in dogs may occur through the inadvertent use of aflatoxin-contaminated corn or peanut meal during the commercial production of dog food, or after ingestion of homemade pet foods, moldy garbage, or improperly stored dog food.[161] Dogs are relatively susceptible to aflatoxins and the liver is the target organ. Clinical cases of aflatoxicosis in cats have not been reported. Aflatoxin B1 is most commonly implicated in hepatotoxicity and toxic effects are seen when levels exceed 60 μg/kg of food.[161] Aflatoxin B1 is readily absorbed from the GI tract and undergoes hepatic metabolism by cytochrome P450 enzymes, to a toxic intermediate (aflatoxin B1 8,9-epoxide), which binds to essential molecules within the cell, leading to hepatocyte necrosis and decreased protein synthesis. Detoxification of aflatoxin B1 8,9-epoxide occurs by conjugation to glutathione.

Depending on the amount consumed, dogs may present with acute, subacute, or chronic liver disease. High-dose exposure is associated with acute hepatic failure, jaundice, DIC, and death. Repeated exposure to low doses can lead to chronic liver disease and cirrhosis. In 2005, an outbreak of aflatoxicosis occurred in at least 100 dogs, as a result of eating a commercially available dog food manufactured with aflatoxin-contaminated corn.[138] Severity of clinical signs varied significantly among dogs. Some dogs died suddenly without preexisting signs of illness. Other dogs were presented with signs of anorexia, lethargy, vomiting, jaundice, diarrhea (including melena and hematochezia), abdominal effusion, HE, and evidence of a bleeding disorder. Common biochemical features included increased liver enzyme activity (especially ALT), hyperbilirubinemia, electrolyte disturbances, hypoalbuminemia, hypocholesterolemia, and prolonged clotting times. Reduced plasma antithrombin III and protein C activities and hypocholesterolemia were suggested to be the most sensitive biomarkers of aflatoxin ingestion in dogs with minimal clinical signs, possibly reflecting an early effect of aflatoxin on biosynthesis of certain proteins and cholesterol.[138]

In dogs with acute or subacute aflatoxicosis, the liver is enlarged and pale yellow with histologic features of diffuse hepatic vacuolation (lipid accumulation), scattered individual hepatocyte necrosis, biliary hyperplasia, and modest inflammation. Collapse of zone 3 hepatocytes around the central vein, associated with perivenular inflammation, may explain clinical features of portal hypertension. With chronic low-level exposure, findings include a small liver with regenerative nodules, acquired PSS, and histologic evidence of marked biliary hyperplasia and periportal fibrosis.

Aflatoxicosis associated with consumption of a commercially manufactured pet food product should be suspected when there is a geographic or temporal cluster of cases in a household, kennel, or region. The history may reveal recent changes in diet or feeding from a new bag. It should be noted that some dogs may consume contaminated food for weeks to months before signs develop. Definitive diagnosis of aflatoxicosis is based on chemical detection of increased levels of aflatoxin (>60 µg/kg) in the food. When aflatoxicosis is suspected, the owner should be advised to retain 1 kg of food in an airtight zippered plastic bag (or four cans of food), for laboratory testing. It is also recommended to save packaging information, including product and date code, to help identify contaminated lots of food. If a sample of food is no longer available, serum or liver samples can be submitted for testing for aflatoxin M1 (aflatoxin metabolite), although usefulness may be limited because of the rapid metabolism and excretion of aflatoxin. Detection of aflatoxin M1 in urine is only useful if the dog is still consuming the contaminated diet, as levels fall below detectable levels within 48 hours.

There is no specific antidote for aflatoxicosis and treatment consists of symptomatic and supportive management of liver failure. Nonspecific hepatoprotective therapy with antioxidants (vitamin E), glutathione replacement (NAC, SAMe), milk thistle (silymarin), and L-carnitine have been recommended.[138] The prognosis is guarded if clinical signs of aflatoxicosis are present, with a reported mortality rate of 64% in a series of 72 dogs that consumed aflatoxin-contaminated dog food.[138] Dogs that survive acute liver injury have the potential to develop chronic liver disease. Consequently, monitoring of liver function is recommended in recovering dogs and treatment with thiol donors such as SAMe for 2 months has been empirically recommended.[138]

Amanita *Mushrooms*

Amanita phalloides (and other varieties such as *Amanita verna* and *Amanita bisporigera*), are poisonous mushrooms found throughout North America that can cause acute hepatic necrosis in dogs and cats.[162,163] Toxicity is attributed to extremely toxic cyclopeptide toxins called amanitins. Ingestion of two *A. phalloides* mushrooms can be lethal to an adult dog.[163] Clinical signs occur within 6 to 24 hours after ingestion and are characterized initially by GI signs such as vomiting, bloody diarrhea, and abdominal pain. The late phase (36 to 84 hours after exposure) is characterized by ALF (hemorrhage, marked hypoglycemia, HE, and terminal coma) caused by severe massive hepatic necrosis (see Figure 61-20). Toxin-induced renal tubular necrosis may also result in renal failure.[162] Biochemical features reflect severe hepatic injury and include increased liver enzyme activity (ALT exceeds ALP), refractory hypoglycemia, and hyperbilirubinemia. Diagnosis is usually made based on positive identification of the suspect mushroom, evidence of its ingestion, and consistent clinical features. Mushroom pieces in gastric contents can confirm exposure, but are difficult to identify. Accurate mushroom identification requires consultation with an experienced mycologist. The suspect mushrooms should be wrapped in paper towels and stored in a paper (not plastic) bag.[162] Definitive confirmation can be established by detecting amanitins in liver or kidney tissue (or serum and urine samples collected during the GI phase) by liquid chromatography-mass spectrometry, through the California Animal Health and Food Safety Laboratory.[163]

GI decontamination procedures are recommended as soon as possible after exposure, as described in the "Treatment" section of "Drug and Toxin-Induced Liver Injury". Symptomatic and supportive treatment for ALF is indicated, including close monitoring and treatment of marked hypoglycemia. Silymarin is believed to reduce hepatocyte uptake of amanitins and has been shown to be protective against experimental *A. phalloides* liver damage in Beagles, when given at a dose of 50 mg/kg IV twice, at 5 and 25 hours after exposure.[141] However, an intravenous form of silymarin is not currently available for clinical use in the United States. Experimental studies suggest that penicillin G may also reduce hepatic uptake of amanitins, even several hours after ingestions.[162] IV NAC may be beneficial as described for treatment of acetaminophen toxicity. Overall mortality rate with *Amanita* mushroom toxicity is high.

Blue-Green Algae

Ingestion of toxin-producing blue-green algae (*Microcystis aeruginosa*) is a rare cause of hepatotoxicity and ALF in dogs.[164] Algae proliferate in shallow, stagnant water, especially in hot, dry weather. Dead or dying algae form a thick blue-green scum on the water's surface, and release the toxic principle, microcystins. Toxicity is caused by ingestion of algae-contaminated water. Signs occur rapidly (within 1 hour of ingestion) and include vomiting, diarrhea, and lethargy, followed by progressive tachypnea and dyspnea, icterus, and coma. Biochemical features reflect hepatocellular injury with increased ALT and AST activity (that typically exceed increases in ALP activity), and hyperbilirubinemia. However, profound or protracted increases in ALT activity may not be detected, because microcystins can interfere with transaminase biosynthesis.[7] Hepatic lesions consist of massive hepatic necrosis of the centrilobular to midzonal hepatocytes. Treatment is symptomatic and supportive. Oxidative injury may play a role,[164] which suggests that glutathione supplementation (NAC or SAMe) may be of benefit. The prognosis is guarded.

Cycads (Sago Palms)

Cycads (Sago palms) are native to tropical and subtropical regions, and are used as houseplants and in residential landscaping. Concentrations of cycasin, the primary toxin in cycads, are highest in the seeds and roots, but present in all parts of the plant.[165] Ingestion of as few as one to two seeds can be fatal in dogs. Following ingestion, cycasin is metabolized by GI bacteria to its active compound, methylazoxymethanol, which causes GI and hepatic toxicity in dogs.[165] Most dogs that ingest cycads develop GI signs, including vomiting, diarrhea, and abdominal pain. Neurologic signs (weakness, ataxia, depression, proprioceptive deficits, seizures, coma) are also common, but it is not clear if they are a result of a neurotoxin or HE.[165] Onset of clinical signs ranges from 15 minutes to 3 days and may last from 24 hours to 9 days.[165] Hepatic injury is suggested by findings of progressive depression, icterus, HE, and excessive bleeding accompanied by increased liver enzyme activity, hyperbilirubinemia, hypoglycemia, and hypoabuminemia.[166,167] Centrilobular hepatic necrosis is found on liver biopsy.[166] No specific treatment is available. Mortality has been reported to vary between 32% and 58%.[165,167]

Xylitol

Xylitol, a 5-carbon sugar alcohol used as a sugar substitute, is associated with hypoglycemia and hepatic necrosis in dogs.[168,169] Xylitol is safe in humans and is commonly used in sugar-free gum and other oral care products, and is available as a granulated powder for baking. Xylitol was first introduced into the United States in 2002, and since that time, reports of toxicity to the ASPCA Animal Poison Control Center have increased from two dogs in 2002 to 2512 dogs in 2008.[168] Ingestion of more than 0.1 g/kg in dogs is associated with a rapid, severe, increase in blood insulin, which results in signs of hypoglycemia within 30 to 60 minutes of ingestion. When amounts exceed 0.5 g/kg, ALF may occur within 9 to

72 hours.[169] ALF is not necessarily preceded by early signs of hypoglycemia. The mechanism of hepatotoxicity is unknown, but has been speculated to be caused by cellular depletion of adenosine triphosphate resulting in hepatocellular necrosis, or production of reactive oxygen species causing oxidative injury.[169] In addition to signs of hypoglycemia, dogs with ALF may have vomiting, icterus, and evidence of excess bleeding. Biochemical findings include markedly increased ALT and AST activity, mild to moderate increased ALP activity, hyperbilirubinemia, hypoglycemia, hyperphosphatemia, prolonged PT and aPTT, and thrombocytopenia.

If ingestion occurred within the last few hours, induction of emesis is recommended (unless showing signs of hypoglycemia). Activated charcoal may be of limited value in adsorbing xylitol, but is still recommended if large amounts have been ingested.[168] Treatment recommendations include hospitalization for observation and monitoring, dextrose supplementation for control of hypoglycemia, and symptomatic and supportive care for complications of liver failure. Hepatoprotective therapy with NAC, SAMe, and silymarin may be beneficial. The prognosis is good for recovery in dogs with uncomplicated hypoglycemia and guarded to poor for dogs in liver failure. However, survival after liver failure does not necessarily correlate with amount of xylitol ingested.[169]

VASCULAR DISORDERS

Viktor Szatmari

Vascular hepatic diseases include congenital and acquired disorders of the *portal vein*. *Congenital* anomalies result from (a) hypoplasia or aplasia of the portal vein, (b) macroscopic communications between the portal vein and a systemic vein, or (c) between the portal vein and an artery. *Acquired* diseases result from conditions that increase the hydrostatic pressure in the portal vein (i.e., portal hypertension).

Macroscopic venous connections between the portal and systemic venous systems result in *portosystemic shunting* (i.e., blood flows from the portal to the systemic veins) via a CPSS or *acquired portosystemic collaterals* (APSC).

Clinical Manifestations

Congenital Portosystemic Shunt

Neurologic Signs

HE is a reversible central neurologic manifestation of hepatic insufficiency.[1] CPSS causes chronic HE. The following grades of chronic HE are recognized[2]: *grade 1*—depression, behavior changes; *grade 2*—ataxia, compulsive pacing, circling, hypersalivation, head pressing, blindness; *grade 3*—stupor and seizures; and *grade 4*—coma.

Chronic HE is characterized by periods of severe (grades 2 to 3) signs (lasting usually several hours to a few days alternating with longer periods (days to weeks) of no or mild (grade 1) symptoms.[2] Periods of cortical blindness are accompanied by apparent mydriasis. Signs of HE may be triggered by ingestion of protein-rich meals.

Polyuria and Polydipsia

PD means excessive fluid intake (in dogs >100 mL/kg body weight/24 h and in cats >50 mL/kg body weight/24 h). PU may be more difficult to diagnose than PD, as pet owners cannot readily measure urine volume. Repeated low specific gravity of morning urine (<1.025 in dogs and <1.030 in cats) is compatible with PU.

Lower Urinary Tract Disease

Ammonium biurate uroliths are formed most of the time in the bladder (and rarely in the renal pelvis) and can cause dysuria, urethral obstruction in males, and seldom uroabdomen as a result of chronic inflammation and subsequent devitalization of the bladder wall.[3]

Ammonium biurate crystalluria is not pathognomonic for portosystemic shunting, and it may occasionally occur in normal dogs and cats, or be found in certain breeds, such as Dalmatians, because of an inborn error of metabolism.

Anesthesia Intolerance

Prolonged recovery from anesthesia or sedation may occur in seemingly normal dogs and cats that have CPSS. The liver plays a crucial role in the detoxification process of toxins and drugs, including anesthetics. Patients with CPSS or APSC have insufficient functional hepatic mass for detoxification. In addition, dogs with portosystemic shunting have increased endogenous benzodiazepine and GABAergic activities.[4] Therefore administration of diazepam or barbiturate to these animals may have prolonged and exaggerated effects (see "Pathogenesis" section).

Fever

Recurrent fever together with resultant depression and anorexia can be the only clinical manifestation of CPSS in some dogs.[5] Portosystemic shunting should be excluded in dogs experiencing recurrent fever.

Episodic Weakness

This rare manifestation has only been reported in a few dog.[6] Its pathogenesis is not understood.

Hypercortisolism (Pseudo-Cushing Disease)

Elderly dogs with extrahepatic CPSS may present with characteristic signs of hypercortisolism (e.g., PU/PD, polyphagia, thin skin, symmetric alopecia, muscle wasting, pot belly) as primary complaints. These are unusual clinical manifestations of CPSS.

Stunted Growth

Although small body size is observed in cats with CPSS, it infrequently occurs in dogs.

No Symptoms

Many dogs with extrahepatic CPSS show no or only nonspecific clinical signs throughout their lives and the shunt is detected as a coincidental finding at the time of necropsy. It is not understood why certain dogs become clinically ill and others do not with the same type of portal vein anomaly.

No Jaundice, No Ascites, No Hemorrhagic Diathesis

CPSS never cause icterus, ascites, or spontaneous hemorrhages.

In Cats

Portal vein disorders are much less common in cats than in dogs. Most cats are younger than 6 months of age when the first signs appear.[7] Cats with CPSS are often of smaller stature and have unkempt hair coat. Episodic salivation and/or central neurologic signs, for example, compulsive pacing or seizures, as manifestations of HE are the most typical presenting complains.[8,9]

Portal Hypertension

Clinical signs can develop at any age and arise from the presence of increased hydrostatic portal venous pressure, portosystemic

shunting via APSC, and the underlying disease that led to portal hypertension.

Signs from Acquired Portosystemic Collaterals

Clinical signs of portosystemic shunting are similar, regardless whether it is congenital or acquired in origin (see "Clinical Manifestations" section).

Ascites

Accumulation of a large amount of pure transudate or modified transudate (clear, straw-colored, or slightly turbid blood-tinged fluid) in the abdominal cavity is commonly detected with physical examination and abdominocentesis. The absence of free abdominal fluid does not exclude portal hypertension.

Signs from Acquired Underlying Diseases

Depending on the etiology and the anatomic location of the underlying disease that led to the development of portal hypertension various signs may be seen such as jaundice, periodic vomiting, and anorexia.

Signs from Congenital Underlying Diseases

Jaundice and hemorrhagic diathesis are absent in congenital vascular disorders. Congenital arterioportal fistula causes transudative ascites in puppies between 2 and 6 months of age.[10]

Primary hypoplasia of the portal vein (PHPV), also described as "noncirrhotic portal hypertension,"[11] may result in ascites, vague GI signs, and HE, or may be entirely subclinical.[12,13]

When the PHPV is not severe enough to cause portal hypertension, clinical signs may not be obvious. This mild form of PHPV is also known as *hepatic microvascular dysplasia*[14] and may be detected serendipitously if plasma bile acid concentrations are measured for unrelated reasons.

In Cats

Portal hypertension is rare and is not typically associated with ascites in cats.[15] Portosystemic shunting because of CPSS or APSC tend to cause similar signs, for example, periodic salivation and seizures, as manifestations of chronic HE.

The most common acquired disease causing intrahepatic portal hypertension is biliary cirrhosis caused by chronic bile duct obstruction. Jaundice and acholic feces are typical findings in extrahepatic cholestasis.

Pathogenesis

Hepatic Blood Flow

Normal Hepatic Circulation

The liver receives its blood supply from the portal vein (approximately 75%) and the hepatic artery (approximately 25%). With diversion of portal venous blood flow, a compensatory increase of the hepatic arterial flow occurs. Arterial vasodilation is mediated by adenosine from energy-depleted hepatocytes.

The portal vein transports blood from the spleen and the GI tract to the liver.[16] The smallest portal venous and hepatic arterial branches terminate in the capillary system of the liver, the so-called hepatic sinusoids. A large amount of plasma is filtered through the fenestrated walls of the sinusoids to the space of Disse. From here the filtered plasma is taken by lymphatic vessels to the systemic venous system. The remaining sinusoidal blood is then collected by the hepatic veins, which enter the caudal vena cava. Normally no macroscopic connections exist between major vessel systems or their tributaries.

Portosystemic Shunting

Single or multiple portosystemic venous connections allow the portal venous blood to flow directly to the systemic venous system without first flowing through the hepatic sinusoids. This toxin-rich blood will be delivered to all cells of the body through the following route: gut > portal vein > shunt > systemic vein > right heart > lungs > left heart > arteries. A connection through a single, or rarely double, large-bore vein without the presence of portal hypertension is considered to be a CPSS. Single or multiple connections in the presence of portal hypertension are APSC.

Whenever a macroscopic venous connection is present between the portal vein (or one of its tributaries) and a systemic vein, the blood will flow from the portal vein to the systemic vein, because the pressure in the portal vein is higher (8 to 10 mm Hg) than that in the systemic veins.[8]

Portal Hypertension

Normal portal venous pressure is approximately 8 to 10 mm Hg (10 to 13 cm H_2O). Increased pressure in the portal venous system results in portal hypertension. Anatomically, portal hypertension can be classified[17] as (a) prehepatic (i.e., portal vein), (b) intrahepatic or (c) posthepatic (i.e., hepatic veins, thoracic caudal vena cava, or heart).

Posthepatic Portal Hypertension. All cardiac diseases that result in right-sided congestive heart failure cause posthepatic portal hypertension. These diseases include the (a) congenital or acquired insufficiency of the tricuspid valve (e.g., dysplasia with or without stenosis, myxomatous degeneration, annulus dilation caused by dilated cardiomyopathy, pulmonary hypertension), (b) pericardial diseases (pericardial tamponade caused by idiopathic or neoplastic effusion or constrictive pericarditis), (c) cor triatriatum dexter, (d) intracardiac tumors affecting the right heart, and (e) caval syndrome (caused by *Dirofilaria immitis* heart worms). Kinking or compression of the thoracic caudal vena cava occurs rarely. Compression or thrombosis of the hepatic veins (the so-called Budd-Chiari syndrome) does not occur in dogs and cats.[13]

In posthepatic portal hypertension the portal and caval pressures increase equally, so no pressure gradient is present. Therefore no APSC develop, and the blood ammonia concentration remains within reference range. The high sinusoidal hydrostatic pressure causes a large amount of protein-rich hepatic lymph to be filtered through the hepatic capsule into the abdominal cavity causing accumulation of a modified transudate. Modified transudate has high protein content because the fenestrated endothelial cells of the hepatic sinusoids keep only 10% to 20% of the plasma proteins in the capillary lumen. Marked generalized hepatomegaly and dilated hepatic veins as well as caudal vena cava are hallmarks of posthepatic portal hypertension.

Intrahepatic Portal Hypertension. Chronic *acquired* parenchymal liver diseases lead to hepatocyte necrosis and subsequent collagen deposition. The resultant disorganization of the hepatic architecture and contraction of the connective tissue results in obstruction of the intraparenchymal vessels. The underlying disease processes include viral, bacterial, protozoal, immune-mediated, or copper-associated chronic hepatitis; toxic, drug-induced, or idiosyncratic liver damage; lobular dissecting hepatitis; and chronic bile duct

obstruction. The resultant increase in portal pressure may cause development of APSC as well as ascites.

Modified transudate may accumulate in the abdominal cavity when the disease process predominantly obstructs the postsinusoidal hepatic venules. However, when the disease process affects predominantly the intrahepatic portal vein branches (presinusoidal portal hypertension) pure transudate will accumulate in the abdomen.

Primary hypoplasia of the portal vein is caused by insufficient development of the intrahepatic portal venous branches, the left portal vein branch, or the whole portal venous system.[12,18]

When the hypoplasia is severe enough to cause intra- or prehepatic portal hypertension, APSC develop. This condition is also known as "noncirrhotic portal hypertension."

If hypoplasia is not severe enough to cause portal hypertension, clinical signs will not develop. Because no portosystemic shunting is present, the results of rectal ATT, portal scintigraphy, and portography are all normal (see "Differential Diagnosis" section). If either macroscopic or microscopic portosystemic communications is present, hyperammonemia or abnormal ATT should also be present, but this has never been documented. The only abnormality that could be detected in these dogs is elevation of serum bile acids levels.[14] The most plausible explanation for this is that the hepatic clearance of bile acids by the hypoperfused liver is probably less effective than that of ammonia. The disease can only be diagnosed by histopathologic examination of liver biopsy specimens. This condition also has been described as "hepatic microvascular dysplasia." Although the terms *noncirrhotic portal hypertension* and *hepatic microvascular dysplasia* have been used to describe this syndrome, both have been replaced by the term PHPV.[13] The occurrence of PHPV in the cat is very rare and poorly documented.

The most common congenital cause of portal hypertension in cats is congenital hepatic fibrosis as a part of polycystic kidney and liver disease complex.[19] This disease may cause clinical signs with or without the presence of macroscopic hepatic or renal cysts.[20]

Prehepatic Portal Hypertension. Narrowing of the portal vein lumen may be caused by (a) extravascular compression by a tumor, enlarged lymph node, cyst, abscess, or hematoma, (b) idiopathic circumscribed stenosis,[21] or (c) intravascular obstruction by a thrombus or parasites, all of which can lead to portal hypertension.[22] Portal vein thrombosis is always secondary either to neoplasia, or to a systemic disorder that causes hypercoagulability such as nephrotic syndrome, immune-mediated hemolytic anemia, hypercortisolism, acute pancreatitis, peritonitis, or sepsis.[23] Parasites in the portal vein also may occur, for example, *Heterobilharzia americana* in North America[24] and *Schistosoma japonicum* in East Asia.[13]

Depending on the degree of portal vein occlusion, increased portal pressure with APSC and ascites may develop. As the hydrostatic pressure in the sinusoids does not increase (in contrast to posthepatic portal hypertension), the resultant ascitic fluid will have a low protein content. The narrowed lumen of the portal vein causes reduced portal flow to the liver, resulting in reduction in the size of the liver. Portal vein thrombosis itself rarely causes clinical signs and is usually a coincidental finding.

Congenital Arterioportal Fistula. Single or multiple macroscopic connections between the main portal vein and hepatic artery are rare congenital anomalies. The high arterial blood pressure causes (a) severe dilation and tortuosity of the affected portal venous branch, (b) hepatofugal flow in the portal vein (i.e., flow away from the liver), (c) development of portal hypertension and APSC, and (d) histologically detectable arterialization of the portal venous wall. The hepatofugal portal flow prevents the splanchnic venous blood from entering the liver and causes the development of alternative pathways and often times accumulation of pure transudate in the abdomen. Interestingly, PHPV always accompanies congenital arterioportal fistulas both in dogs and cats.[5,10,25] When a CPSS and arterioportal fistulas are concomitantly present, APSC and ascites generally do not develop.[25] Arterioportal fistula can be extrahepatic in cats..

Acquired Portosystemic Collaterals. In healthy mammals, multiple nonfunctional venous connections may exist between the portal and systemic veins. These virtual communications become functional when their lumen becomes sufficiently widened. Gradual dilation takes place when sustained increase of the portal pressure takes place without the simultaneous increase of caval pressure. The resultant APSC are multiple, usually thin, tortuous veins with species-specific anatomical locations; however, large-bore veins may also develop. These latter cases should not be misinterpreted as simultaneous CPSS and APSC. In the presence of an existing CPSS, no APSC would develop even if hepatic cirrhosis develops as there *is* an already existing portosystemic connection that is able to drain 100% of the portal blood without allowing the development of portal hypertension.[26] Splenorenal collaterals are consistently present in almost every dog with APSC.[10,27] These APSC drain the portal venous blood via the splenic vein through acquired connections to the left gonadal vein. The left gonadal vein enters the left renal vein, which later empties into the caudal vena cava. These splenorenal APSC are thought to prevent the spleen from undergoing congestion,[17] which is why splenomegaly is not a feature of canine pre- and intrahepatic portal hypertensive disorders.[10]

Consequences of Hepatic Hypoperfusion for the Liver

Shunting of the portal blood is not only detrimental for the brain, but for the liver as well. Normal hepatic development and function requires sufficient amount of portal venous perfusion of the hepatic sinusoids. Increased arterial perfusion is unable to compensate for portal hypoperfusion. Regardless of whether the insufficient portal venous perfusion is caused by CPSS or by prehepatic portal hypertension, the result is the same: reduced hepatic mass and function. In both cases, histopathologic evaluation of the liver shows stereotypical reaction: small or invisible portal branches, increased number of arterioles and sometimes bile ductules in the portal tracts, hepatocellular atrophy, and periportal sinusoidal dilation.[13] This *secondary* portal vein hypoplasia is reversible and is histologically indistinguishable from PHPV. Because primary and secondary portal vein hypoplasia show identical microscopic features, histopathologic evaluation of liver biopsy specimens is unable to diagnose simultaneous PHPV and CPSS.

Hepatic Encephalopathy

Glycine and GABA are the most important inhibitory neurotransmitters, whereas glutamate and dopamine are the most abundant excitatory neurotransmitters in the brain. In HE, a net increase in inhibitory transmission occurs.[28] This results from upregulation of GABA receptors and downregulation of dopamine receptors.[29] Activation of GABA receptors causes opening of chloride channels, which leads to hyperpolarization of the postsynaptic membrane. In the presence of GABA, benzodiazepines increase the frequency, whereas barbiturates increase the duration of the chloride channel opening.[30] The cause of increased GABAergic tone in HE is thought to be gut derived,[4] but GABA may also be formed in the neurons from glutamate.[28] Endogenous benzodiazepines are proven to be

produced in the intestines of dogs with CPSS.[4] Their source is not quite clear: they could arise from the diet, intestinal flora, or by endogenous modification of inactive gut precursors.[4]

In all forms of portosystemic shunting the concentration of aromatic amino acids are increased in the systemic circulation whereas the concentration of branched-chain amino acids is decreased. High aromatic amino acid concentration results from impaired hepatic clearance and increased production caused by muscular breakdown exacerbated by hyperglucagonemia.[28,31] The decreased concentration of branched-chain amino acids results from their increased utilization for gluconeogenesis.[28,32] This amino acid imbalance may result in the development of "false" neurotransmitters (e.g., octopamine) in the brain, which contribute to the development of HE.[33,34] These "false" neurotransmitters have a fraction of dopamine's excitatory effect on dopamine receptors. Drugs with dopaminergic effect, such as bromocriptine, may improve signs of HE.[35-37]

Intestinal toxins such as ammonia and bacteria are normally inactivated by hepatocytes and hepatic macrophages (Kupffer cells), respectively, so that toxin- and bacterium-free blood can enter the systemic circulation. In patients with portosystemic shunting the majority of the portal venous blood bypasses the liver, allowing the toxin- and bacterium-rich blood to enter the systemic circulation. Ammonia is a neurotoxin and can contribute to the clinical signs of HE.[38] Other toxins that are believed to play a role in HE are endogenous benzodiazepines, GABA, tryptophan, glutamine, serotonin, mercaptans, indoles, and skatoles.[4,34,39]

Hyperammonemia also leads to impaired glial function through increased intracellular glutamine concentration.[38] Glutamine is made in the glial cells through incorporation of ammonia into glutamate by glutamine synthetase.[28] Chronically increased glutamine concentrations cause swelling of the glial cells resulting in so-called Alzheimer II type degeneration of astroglias.[40,41] Glial dysfunction contributes to the development of HE.[40,42] During hyperammonemia, the reserve capacity of the astrocytic glutamine synthetase is exceeded, and ammonia can enter the neurons.[42] In the neurons ammonia inhibits glutaminase, an enzyme that converts glutamine to glutamate. Because glutamate is an excitatory neurotransmitter, its reduced level contributes to the development of HE.[28]

Portosystemic shunting or an atrophic liver alone is insufficient to allow HE to develop; HE can only develop when they are both simultaneously present.[28] The reserve capacity of the liver ensures that even in advanced chronic parenchymal liver diseases, HE does not develop in the absence of portosystemic shunting. Alkalosis and hypokalemia can worsen the signs of HE. In alkalosis the $NH_3 + H^+ = NH_4^+$ reaction shifts to the left, causing the more lipophilic ammonia to enter the cells of the CNS. During hypokalemia, potassium ions (K^+) move from the cells to the extracellular space in exchange for H^+, which later results in extracellular alkalosis and intracellular acidosis. Intracellular acidosis causes NH_4^+ trapping within the cells. This might explain why the blood concentration of ammonia is not closely related to the severity of the clinical signs of HE in individual cases.

Polyuria and Polydipsia

Several mechanisms contribute to the development of PU/PD in portosystemic shunting.

Hypoosmotic Renal Medulla

High concentrations of sodium and urea in the renal medullary interstitium are essential for the production of concentrated urine. These create a high osmotic gradient between the renal tubular lumen and interstitium, which is necessary for water reabsorption. When the liver receives little portal venous blood, an insufficient amount of substrate (i.e., ammonia) is available for hepatic urea production. This theoretically results not only in a low plasma urea concentration, but also in a lower renal medullary urea concentration, which impairs renal concentrating ability and causes PU.

Hypercortisolism

Increased basal plasma concentrations of ACTH and cortisol as well as increased urinary cortisol-to-creatinine ratios are invariably present in dogs with portosystemic shunting.[43-46] Cortisol interferes with the action of arginine-vasopressin at the renal tubule, causing a *nephrogenic-type* diabetes insipidus.[47] Hypersecretion of ACTH (and α-melanocyte stimulating hormone [α-MSH]) has been shown to arise predominantly from the intermediate lobe of the pituitary.[43,48] The hormone secretion of this lobe is regulated by tonic dopaminergic inhibition. ACTH-hypersecretion can be explained by the production of "false" neurotransmitters (e.g., octopamine), whose effect is about one-fiftieth that of dopamine on the dopamine receptors.[35]

Diabetes Insipidus

Central diabetes insipidus also contributes to PU in dogs with HE. Impaired release of arginine-vasopressin from the posterior lobe of the pituitary is caused by a reduced magnitude of response and a highly increased threshold to increased plasma osmolality.[45] Release of arginine-vasopressin is inhibited by the GABA inhibitory neurotransmitter system, whose activity is increased in HE.[29,45]

Pseudohyperaldosteronism

Cortisol and aldosterone have similar affinities to bind aldosterone receptors. However, cortisol is normally inactivated by 11β-hydroxysteroid dehydrogenase in tissues where aldosterone action is required.[49] High serum bile acids concentrations inhibit this enzyme, and cortisol can bind to aldosterone receptors resulting in increased mineralocorticoid effect.[45] Plasma cortisol concentrations are 10-fold those of aldosterone, causing constant and inappropriate pseudohyperaldosteronism. The resultant sodium retention causes secondary water retention and subsequent PU by pressure diuresis. Hypokalemia caused by hyperaldosteronism also contributes to PU[50,51] according to the following mechanism. The presence of aquaporin-2 channels in the renal collecting ducts' cell membranes is necessary for water reabsorption. Intracellular signaling pathways through cyclic adenosine monophosphate regulate the insertion of these channels. Hypokalemia decreases the sensitivity of cyclic adenosine monophosphate to arginine-vasopressin, which results in decreased insertion of aquaporin-2 channels into the cell membrane.[50] This leads to nephrogenic diabetes insipidus and PU.

Renomegaly and Renal Hyperfunction

Congenital portal venous anomalies in dogs are typically associated with enlarged kidney volume. Increased renal gluconeogenesis as a compensation of insufficient hepatic gluconeogenesis may cause the kidneys to enlarge.[52] In addition, increased systemic circulating growth factor concentrations released from the pancreas may play a role in this increased volume.[53] Normally, these growth factors act only in the liver, as they do not reach the systemic circulation in high concentrations.

Primary Polydipsia

Behavior changes and abnormalities in the thirst center due to HE may contribute to PD; however this is difficult to prove in individual patients.

Urolithiasis

Hyperammonemia results in a higher filtered load and urinary concentration of ammonia. High urinary concentration of uric acid results from decreased hepatic conversion of uric acid to allantoin because of reduced hepatic mass and function.

Fever

The portal vein carries bacteria and endotoxins from the intestines, which are normally phagocytized by the Kupffer cells. Shunting of portal blood permits these bacteria and/or endotoxins to enter the systemic circulation causing bacteremia and/or endotoxemia, and subsequent fever.[5] Systemic antibiotics may result in temporary resolution of clinical signs, however give no definitive cure.

Etiologies

Congenital Portosystemic Shunt

If a CPSS occurs within hepatic parenchyma it is called *intrahepatic*.[54,55] Intrahepatic CPSS arise either from the left or right portal branches. A left divisional intrahepatic CPSS results from the failure of postnatal closure of the embryological *ductus venosus*.[56,57] The intrahepatic CPSS arising from the right portal branch and all *extrahepatic* CPSS are thought to be developmental anomalies with poorly understood etiology. In dogs the anatomy of the shunting vessel is fairly consistent: intrahepatic CPSS may be left, right, or central divisional, whereas extrahepatic shunts drain the portal venous blood via the splenic or the right gastric vein to the caudal vena cava or the azygos vein.[15] The course of the shunting vein in the cat is much more variable.[15,58]

The inherited nature of the disease has been established in several breeds including the Irish Wolfhound and the Yorkshire and Cairn Terriers.[59-61]

Portal Hypertension

PHPV is a congenital anomaly of unknown etiology. Although arterioportal fistulas may develop as a result of neoplasm or trauma (e.g., shot wound or liver biopsy), only the congenital form has been reported in dogs and cats. Congenital hepatic fibrosis caused by polycystic kidney disease (PKD) is a genetic disease.[19,62]

Differential Diagnosis

Hyperammonemia

High fasting venous blood ammonia concentrations together with high fasting serum bile acid concentrations are very specific and sensitive tests for diagnosing portosystemic shunting.[63]

Urea Cycle Enzyme Deficiency

Reduced activity of one or more enzymes of the urea cycle may result in elevated blood ammonia concentration.[10,64] Serum bile acids levels should remain within reference range in patients with urea cycle enzyme deficiencies. Normal hepatic scintigraphy and liver histopathology results should confirm the absence of portosystemic shunting. Certain metabolites (e.g., citrulline) and enzyme activities (e.g., argininosuccinic acid synthetase) can be measured in urine and liver biopsy specimens, respectively, to establish a definitive diagnosis. The condition is rare in dogs. One suspected feline case has been reported.[65]

Irish Wolfhound Puppies

Healthy Irish Wolfhounds commonly have moderate hyperammonemia (<120 µmol/L) at the age of 6 to 7 weeks.[66] This is thought to result from reduced enzyme activity of the urea cycle. As no clinical signs are present, no treatment is required. The condition resolves spontaneously with age because these pups develop enhanced incorporation of ammonia into glutamine.

Uroabdomen

Peritoneal absorption of ammonia-containing urine can cause hyperammonemia, however in such a patient the clinical signs of acute uremia predominate. The presence of urease-producing bacteria (e.g., *Staphylococci*) are necessary to split urinary urea to ammonia.[67]

Fulminant Hepatic Failure

Ingestion of blue algae or certain mushrooms (e.g., *A. phalloides*) results in peracute insufficiency of hepatic function. These animals develop hepatic coma and die shortly thereafter. Hyperammonemia, DIC, and icterus are present in most affected patients.

Arginine Deficiency in Cats

Arginine is an essential amino acid in the cat. In anorectic cats hyperammonemia may develop along with hepatic lipidosis because of the insufficient amount of hepatic arginine needed for urea synthesis in the urea cycle.[68] Thus, in contrast to adult dogs, hyperammonemia in cats can occur without portosystemic shunting.

Miscellaneous Disorders

Methylmalonic acidemia associated with cobalamin deficiency in a cat[69] and a suspected "transient hyperammonemic syndrome" in a German Shepherd dog[70] have been reported as extraordinarily rare causes of hyperammonemia.

Sampling or Laboratory Error

If blood sampling and sample processing are performed inappropriately hyperammonia may be erroneously diagnosed.

High Serum Bile Acid Concentrations

High bile acids concentration may result not only from portosystemic shunting, but also from any primary or secondary hepatic diseases associated with intra- or extrahepatic cholestasis.[71] Therefore, the presence of high serum bile acids concentrations is very sensitive, but not a specific indicator of portal venous disorders.[63]

Ascites

The simultaneous presence of hyperammonemia and a large amount of pure or modified transudate in the abdominal cavity indicates the presence of severe pre- or intrahepatic portal hypertension with APSC. Biochemical and cytologic analysis of the peritoneal effusion, ultrasonography and central venous pressure measurement may be useful in identifying the source of ascites.[17] Suspected intrahepatic causes should be further evaluated by histopathologic examination of liver tissue.

Central Neurologic Signs

In any animal that is presented with central neurologic signs, portosystemic shunting (along with other metabolic encephalopathies, e.g., hypoglycemia or electrolyte imbalance) should be investigated with appropriate blood tests.

Diagnosis

No single finding is pathognomonic for diagnosing vascular liver disorders. Therefore, a combination of history, physical

examination, laboratory tests, diagnostic imaging results and histopathology of liver biopsy specimens are often required to establish a specific diagnosis.

Signalment

Intrahepatic CPSS tend to cause clinical signs between 2 months and 1 year of age in large-breed dogs. Bernese mountain dogs, Irish Wolfhounds, Hovawarts, and Retrievers are predisposed. Australian Cattle dogs and male dogs more likely have right-sided than left-sided intrahepatic CPSS,[72] whereas Irish Wolfhounds tend to have left-sided intrahepatic CPSS. Intrahepatic CPSS in small-breed dogs are very rare. Extrahepatic CPSS usually occur in small breeds and can cause clinical signs at any age.[73] The most commonly affected breeds are Maltese dogs, Miniature Schnauzers, Dachshunds, Yorkshire Terrier, Jack Russell Terrier, and Cairn Terrier. No clear sex predisposition is known.

History

The waxing–waning nature of central neurologic signs is suggestive of chronic HE. Symptoms may improve spontaneously.

Physical Examination

Congenital Portosystemic Shunts

Physical examination often fails to detect abnormalities. Occasionally an enlarged left kidney is palpated. The presence of ascites detectable with physical examination should exclude CPSS. Some authors suggest that copper-colored iris is a typical finding in cats with CPSS; however, no reports exist about its positive or negative predictive value.

Portal Hypertension

Dogs with intra- or prehepatic portal hypertension may have ascites. Jaundice is absent in congenital portal hypertensive disorders, but may be present in acquired parenchymal liver diseases.

Laboratory Examination

Blood Ammonia Concentration

Fasting (12-hour) venous hyperammonemia is a very specific and sensitive indicator of portosystemic shunting. As a single test, increased blood ammonia level is usually sufficient to diagnose portosystemic shunting. Because ammonia is formed from amino groups of proteins and urea also in the collection tube, the blood sample (in an ethylenediaminetetraacetic acid tube) should be placed directly on ice after sampling and the measurement should be performed within 30 minutes. Because contamination of the sample with airborne ammonia may cause false-positive results, samples should be taken using a closed system (needle on a syringe or directly into a Vacutainer). Hemolysis may artificially increase ammonia concentration because erythrocytes contain two to three times more ammonia than the plasma. Measurement of ammonia should be performed in a clean location, where the air is not contaminated with ammonia from congested urine or cigarette smoke. A number of analyzers offer the possibility of ammonia measurement; however some of them are unreliable.[46] Measuring *arterial* ammonia concentration provides no additional value.

Ammonia Tolerance Test

If venous ammonia concentration is within the reference range or only slightly elevated, rectal ATT is the cheapest and quickest test to exclude or justify the presence of portosystemic shunting in patients with a suggestive history. Most of these "suspicious" animals also have high fasting plasma bile acids levels.[74] Ammonium chloride (NH_4Cl) solution of 5% is administered at a dose of 2 mL/ig 10 mg/kg maximum 3 grams to 15 cm into the rectum using a soft feeding tube.[75] Venous blood ammonia is measured before and 20 and 40 minutes thereafter. In the presence of portosystemic shunting the ammonia concentration will increase at least twofold by the 20- and/or 40-minute sampling times. Normal ATT result excludes portosystemic shunting (Figure 61-21). The degree of increment is a semiquantitative measure of the degree of portosystemic shunting. It should be noted that rectal administration of NH_4Cl solution may cause transient irritation of the colonic mucosa during the first 10 minutes. Rectal ATT is a safe procedure, with signs of HE rarely occurring. ATT should not be performed in patients with very high (>150 μmol/L) blood ammonia levels.

Postprandial measurement of ammonia is thought to decrease the possibility of iatrogenic hyperammonemic HE; however the increase of blood ammonia concentration after feeding takes longer and its peak time point is poorly predictable.[76]

Serum Bile Acid Concentrations: Pre- and Postprandial

Markedly increased preprandial (i.e., 12-hour fasting) bile acids concentrations are often found with portosystemic shunting as a result of interrupted enterohepatic circulation of the bile acids.[77,78] High 12-hour fasting plasma bile acid concentration is a sensitive, but nonspecific indicator of portosystemic shunting. Specificity can be increased by simultaneous measurement of venous ammonia. As plasma bile acids concentrations are invariably high in icteric animals, the presence of APSC can only be justified or excluded by measuring blood ammonia concentration or performing an ATT.

In case of a normal 12-hour fasting bile acids concentration (<15 μmol/L), measuring an increased postprandial plasma bile acids concentration (>25 μmol/L) 2 hours after a meal increases the sensitivity, but not the specificity of the bile acids test in diagnosing portosystemic shunting.[79] Meal-induced gallbladder contraction causes an endogenous bile acid load, which will be absorbed in the ileum and will substantially increase the plasma bile acids concentration when portosystemic shunting is present. An abnormal postprandial increase of bile acids occurs also in cholestatic liver diseases.

Miscellaneous Biochemical Alterations

In patients with portosystemic shunting hypoalbuminemia, hypoproteinemia, hypocholesterolemia, and low plasma urea concentration may be found as a result of their reduced hepatic synthesis. Hypoglycemia may be seen as a result of reduced hepatic glyconeogenesis and glycogen storage. Low creatinine concentration reflects the increased glomerular filtration rate.[53] None of these biochemical changes is specific for portosystemic shunting; furthermore, many of these findings may be present in healthy pups. The cause of mild increase of plasma ALT and alkaline phosphatase activities is not fully understood.

Hematologic Alterations

Microcytosis with or without mild nonregenerative anemia and leukocytosis may accompany portosystemic shunting. Relative iron deficiency is thought to cause the microcytosis[80-82] and bacteremia may induce the leukocytosis.

Coagulation Abnormalities

Although aPTT is often moderately prolonged in dogs with CPSS, no spontaneous bleeding tendency or hemorrhage occurs.[83,84] Hemoabdomen is a possible postoperative complication after surgical attenuation of a CPSS. Acquired parenchymal hepatic diseases

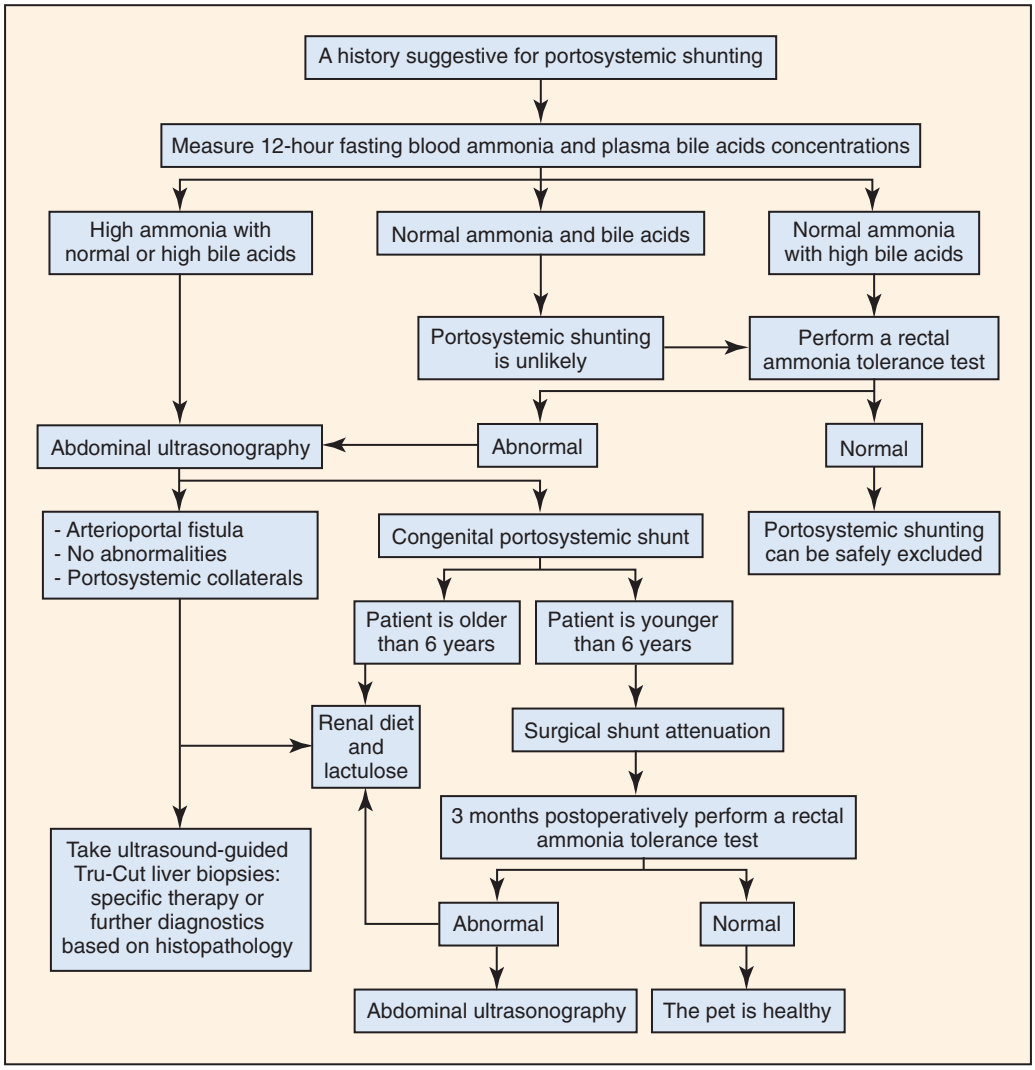

Figure 61-21 Algorithm of diagnostic steps for vascular liver disorders.

may lead to spontaneous hemorrhages because of the presence of DIC.

Diagnostic Imaging

Radiography

Plain radiographs give very limited additional information (such as small liver, possibly enlarged kidneys, and sometimes visible uroliths) to the history and laboratory results, so they don't have to be part of the routine diagnostic workup of vascular liver diseases. Pure ammonium biurate uroliths are radiolucent.

Ultrasonography

Abdominal ultrasonography is the first choice of diagnostic imaging modality, once the presence of portosystemic shunting has been established by fasting hyperammonemia or abnormal rectal ATT (see Figure 61-21). The major advantage is that ultrasonography requires no sedation or anesthesia. Its drawback is in the operator dependence. By using a systematic examination protocol one can accurately differentiate CPSS from APSC, and intrahepatic from extrahepatic CPSS, as well as readily diagnose arterioportal fistulas and prehepatic portal hypertensive disorders.[15,85,86] Although color-flow Doppler highly facilitates evaluation of portal vascular anomalies, a high-resolution grayscale ultrasound is often sufficient to establish a definitive diagnosis.[10]

Although certain secondary changes (such as small liver, large kidneys with hyperechoic medulla, and sediment or stones in the urinary bladder) suggest the presence of CPSS, diagnosing a CPSS requires the visualization of the anomalous vein from its origin to its termination. The urinary bladder should always be evaluated for the presence of urinary calculi. Ultrasonography can be used not only during the initial diagnostic workup, but also during the surgical treatment and postoperative followup of CPSS.[86] Intraoperative grayscale ultrasonography facilitates localizing the course of an intrahepatic CPSS,[26] whereas intraoperative color and spectral Doppler examination helps to determine the optimal degree of shunt attenuation.[87]

Scintigraphy

Free ^{99m}Tc-pertechnetate administered into the colon is absorbed into the portal vein and appears in the healthy liver first or in the heart with portosystemic shunting.[88] Isotopically labeled albumin macroaggregates may be directly administered into a splenic vein with ultrasound guidance.[89] The macroaggregates are trapped in the first capillary bed, which is normally the liver. The fraction of portal

blood that bypasses the liver will be trapped in the pulmonary capillaries. Splenic venous injection of isotopes makes exact calculation of the shunting fraction possible (i.e., activity in lungs/activity in liver + lungs); however, the procedure requires anesthesia.

Scintigraphy is the gold standard diagnostic imaging method to justify or exclude the presence of portosystemic shunting. However, differentiating congenital from acquired portosystemic shunting or intrahepatic from extrahepatic CPSS is not possible. Information provided by a scintigram is a "yes" or "no" answer to the question: Does the patient have portosystemic shunting? This answer can be reached much more easily and without using radiopharmaceuticals by documenting a single high blood ammonia concentration or by rectal ATT.

Angiography

Injection of iodinated contrast agent into the portal vein or into one of its tributaries under fluoroscopy used to be the only form of diagnostic imaging available to diagnose anomalous vessels. Angiography allows identification of extra- and intrahepatic CPSS as well as APSC.[90] The major drawback of selective portography is its invasiveness and the need for general anesthesia. Whereas *mesenteric* portography requires catheterization of a mesenteric vein during laparotomy,[91] *splenic* portography can be performed by ultrasound-guided percutaneous injection of contrast material into a parenchymal splenic vein. Visualizing portal vein segments with hepatofugal flow or shunt segments with hepatopetal flow (Figure 61-22) is problematic, as no contrast reaches these parts of the vessels.

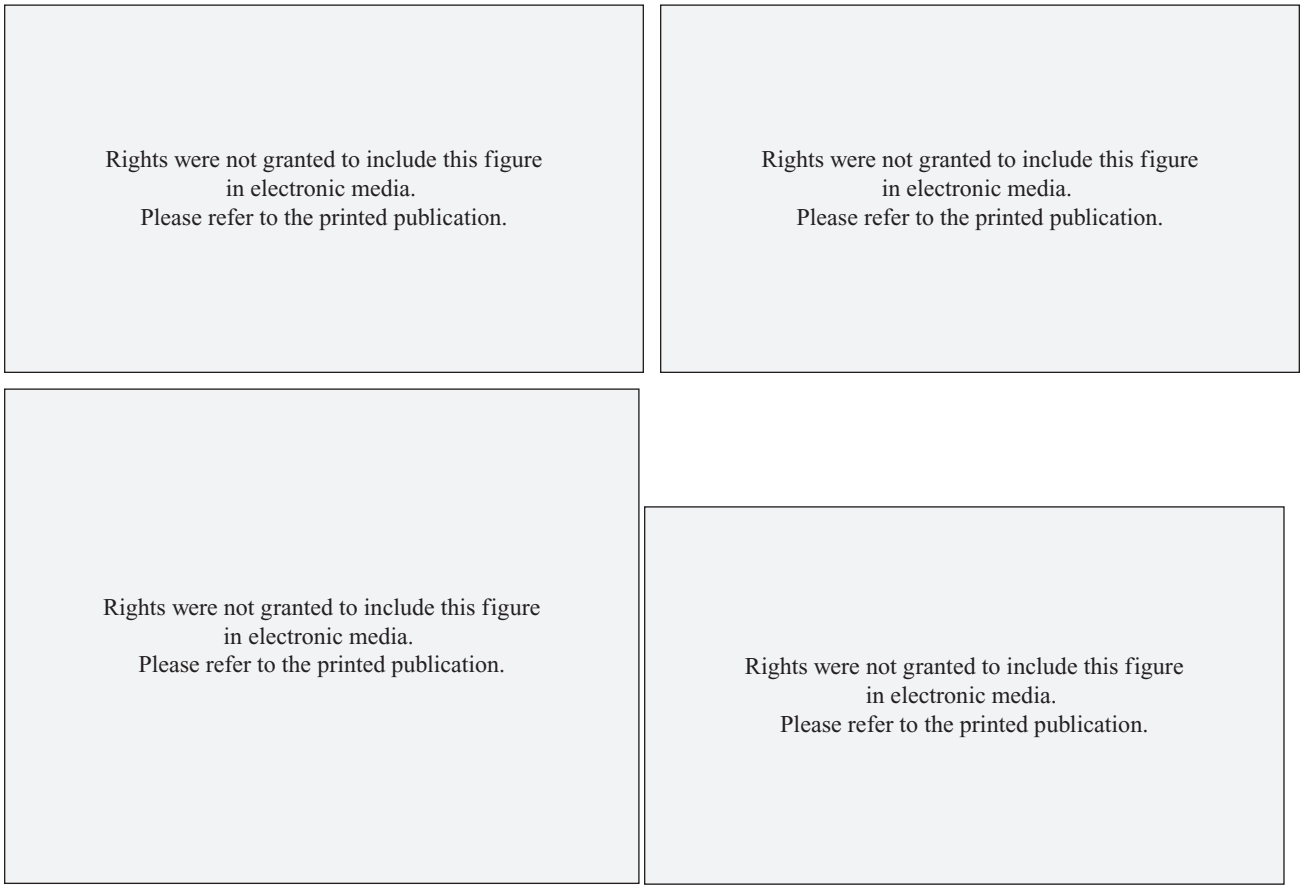

Figure 61-22 Hemodynamic features of the portal flow in the most common type of congenital extrahepatic portosystemic shunt in a dog (**A, C**), and the effect of shunt attenuation (**B, D**). The vascular structures on the schematic pictures (**C, D**) within the rectangle correspond to the vessels shown on the ultrasound images (**A, B**). *Arrows* indicate the direction of blood flow. **A** and **B,** Intraoperative color-flow Doppler ultrasound images of the portal vein at the point where the congenital splenocaval shunt originates. Note that the diameter of the shunt (*SH*) is larger than that of the portal vein (*PVcaudSH*). The portal vein cranial to the origin of the shunt (*PVcrSH*) becomes narrower than the portal vein caudal to the shunt origin (*PVcaudSH*) because of hypoperfusion. **A** and **C,** Because blood always flows toward the lowest resistance, 100% of the portal venous blood flows through the shunt (*SH*) to the caudal vena cava (*CVC*). Note that the blood from the gastroduodenal vein (*GDV*) finds lower resistance to flow caudally toward the shunt, than toward the liver. This creates a hepatofugal flow (i.e., flow away from the liver) in the portal vein segment between the entering point of the *GDV* and the origin of the shunt (*PVcrSH*). Note that the portal vein becomes even narrower cranial to the point where the *GDV* enters it (*PVcrGDV*). The diameter of the various portal vein segments varies because of the varying amount of blood that flows through a certain segment. **B** and **D,** Note that *partial* occlusion of the shunt increases the resistance in the shunt to such an extent that the blood from the splenic vein (*SPLV*) finds lower resistance to flow through the shunting vessel toward the portal vein. This reversed flow in the shunting vessel (*) prevents the portal venous blood from shunting. Thus, even though the shunt is only partially closed, it is *nonfunctional*. Also note that the blood in the whole length of the portal vein is forced to flow toward the liver (i.e., hepatopetal flow direction), establishing normal perfusion of the sinusoids. A portion of the splenic venous blood will continue to flow through the attenuated shunt to the *CVC*, but the splenic blood contains no more toxins than any systemic vein, so no hyperammonemia develops. "Blue," flow from top to bottom, "red," flow from bottom to top; Caud, caudal; Cr, cranial; D, dorsal; PVbrR and PVbrL, right and left portal vein branches; V = ventral. (Reproduced from Szatmári V, van Sluijs FJ, Rothuizen J, Voorhout G: Ultrasonographic assessment of hemodynamic changes in the portal vein during surgical attenuation of congenital extrahepatic portosystemic shunts in dogs. *J Am Vet Med Assoc* 224(3):395, 2004, with permission.)

Computed Tomography

Helical CT, especially the multiscale versions, makes excellent images of the abdominal vasculature (including CPSS) relatively quickly after intravenous injection of iodinated contrast agents.[92] Three-dimensional reconstruction provides impressive anatomic details of shunting vessels.[93] The drawback is the limited availability of the new-generation scanners and the need for patient anesthesia.

Magnetic Resonance Imaging

Although magnetic resonance angiography can provide high-quality images of the abdominal vessels,[94] it has not become popular because of its limited availability and high costs. Patents require general anesthesia and the examination lasts longer than CT angiography.

Characteristic MRI changes have been described in the brains of dogs and cats with CPSS,[95] but these findings are more of research than of clinical interest.

Histopathology

Histopathologic examination of liver biopsy specimens is essential in identifying the underlying disease process in intrahepatic portal hypertensive disorders. In the routine diagnostic workup of canine CPSS liver histopathology gives no additional information.

Currently, the presence of coexistent PHPV cannot be diagnosed preoperatively in dogs with CPSS.[18] This is because the histologic findings of liver biopsies are identical in the following conditions: CPSS, PHPV, CPSS with PHPV, congenital arterioportal fistula, any prehepatic portal hypertensive disorder (e.g., portal vein thrombosis).[13] However, taking liver biopsies for histopathologic examination is recommended in cats before deciding about surgical closure of a CPSS. This is because congenital hepatic fibrosis as part of PKD can be present simultaneously, especially in Persian and Persian crossbreeds.[20] Surgical shunt attenuation is not recommended when congenital hepatic fibrosis and a CPSS are simultaneously present in a cat.

Treatment

Emergency Treatment of Hepatic Encephalopathy

Patients with grades 2 to 4 HE may present on an emergency basis. The source of ammonia and other protein breakdown products, which cause the clinical signs of HE, is the colon. The purposes of the treatment are (a) to reduce the production and amount of ammonia in the colon by removing its content with warm water enema, and (b) to inhibit the absorption of ammonia by administering lactulose syrup into the emptied colon. Lactulose may be given as a retention enema with a soft feeding tube 0.5 to 1.0 mL/kg deep rectally). Lactulose is a nonabsorbable disaccharide, which is metabolized by the colonic bacteria into short-chain fatty acids. These fatty acids acidify the intraluminal content causing to form ammonia (NH_3) and ammonium ion (NH_4^+). Because of its polarity, NH_4^+ will not pass the enterocystic membrane, and is instead trapped in the colonic lumen.[96] It is also essential (c) to correct the acid–base and electrolytic disorders of the patient with IV fluid therapy as alkalosis and hypokalemia can worsen the signs of HE.

Seizures caused by HE can be controlled with intravenous propofol. Administration of benzodiazepines (e.g., diazepam) and barbiturates should be avoided as they can worsen the clinical signs.[97] Binding of a benzodiazepine molecule to its neuronal benzodiazepine receptor increases the effect of GABA on its $GABA_A$-receptor.[4]

Conservative Maintenance Therapy for Hepatic Encephalopathy

The cornerstone of therapy in cases of CPSS (until definitive surgical therapy) and in all cases of APSC is a high-quality, low-protein diet.[32,33,98,99] Commercially available renal prescription diets are ideal and preferable to most hepatic diets, as the protein content is higher in the latter.[28] To decrease colonic transit time and reduce the production of ammonia, oral administration of lactulose is recommended. The dosage of lactulose should be titrated in individual patients to yield soft feces, but not diarrhea. An initial dosage 0.5 mL/kg q12h is recommended. If diarrhea results the dosage should be reduced. Lactulose also stimulates the growth of colonic bacteria that can incorporate ammonia into bacterial protein.

Additional use of antibiotics (e.g., neomycin, metronidazole) has been recommended by some to diminish ammonia-producing colonic flora. Antibiotic administration is usually not necessary to control clinical signs of HE; moreover, neomycin is thought to antagonize the action of lactulose and may cause the release of endotoxins.[100] Furthermore, chronic antibiotic use may contribute to the development of antibiotic resistance.

Surgery of Congenital Portosystemic Shunts

Surgical closure of APSC is generally impossible because of their multiple nature, but also contraindicated, as APSC are usually a compensatory mechanism to resolve high portal venous pressures. Surgical narrowing (i.e., banding) of the caudal vena cava to reduce shunting by increasing the caval pressure is currently not recommended.

In cases of CPSSs, attenuation or complete closure of the shunting vein is the choice of treatment. The goals of shunt occlusion are (a) reducing portal flow via the CPSS and (b) simultaneously increasing portal venous perfusion of the liver.[86] The shunt should be attenuated as close as possible to the point where it enters the systemic circulation. Attenuating intrahepatic CPSS is more risky because of the possibility of major bleeding because of excessive dissection of hepatic parenchyma. There are several techniques described, of which none are perfect.

The major problem with shunt reduction is that blood from the portal vein will be redirected to newly perfuse the liver and its vasculature. Poorly developed portal branches have insufficient capacity to accept even normal amounts of portal venous blood, and in the case of complete shunt occlusion, splanchnic congestion will develop. The goal of surgery is to sufficiently reduce the amount of shunting blood without causing portal hypertension to develop.[86]

Although complete shunt occlusion would theoretically be ideal, partial shunt attenuation is often sufficient because (a) partial attenuation often results in *functional* closure[18] (see Figure 61-22), and moreover (b) complete anatomic occlusion may follow in many cases.[101] Partial occlusion of extrahepatic CPSSs often results in a better outcome because the chance for development of postligation portal hypertension is much smaller compared to complete occlusion.[86]

The liver, which may be less than 30% of its normal size, grows very quickly following successful surgery. Regeneration may take 2 to 3 weeks to complete in uncomplicated cases. The regenerating liver receives progressively more portal blood flow usually resulting in spontaneous complete closure of the CPSS.

Gradual shunt attenuation is believed to reduce the risk of portal hypertension by allowing the portal venous branches to adapt gradually to the increased flow.[102,103] APSC do develop with gradual shunt attenuation techniques (e.g., cellophane banding and ameroid constrictor ring).

Cystic calculi should be removed during the same surgical procedure, because resolution of ammonium biurate uroliths with dietary management can only be achieved in 30% of cases.

Surgical Ligation

The shunting vessel is identified by midline laparotomy and narrowed or completely occluded by a nonabsorbable ligature.[104] Portal hypertension is determined by direct measurement or estimated based on subjective criteria including severe cyanosis, increased intestinal peristalsis, reduction in arterial blood pressure, and compensatory tachycardia as a result of stasis in the splanchnic circulation.[105] Intraoperative Doppler ultrasonography will greatly facilitate determination of the optimal degree of shunt attenuation in extrahepatic CPSS, helping to prevent severe portal hypertension.[86,87]

Cellophane Banding

Instead of a ligature, a 3-mm–thin, three-layer–thick cellophane band is placed around the shunting vessel with or without narrowing of the shunt diameter.[106] Gradual shunt occlusion takes place as a result of inflammation induced by the cellophane.[107,108]

Ameroid Constrictor Ring

A metal ring filled with a thick layer of casein is placed around the shunting vessel. Swelling of the casein occurs as it absorbs fluid. Because of the outer metal ring, the casein can only expand centripetally causing gradual occlusion of the shunt over 1 to 3 months.[102,109,110] The major drawback of this simple technique is that the rate and magnitude of occlusion is uncontrollable and kinking caused by the weight of the device may cause acute fatal portal hypertension. Moreover, because of its relatively large size it can only be easily applied on extrahepatic CPSS.[111,112]

Laparoscopy

Laparoscopic shunt narrowing (by clips) is a less-invasive alternative for shunt ligation (see Chapter 28).[113]

Coil Embolization

With this minimally invasive intravascular technique one or more metal spirals with thrombogenic fibers are placed in the shunting vessel. The coils are delivered via a catheter, which is inserted through the jugular vein into the shunt under fluoroscopic guidance in anesthetized animals.[114,115] The coils cause thrombus formation in the shunt resulting in its partial or complete occlusion. To prevent coil dislodgment from the shunt, an intravascular stent is often placed in the caudal vena cava to cover the point where the shunt enters the caudal vena cava. Coiling is an especially attractive method for treating intrahepatic shunts because liver dissection is thereby avoided.

In my opinion, the safest and most effective way for attenuation of extrahepatic CPSS is Doppler ultrasound-guided *partial* attenuation via surgical ligature.[86,87] For intrahepatic CPSS, coil embolization appears to be an excellent method. Ameroid constrictor and cellophane banding would be ideal in extrahepatic CPSS, when the portal vein cranial to the shunt origin is severely hypoplastic and the patient is at risk for severe portal hypertension.

Postoperative Complications of Shunt Occlusion

Portal Hypertension

Acute Portal Hypertension. Variable degrees of portal hypertension necessarily develop subsequent to any CPSS attenuation. If portal hypertension is severe, circulatory collapse may develop because of sequestration of blood in the splanchnic veins.[116] Slight abdominal enlargement as a result of ascites requires no intervention. This usually resolves spontaneously within 1 week of surgery. Severe ascites with signs of shock (e.g., depression, tachycardia, hypotension, prolonged capillary refill time, hemorrhagic diarrhea) necessitates emergency surgery and removal of the ligatures or constrictor rings from around the shunt. These signs usually develop within 24 hours postoperatively. Unfortunately, the prognosis following emergency surgery is poor.

Portal Vein Thrombosis. This rare postoperative complication causes sudden onset of shock usually within several days of shunt attenuation.[87,117] Exaggerated shunt occlusion, severe portal hypertension, and stasis of portal venous blood are believed to be the cause of the thrombosis. No survivals have been reported.

Chronic Portal Hypertension. When the growth of the liver and development of portal branches is insufficient following partial shunt closure, chronic portal hypertension may induce formation of APSC. This may occur as late as 4 to 8 weeks postoperatively. In such cases, evaluation usually reveals partially patent shunt and increased portosystemic shunting as a result of newly formed APSC. The development of APSC has been documented with all surgical methods. APSC can develop as a result of underdeveloped portal branches or exaggerated shunt attenuation.[18] In most dogs, these APSC remain clinically silent because the hepatic mass has substantially increased following shunt attentuation.[18]

All patients should be re-evaluated at 1 month postshunt attenuation by fasting blood ammonia concentration and abdominal ultrasonography. If fasting blood ammonia concentration is within the reference range, rectal ATT should be performed. If fasting hyperammonemia is present or the ATT is abnormal, ultrasonography should identify whether shunting occurs via the narrowed CPSS, APSC, or both. In the latter cases, lifelong conservative therapy with dietary modifications and lactulose is recommended. A normal ATT result implies complete shunt occlusion and the pet will generally have a very favorable prognosis. A second surgery to reach further shunt attenuation should only be attempted in patients with persistent clinical signs that have high fasting blood ammonia concentration or abnormal rectal ATT result 3 months after the first surgery.[18,86] Spontaneous gradual shunt closure would not occur beyond 3 months after surgical ligation.

Postligation Seizures: Cerebrocortical Necrosis

This rare and usually fatal complication of shunt attenuation causes generalized seizures 1 to 3 days postoperatively, almost exclusively in cats and small-breed dogs (often in Maltese dogs).[31,100,118,119] Its occurrence is unpredictable. The pathogenesis is unknown, but the sudden decrease of endogenous benzodiazepine ligands is thought to play a role (i.e., "benzodiazepine withdrawal syndrome").[4] Because cerebral edema is suspected to be the initial disorder, intravenous mannitol (0.5 to 1.0 g/kg IV, during 20 minutes) may be administered when a patient shows subtle central neurologic signs during the first three postoperative days. Once seizures have developed, the prognosis is usually very poor. Most patients are euthanized because of uncontrollable seizures or persistent neurologic defects. Propofol

(1 to 5 mg/kg, IV) followed by constant rate infusion [CRI]) may be used to control seizures.[120] Prophylactic treatment with phenobarbital does not reduce the risk of development of postligation neurologic complications,[118] but may be used in long-term seizure management. Preventive use of potassium bromide has not been shown to reduce the possibility of postoperative seizures. In every patient with central neurologic signs in the early postoperative period, hypoglycemia and HE should be excluded by measuring venous glucose and ammonia concentrations, respectively.

Blindness and other types of central neurologic signs may develop in cats shortly after surgery. The pathogenesis of these changes is unknown.

Hemoabdomen

Hemorrhage from liver biopsy sites or shunt dissection in cases of intrahepatic CPSS can lead to hypovolemic shock and death in the early postoperative period. Dogs with hepatic insufficiency are prone to develop hemorrhagic complications because of decreased concentrations or abnormal synthesis of coagulation factors.[84] Postoperative portal hypertension may also contribute to bleeding tendency from hepatic parenchymal dissection. Hemoabdomen should be carefully differentiated from severe portal hypertension as they both cause shock and variable degrees of abdominal distention. Coagulation parameters (e.g., PT, aPTT) should be routinely monitored after surgery and if they are abnormal or if there is evidence of clinical bleeding, fresh-frozen plasma transfusion should be administered (10 to 20 mL/kg, IV).

Hypoglycemia

Small-breed dogs are prone to develop hypoglycemia during or shortly after surgery.[100] Blood glucose concentrations should be regularly monitored and hypoglycemia should be treated with glucose-containing infusions.

Portal Hypertensive Disorders

Specific treatment should address the underlying parenchymal liver disease based on the histologic results of liver biopsy. HE can often be controlled with dietary modification and lactulose.

Primary Hypoplasia of the Portal Vein

Currently, no specific treatment exists for portal venous hypoplasias. Renal prescription diets and lactulose may alleviate clinical signs of HE in case of APSC. Diuretic agents may be useful in dogs with ascites.

Congenital Arterioportal Fistulas

Liver lobe resections have been reported in animals with congenital arterioportal fistulas. However, simultaneous presence of PHPV in the whole liver prevents postoperative resolution of portal hypertension and the portosystemic shunting via APSC.[10,25] Therefore, the pet owner should be educated that partial hepatectomy may not result in complete recovery of portosystemic shunting, and that lifelong dietary support and/or lactulose will likely be required.

Ascites

Severe abdominal effusions should be treated with diuretic agents.[121] The first choice is spironolactone (1 to 2 mg/kg q12h), an aldosterone receptor antagonist as (a) chronic hepatic insufficiency is associated with hyperaldosteronism, (b) concurrent hypercortisolemia is associated with cortisol binding to the mineralocorticoid receptor, and (c) potassium-sparing diuretics prevent development of hypokalemia and alkalosis, both of which would worsen signs of HE. If spironolactone alone does not resolve ascites, furosemide may be added to the therapy. Abdominocentesis for removal of abdominal effusion is not recommended because of loss of protein and exacerbation of Starling forces permitting further fluid accumulation.

Prognosis

Congenital Portosystemic Shunts

Conservative Treatment

Dietary and medical management relieves clinical signs only temporarily.[99] Without surgical shunt attenuation, gradual deterioration of liver function occurs; consequently, conservative therapy alone offers a guarded to poor prognosis. In older animals (>6 years) with newly reported signs of CPSS, lifelong conservative treatment may be recommended because of the significantly higher complication rates of surgical therapy in these patients.[105]

Surgical Treatment

The prognosis depends on (a) whether the CPSS is intra- or extrahepatic, (b) the coexistence of PHPV, (c) the extent of shunt attenuation, (d) experience of the surgeon, and (e) the age of the dog at the time of diagnosis. Intrahepatic CPSS generally has poorer prognosis. Complete resolution of clinical signs can be expected in approximately 60% to 80% of dogs with extrahepatic CPSS in the hands of an experienced surgeon. This same parameter is approximately 50% to 70% for intrahepatic CPSS.[102-105] With extrahepatic CPSS, an excellent prognosis can be expected when blood flow is hepatopetal (i.e., toward the liver) in the portal vein segment, which is cranial to the shunt origin. This can be established preoperatively with Doppler ultrasound.[86] In cats, regardless of the shunt type and the surgical method, the success rate is approximately 30% to 50% because of the development of postoperative central neurologic signs.[105,122,123]

Portal Hypertension

The prognosis of portal hypertensive disorders depends on the underlying disease. In the majority of acquired diseases the underlying disorder is chronic and so severe that even stopping the disease process will not cause regression of APSC.

NEOPLASTIC DISORDERS

Josep Pastor and Marta Planellas

Hepatobiliary Neoplasia

Primary liver neoplasms are infrequent in the dog and cat, with an estimated prevalence in necropsy studies of 0.6% to 2.6% in the dog and 1.5% to 2.3% in the cat. Liver metastases are more frequent than primary hepatic tumors in the dog, and tend to originate from the spleen, pancreas, and GI tract. Primary hepatobiliary tumors are more common than metastatic disease in the cat.[1-5]

Etiology

The etiology of liver cancer in dogs and cats is incompletely understood. Potential causes such as aflatoxins, nitrosamines, food additives, parasites, and radioactive compounds have been reported.[6-8] Liver cancer in the dog has many clinical, pathologic, and histologic homologies with liver cancer in humans.[9-12]

In human medicine, chronic diseases of the liver, such as hepatitis B or C infection, as well as cirrhosis, are often associated with

hepatocellular tumors; however, there is no established association between hepatic tumors and viral infections in the dog or cat. Moreover, canine hepatic cirrhosis does not appear to predispose to hepatocellular carcinoma (HCC).[1] A possible association between hookworm or whipworm infection and liver cancer has been reported, and cats with chronic cholangitis may have an increased predisposition to biliary carcinoma.[7,13]

Several liver mitogens and tumor suppressor genes such as epidermal growth factor, TGF-α, vascular endothelial growth factor (VEGF), p53, and TGF-β and its receptors (TGF-β-r) have been associated with liver cancers in humans and these may play a similar role in the dog.[14-17]

In human medicine a small percentage of HCCs or cholangiocarcinomas originate from hepatic progenitor stem cells. Dogs diagnosed with HCC or cholangiocarcinoma do demonstrate activation of hepatic progenitor stem cells in response to liver injury, but hepatic progenitor stem cell expression in liver tumors is relatively low.[18]

Pathophysiology

The hypothesis of cancer development as a multistep process applies to liver tumors in the dog and the cat, as well.[7,19] Precancerous lesions, such as dysplastic nodules, can be identified before the development of overt malignancy in humans. Dysplastic nodules are characterized by cell atypia, cellular crowding, trabecular thickness, microacini, and histochemical markers.[20] Dysplastic nodules have not been reported in the dog or cat and further studies are needed to understand the chronology of hepatic malignancy in domestic animals. Preliminary reports of histochemical markers have been reported in dogs with hyperplastic hepatic lesions and hepatocellular and biliary neoplasms.[11]

Liver tumors cause damage to the liver by several mechanisms: inflammatory effects, obstruction of the biliary system, obstruction of the vascular compartment or adjacent organs, and spontaneous rupture with hemoabdomen.[21]

Hepatic tumors are usually resistant to chemotherapy.[7,19] In one recent study, P-glycoprotein was more highly expressed in HCC than in cirrhosis, which is consistent with the known resistance of HCC to chemotherapy. P-glycoprotein, which is encoded by the multidrug resistance gene (MDR-1), is normally expressed in tissues with excretory function, including the jejunum, kidney, liver, and adrenal gland.[22]

Primary liver neoplasms are usually classified according to their cellular origin and macroscopic appearance. With respect to cellular origin, these tumors may be hepatobiliary, hematopoietic, sarcomas, or metastases of other tumors (Box 61-2). In relation to macroscopic appearance, they can be classified as lobular, multiple nodular, or diffuse (). The combination of histopathologic and morphologic classification has consequences for prognosis and treatment strategy in these animals (Tables 61-6 and 61-7), and the clinician must always address these factors to arrive at correct management decisions. In dogs, malignant tumors are more common than benign lesions. In cats, biliary neoplasms are the most common presentation, particularly intrahepatic benign forms.[6,7]

Clinical Examination

Most animals with liver neoplasia present with nonspecific clinical signs such as anorexia and weight loss. Less-frequent clinical signs include vomiting and diarrhea, PD and PU, pale mucosal membranes, and acute weakness because of anemia and hypovolemia coincident with tumor rupture.[7,19] Up to 25% of affected animals show no clinical signs, and liver cancer is suspected only with increases in serum liver enzyme activities.[3,5,7,23]

Box 61-2 Classification of Liver Neoplasms According to Cellular Origin

Primary

- Hepatobiliary neoplasm
  - Hepatocellular carcinoma
  - Biliary carcinoma (cholangiocarcinoma, biliary adenocarcinoma)
  - Hepatocellular adenoma (hepatoma)
  - Biliary duct adenoma (cystadenoma)
  - Carcinoid tumor (neuroectodermal neoplasm)
- Hematopoietic neoplasm
  - Lymphoma
  - Leukemia
- Sarcomas
  - Hemangiosarcoma
  - Sarcoma
  - Leiomyosarcoma
  - Rhabdomyosarcoma
  - Osteosarcoma
  - Chondrosarcoma

Metastatic

- Gastrointestinal tract
- Spleen
- Pancreas
- Kidneys
- Mammary tissue
- Prostate

The most common physical examination findings are cranial abdominal mass (35%), abdominal bloating (30%), and jaundice (18%). Jaundice is a less common finding in cases of metastatic cancer. Other manifestations include neurologic signs as a result of HE; paraneoplastic syndromes such as hypoglycemia and myasthenia gravis; and skin alterations consistent with hepatocutaneous syndrome.[7,24]

No clear breed predisposition is observed with canine liver cancer, although Poodles, Fox Terriers, Miniature Schnauzers, Labrador Retrievers, and male dogs are overrepresented in some reports of hepatocellular carcinoma.[1,12,19,25,26] Labrador Retrievers and female dogs are overrepresented in reports of bile duct carcinoma.[1,26-28] Whether male and female cats are equally at risk for bile duct carcinomas is unsettled,[28,29] but male cats appear to be at greater risk for bile duct adenomas.[30,31] Neuroendocrine tumors are generally observed in younger animals.[1,32]

Diagnosis

Definitive diagnosis of liver cancer can be made only by liver biopsy. Asymmetrical enlargements of the liver detected on physical examination, abdominal ultrasonography, or survey radiography should not be assumed to be neoplastic in origin. Similarly, laboratory data do not distinguish hepatic neoplasia from other liver pathologies.[33]

The clinical approach to an animal with suspected liver cancer should include basic information such as a complete blood cell count, serum biochemistry, coagulation tests, urinalysis, thoracic and abdominal radiographs, abdominal ultrasound (Figures 61-23 and 61-24), and fine-needle or core biopsy of the liver.

A TNM tumor classification system has been used for staging of liver cancer where T represents tumor (T0, no evidence of tumor;

Table 61-6 Incidence of Histologic Liver Tumor Types, Morphologic Patterns, Metastatic Rates, and Treatment in Dogs

Histologic Tumor Type	Morphologic Pattern	Incidence	Metastatic Rate	Treatment	Reference
Hepatocellular carcinoma		50%			1
	Lobular or massive	53% to 84%	4.8% to 6.6%	Lobectomy	26, 27
	Multiple nodular	16% to 25%	93%	Chemoembolization Metronomic therapy (human medicine)	27, 52
	Diffuse or infiltrating	0% to 19%	100%	Chemoembolization Metronomic therapy (human medicine)	27, 51, 52
Biliary carcinoma		22%	27% to 88%		1, 13, 26, 27
	Lobular or massive	37% to 46%		Lobectomy	26
	Multiple nodular	0% to 21%		Chemotherapy	26
	Diffuse or infiltrating	17% to 54%		Chemotherapy	26
Sarcoma		13%	86%	Lobectomy Metronomic therapy (soft-tissue sarcomas)	1, 7, 19
	Lobular or massive	36%			1
	Multiple nodular	64%			1
	Diffuse or infiltrating	67%			1
Carcinoid tumors		14%	93%		1, 56, 64
	Lobular or massive	0%			1, 56, 64
	Multiple nodular	33%		Cholecystectomy Chemoembolization	64, 66
	Diffuse or infiltrating	0%			1, 56

Diffuse or infiltrating, multiple coalescent nodules in all the lobes, or diffuse disappearance of the liver parenchyma; *lobular*, nodule or large mass in a single liver lobe; *nodular*, several nodules throughout the liver parenchyma, or several affected liver lobes.

Table 61-7 Incidence of Histologic Liver Tumor Types, Metastatic Rates, and Treatment in Cats

Histologic Tumor Type	Morphologic Pattern	Incidence	Metastatic Rate	Treatment	Reference
Hepatocellular adenoma		8% to 22%	25%	Lobectomy	29
Hepatocellular carcinoma		2%	NR		28
Biliary carcinoma		24% to 28%	77%		73
Hepatobiliary cystadenoma		12%	0%	Lobectomy	29, 62
Biliary adenoma		32% to 52%	0%	Lobectomy	29
Sarcoma		2% to 13%	60% to 100%	Lobectomy	29
Carcinoid tumors		4%	100%	Lobectomy, cholecystectomy	64, 65

T1, tumor involving one lobe; T2, tumor involving more than one lobe; and T3, tumor invading neighboring structures); N represents regional lymph nodes (RLNs) (N0, no evidence of RLN involvement; N1, RLN involved; N2, distant LN involved); and M represents distant metastasis (M0, no evidence of metastasis; M1, distant metastasis detected). Although recommended, this system has not been universally adopted.[34]

Table 61-8 illustrates the most typical hematologic and biochemical findings in dogs and cats affected with liver neoplasia. Leukocytosis is a result of inflammation and necrosis of large tumors; anemia tends to be moderate and nonregenerative and is thought to be caused by chronic illness, inflammation, or iron deficiency[19]; thrombocytosis is attributable to a paraneoplastic syndrome characterized by thrombopoietin production, iron deficiency, or anemia.[7]

Serum liver enzyme elevation is a frequent, but not universal, finding in animals with liver neoplasia. It should be noted, however, that the degree of serum enzyme elevation does not correlate with the degree of liver involvement or severity of disease. In one survey, animals with primary liver tumors tended to have greater elevations in serum ALT and ALP activities than animals with metastatic disease, while the latter tended to have greater elevations in serum bilirubin and AST.[35] It also has been suggested that an AST-to-ALT ratio of less than 1 is more compatible with carcinoma, while a ratio of greater than 1 is more indicative of a sarcoma or carcinoid.[1] Other reported biochemical changes include hypoglycemia, hypo- or hyperalbuminemia, and increased serum bile acids. Hypoglycemia as a paraneoplastic syndrome associated with hepatocellular carcinoma is attributed to the secretion of insulin-like growth factor II.[36] Unlike dogs, cats usually present with a high incidence of serum creatinine and BUN elevations.[28,29]

Coagulation factor abnormalities are more commonly associated with hemangiosarcoma, although DIC may be evident in end-stage liver cancer or in decompensated patients. Coagulation studies should always be performed before undertaking invasive diagnostic procedures.[23]

Serum α-fetoprotein has been evaluated in the dog, and increases are reported in 75% of animals with hepatocellular carcinoma, and in 55% of those with biliary carcinomas. The use of this biomarker is limited by the fact that it is increased in cases of hepatic

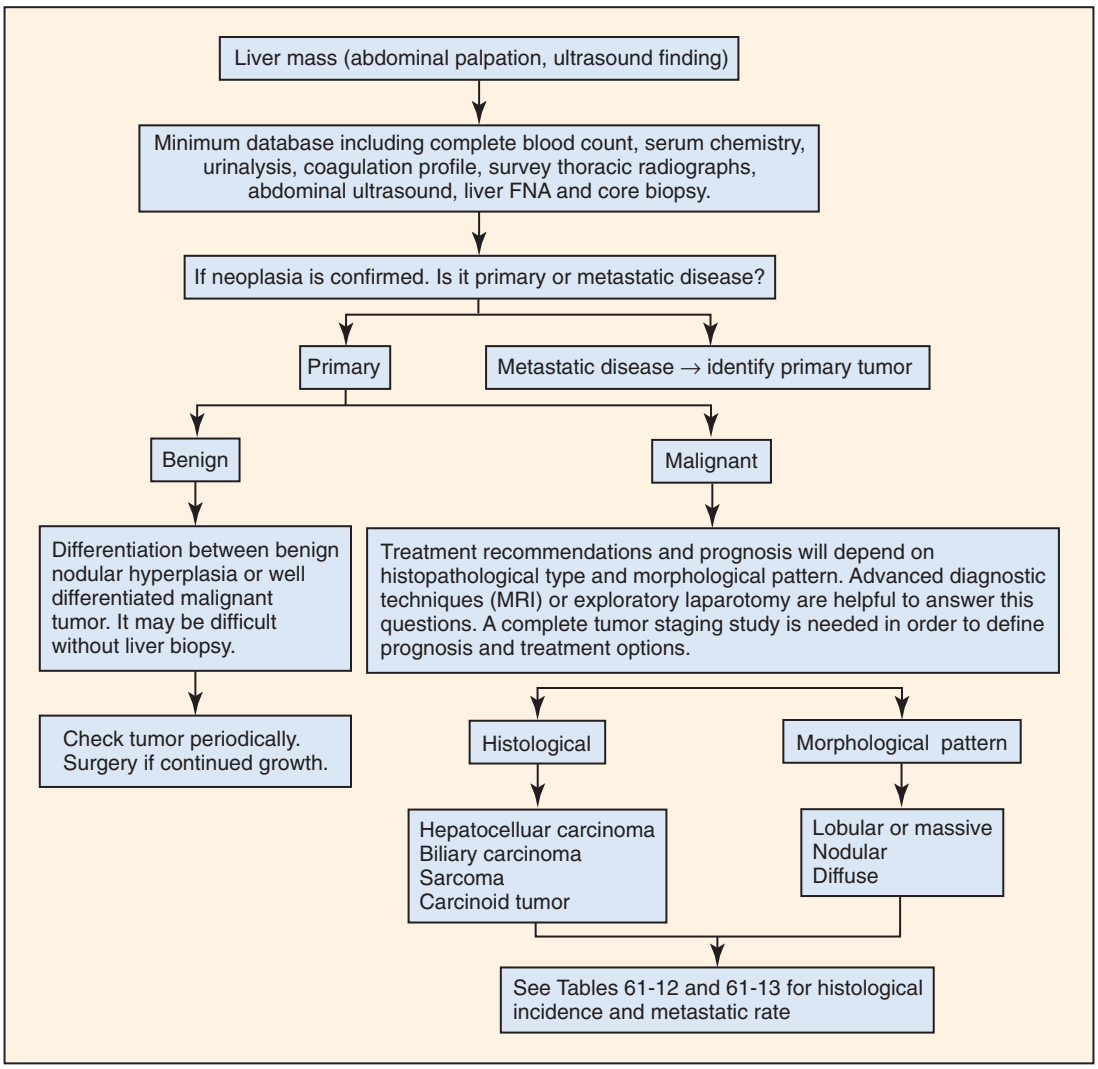

Figure 61-23 Diagnostic decision tree in an animal with a liver mass.

Table 61-8 Hematologic and Biochemical Changes Observed in Dogs and Cats with Liver Neoplasms

Parameter	Change	Incidence in Dog	Incidence in Cat
Hematocrit	Decrease	27% to 50%	ND
Leukocytes	Increase	54% to 73%	ND
Platelets	Increase	50% hepatocellular carcinoma	ND
Alkaline phosphatase	Increase	61% to 100%	10% to 64%
Alanine aminotransferase	Increase	44% to 75%	10% to 78%
γ-Glutamyltransferase	Increase	39%	78%
Total bilirubin	Increase	18% to 33%	33% to 78%
Bile acids	Increase	50% to 75%	67%
Albumin	Decrease	52% to 83%	ND
	Increase	Occasionally	ND
Glucose	Decrease	Occasionally	ND

ND, Indicates percentage not described.
From Thamm DH: Hepatobiliary tumors. In: Withrow SJ, MacEwen EG, editors: *Small Animal Clinical Oncology*, ed 3, Philadelphia, 2001, Saunders; Liptak J: Hepatobiliary tumors. In: Withrow S, Vail D, editors: *Withrow and MacEwen's Small Animal Clinical Oncology*, St. Louis, 2006, Elsevier.

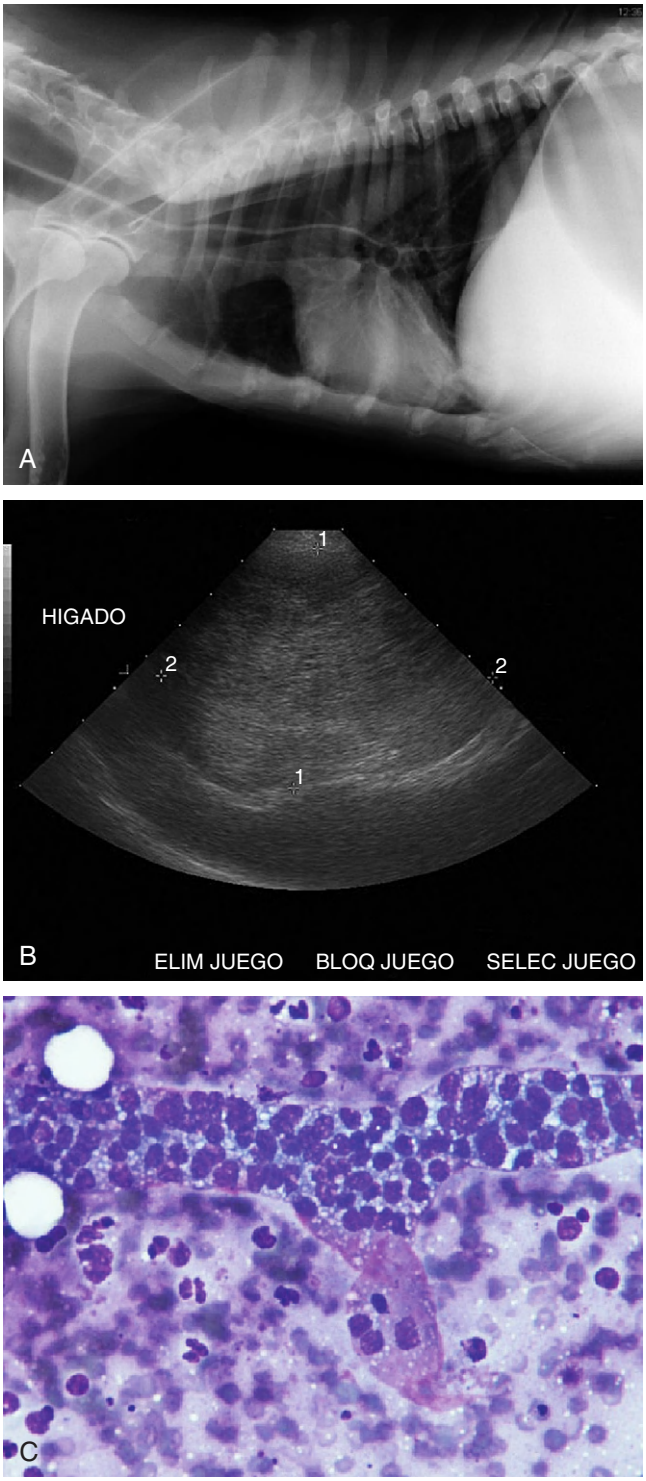

Figure 61-24 **A,** Thoracic radiography of a 10-year-old mixed-breed dog with a large abdominal mass showing megaesophagus. **B,** Abdominal ultrasound of the same dog. Hyperechoic mass with hypoechoic areas in the liver. **C,** Fine-needle cytology of the liver mass, a dense aggregate of large epithelial cells with vacuolated cytoplasm without obvious cytologic criteria of malignancy. A diagnosis of cholangioma or well-differentiated cholangiocarcinoma was made. Histopathologic study of the mass confirmed a cholangioma in this dog.

Box 61-3 Basic Ultrasound Patterns in Liver Neoplasia

Diffuse or multifocal

- Diffuse or multifocal liver neoplasms tend to present with hepatomegaly, but this depends on the degree of infiltration. Liver carcinomas can be diffuse or affect multiple lobes, with variable ultrasound characteristics depending on the presence of necrosis, inflammation, hemorrhage, or cavitation. In these malignant tumors it is common to observe a mixed echogenicity pattern. Lymphoma can affect the liver without detectable ultrasound changes, or cause diffuse hypoechogenicity, hyperechogenicity, or mixed echogenicity with or without hypoechoic nodules. Consequently, if lymphoma is suspected, even if the liver ultrasound findings appear normal, fine-needle aspiration cytology is recommended. Histiocytic neoplasms are more often associated with multiple nodules and hypoechoic masses, although diffuse liver hypoechogenicity has also been described. Mast cell infiltration of the liver tends to produce diffuse hyperechogenicity.
- Nodular patterns
  - Benign nodular hyperplasia is common, particularly in dogs, and accounts for many of the focal liver lesions identified at ultrasound exploration. It has been estimated that 25% to 36% of all nodular masses detected in the liver are nodular hyperplasia.
  - Benign liver adenomas or hepatomas can manifest as a focal mass of variable size and of normally hyperechoic characteristics.
  - The liver is a frequent location of metastatic spread, fundamentally through the portal system that drains most of the abdominal structures.
  - Primary liver neoplasms such as hepatocellular carcinoma can present as focal or multifocal masses, although less often so than in the case of metastases. Focal hypoechoic lesions with a hyperechoic center or core (referred to as target or bull's-eye lesions) are usually associated with metastases, although some benign processes, such as nodular hyperplasia, can generate similar patterns.
- Biliary obstruction: Ultrasound has become an important tool for evaluating biliary obstruction in icteric dogs and cats. Primary tumors of the liver, biliary tract, duodenum, or pancreas are capable of causing biliary obstruction.

lymphoma and other liver pathologies, and only very dramatic elevations in α-fetoprotein may be taken to indicate hepatocellular carcinoma.[37-39]

Abdominal radiographs often reveal a mass effect in the cranial abdomen, although this finding will depend upon the size of the neoplasm and the number and size of metastatic tumors. Other reported findings include dorsal displacement of the stomach, hepatomegaly, loss of abdominal detail (because of the presence of free abdominal fluid), and, occasionally, biliary tract calcification. Thoracic radiography should be considered as part of the staging procedure for animals with metastatic disease.[25,40]

Changes in the ultrasound density of the liver may take a variety of forms (Box 61-3). Most changes are not pathognomonic for a given disease process, and the final diagnosis is established only on the basis of clinical findings, laboratory testing, and results of cytology or histopathology (see Figures 61-24 and 61-25). Ultrasound is also very useful for evaluating other abdominal structures, and for the staging of cancer.[40-42]

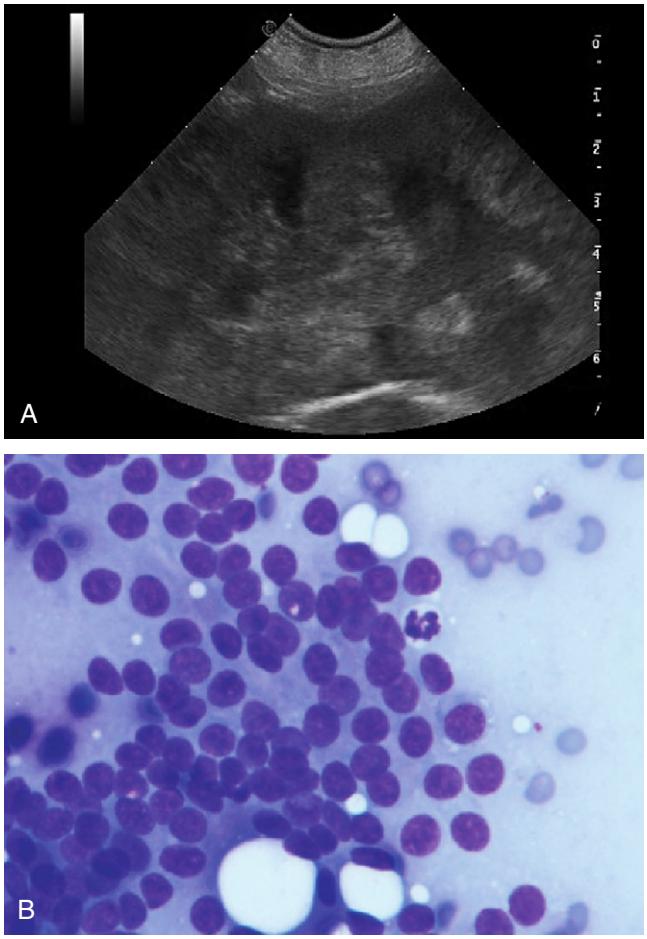

Figure 61-25 **A,** Ultrasonography of a large abdominal mass in a 12-year-old spayed Golden Retriever dog. **B,** Fine-needle aspiration showing round to oval cells that have features consistent with hepatic carcinoid, a neuroendocrine tumor.

High-field MRI scanning has an accuracy of 94% in differentiating malignant from benign lesions with a sensitivity and specificity of 100% and 90%, respectively. MRI classified malignant hepatic lesions as HCC in all confirmed cases and correctly predicted the histologic grade of five HCC lesions. These results suggested that MRI is a useful modality for abdominal imaging in veterinary patients, and that MRI accurately differentiates benign from malignant focal hepatic lesions.[43]

Liver cytology is useful in the initial evaluation of hepatomegaly and usually permits differentiation between primary tumors, metastatic disease, and focal infection (see Figures 61-24 and 61-25). However, cytology does not distinguish between benign focal inflammatory disease and progressive chronic liver disease, and it cannot establish the extent and distribution of disease. Likewise, a definitive diagnosis of regenerative nodular hyperplasia cannot be established, and the technique is unable to differentiate a benign inflammatory reaction from cell changes associated with other pathologies. Contraindications to ultrasound-guided cytology include the following:

- Coagulation abnormalities—If one or more coagulation test parameters are altered, it is advisable to administer vitamin K_1 via the subcutaneous route 12 hours before cytology.
- Cavitary masses—The ultrasound detection of a large cavitary lesion in an elderly dog usually contraindicates cytology, particularly in male German Shepherds or Golden Retrievers, because of the high probability that such lesions correspond to hemangiosarcoma.

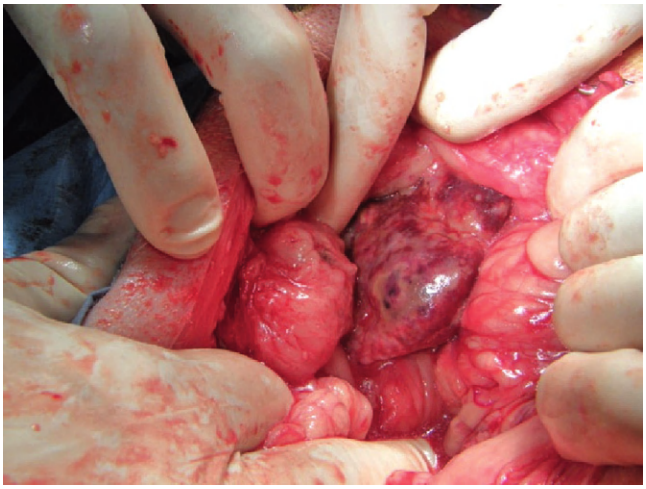

Figure 61-26 Macroscopic appearance of diffuse hepatocellular carcinoma during exploratory laparotomy in a dog. (Courtesy of Félix Gracia.)

Liver cytology has obvious limitations in that it cannot distinguish between liver adenomas and regenerative nodules, and even some hepatocellular carcinoma aspirates may be composed entirely of normal-appearing hepatocytes. In many cases it may prove necessary to resort to ultrasound-guided biopsy, laparoscopy, or exploratory laparotomy. However, cytology may prove useful in determining the presence of lymphoma, mastocytoma, and histiocytic sarcoma, as well as contribute to the initial classification of tumor type. Concordance rates between cytology and histopathology findings may be good for some disease processes, but the reported concordance rate varies from 14% to 86%.[44,45]

Treatment and Prognosis

The treatment to be provided and the prognosis of animals with primary liver cancer depend on the cell of origin, degree of malignancy, and clinical presentation. The clinician should quickly determine if surgery, chemotherapy, radiation therapy, or palliative care is the treatment of choice in individual patients. Palliative treatment is the option for animals that are not surgical candidates, for example, tumors with poor response to systemic chemotherapy, and for whom pain management and general liver failure treatment are the best recommendations.

The success of newer options such as chemoembolization, metronomic therapy, antiangiogenic drugs, and tyrosine kinase inhibitors in the treatment of these patients has not been clearly established.[41-53]

Hepatocellular Carcinomas

The macroscopic presentation is clinically very important (see Figure 61-26), as 100% of the diffuse forms have metastasis at the time of diagnosis, versus 37% of the isolated (massive or nodular) clinical presentations.[27] It should be noted, however, that some dogs with massive HCC present without metastasis, and deaths in these cases may be unrelated to HCC.[1,26,54] Histopathologic subtype and anaplastic characteristics in general influence the prognosis and predictability of metastasis.[1,26,55] Metastatic spread usually affects the regional lymph nodes, lungs, and peritoneum.[26,56]

Prognostic factors in dogs with massive HCC include need for surgery, liver lobe involvement, serum ALT and AST activities, and ratios of ALP to AST and ALT to AST.[26] Liver lobectomy is recommended for cats and dogs with hepatic tumors that have a massive morphologic appearance without metastases. However surgical complications are reported in more than 28% of cases, with a mortality rate of almost 12%.[26] The predilection of massive HCC for left-sided liver lobes has been reported.[27,54] Advanced imaging and intraoperative ultrasonography may provide useful information on the relationship of right-sided and central liver tumors to the caudal vena cava prior to liver lobectomy.[40,41,43] Even though right-sided liver tumors have a poorer prognosis because of intraoperative death, there is no difference in the survival time after successful surgery.[26] The considerable regenerative capacity of the liver can permit successful resection of up to 80% of hepatic mass if the remaining tissue is functionally normal and critical supportive care is provided.[56] The median survival time for dogs with massive HCC following liver lobectomy is greater than 4 years. Without surgery the average life expectancy is 270 days and the prognosis is generally considered poor.[26] Tumor recurrence in dogs with massive HCC is rare and reported to be 0% to 13% after lobectomy.[26,54]

The prognosis for dogs with nodular and diffuse HCC is poor. Surgical resection is usually not possible because of involvement of multiple liver lobes.

No effective systemic chemotherapy or radiation therapy protocols have been described for HCC treatment. HCC is considered chemoresistant in humans although mitoxantrone has been reported to be helpful in some cases.[7,56,57] The most likely reason for the poor response to systemic chemotherapy is the expression of P-glycoprotein in hepatocytes.[22] Treatment options for nodular and diffuse HCC in humans include liver transplantation and minimally invasive procedures for regional control, such as ablation, chemoembolization, immunotherapy, hormonal therapy, and low-dose metronomic chemotherapy.[56,58] A recent report recommends therapy with sorafenib, a multikinase inhibitor and antiangiogenic agent.[47,48]

Chemoembolization is a procedure commonly used in the treatment of diffuse hepatocellular carcinoma in humans with median survival times of 1 to 2 years compared with 3 to 6 months with systemic chemotherapy.[52,51] In veterinary medicine, chemoembolization has been reported with moderate success in the palliation of four dogs with HCC.[52,53] In cats, hepatocellular carcinoma is less frequent, and less data are available.[28,59]

Hepatocellular Adenomas

These tumors are also known as hepatomas and are more common in cats than in dogs. In the dog it is sometimes very difficult to distinguish adenoma from reactive nodular hyperplasia, and biopsy is needed to clarify the diagnosis. The prognosis for adenomas is usually good, but it is advisable to remove focal mass lesions because they can grow and spontaneously rupture with severe bleeding.[19]

Bile Duct Carcinoma (Adenocarcinoma and Cholangiocarcinoma)

Bile duct carcinoma is the most common liver malignancy in the cat, and the second most common liver malignancy in the dog (see Figure 61-27). Tumor behavior is very aggressive in both species, and metastases are present at the time of diagnosis in 60% to 88% of cases. Bile duct carcinomas usually metastasize to the regional lymph nodes, lungs and peritoneum, kidneys, heart, adrenal glands, eye, and bone.[1,60] Bile duct carcinoma can be intrahepatic or extrahepatic, but rarely occurs within the gallbladder. Intrahepatic bile duct tumors are more common in dogs, and extrahepatic bile duct tumors are more common in cats.[1,13, 27,61] Three morphologic forms or presentations have been described: lobular, multifocal, and diffuse. In general, only the lobular form should be considered for surgical removal as long as there is no evidence of metastasis. The prognosis for multifocal and diffuse bile duct carcinomas is very poor, surgery is usually not feasible, and most animals die within 6 months of surgery.[29] No effective chemotherapeutic options have been described for these malignancies in dogs or cats.

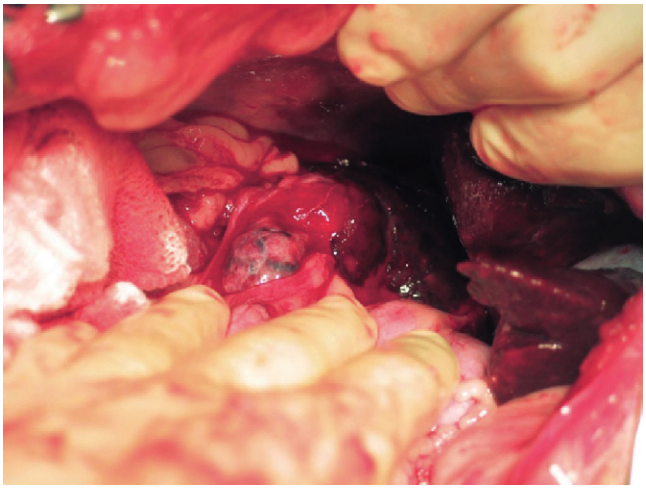

Figure 61-27 Macroscopic appearance of intrahepatic biliary carcinoma during exploratory laparotomy in a dog. (Courtesy of Félix Gracia.)

Bile Duct Adenomas

Also known as biliary cystadenomas, biliary adenomas, cholangiocellular adenomas, and cholangiomas, these tumors are common findings in aging cats. Males appear to be more frequently affected than females (Figure 61-28). In cats, 50% of these lesions are isolated or lobular and 50% are multifocal.[59] Biliary duct adenomas usually do not cause clinical signs unless they grow and compress other structures.[62] Despite the benign nature of these tumors, surgical removal is usually recommended because malignant transformation is always possible and because expansion into the porta hepatis may cause life-threatening consequences.[63] Liver lobectomy is recommended for cats with single bile duct adenoma or multifocal tumors confined to one or two lobes. In cats, surgical resection of biliary adenomas may provide cure or tumor-free survival of several years.[28,29,31,59,62,63]

Carcinoid Tumors

Neuroendocrine (carcinoid) tumors are infrequent in the dog and cat. In dogs, carcinoids have an aggressive biologic behavior and are usually not amenable to surgical resection as they tend to present as diffuse lesions (see Figure 61-25).[1,27] Carcinoid tumors in dogs have also been described in the gallbladder, and these have been managed successfully with cholecystectomy.[64,65]

Carcinoid tumors in cats can be intrahepatic or extrahepatic involving the bile duct and occasionally the gallbladder.[65] The extrahepatic form of carcinoid tumors may cause biliary tract obstruction, icterus, and increases in serum hepatic enzyme activities. Biliary tract diversion procedures should be considered for obstructive lesions involving the extrahepatic biliary tract. Unlike the circumstance in dogs and humans, female cats are more often affected by these tumors than males (female-to-male ratio of 5:1).[66]

The prognosis of carcinoid liver tumors in dogs and cats is generally poor, and metastatic disease is present in 90% of the cases at

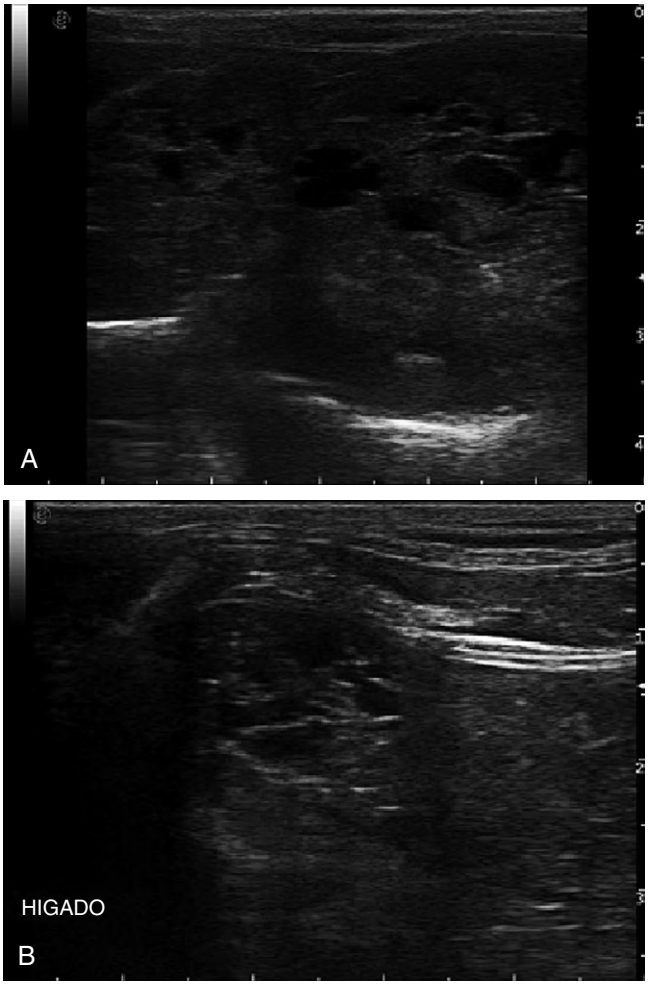

Figure 61-28 **A** and **B,** Liver mass in two cats with multiple anechoic cavities consistent with biliary cystadenomas.

the time of diagnosis.[7] A better prognosis is observed with extrahepatic carcinoids with a life expectancy of more than a year.[64,65]

Liver Sarcomas

Primary liver sarcomas are rare in the dog and cat. Hemangiosarcoma is the most frequent primary hepatic sarcoma in cats and leiomyosarcoma the most common in dogs.[7,19] There also have been reports of hepatic fibrosarcoma, rhabdomyosarcoma, osteosarcoma, liposarcoma, and histiocytic sarcomas in both animal species.[1,28,29,55] These are usually very aggressive tumors, metastasizing in 86% to 100% of cases to the spleen and lungs, or spreading diffusely within the liver.[5] Chemotherapy has not been studied in the treatment of primary hepatic sarcomas, although, similar to other solid sarcomas, response rates are likely to be poor. Histiocytic sarcomas respond partially to CCNU, with a mean duration of remission of 85 days and a survival of 172 days.[67] Continuous low-dose oral chemotherapy may be an effective alternative to conventional high-dose chemotherapy for adjuvant therapy of dogs with hemangiosarcoma.[50] Mass resection may offer some palliation in the circumstance of tumor hemorrhage despite irrefutable evidence of metastasis. A cat with a primary extraskeletal hepatic osteosarcoma was treated with surgery and carboplatin and was alive 42 months after diagnosis with no clinical evidence of disease.[68] On the other hand, metastases must always be considered as a possibility when a hepatic tumor is diagnosed.

Benign mesenchymal neoplasms, such as fibroma and hemangioma, have been described but are quite rare.[6,1,29,59]

Lymphoma

In dogs the liver can be involved in variable forms of lymphoma, including multicentric, alimentary, and hepatosplenic forms. A study in cats documented that abdominal lymphoma is currently the most common anatomic location and the liver occasionally is the only organ involved.[69,70] Many protocols are recommended for treatment of lymphoma in dogs and cats; most include vincristine, cyclophosphamide, and prednisone, with variable combinations of L-asparaginase, methotrexate, and doxorubicin. Careful evaluation of liver function is necessary before starting chemotherapy because many drugs undergo hepatic metabolism and altered hepatic clearance may lead to unpredictable and potentially increased toxicity.[5]

Other Neoplasms

Surgical resection with liver lobectomy is recommended for cats with primary hepatic myelolipoma and the prognosis is excellent with prolonged survival time and no reports of local recurrence.[7]

In dogs with advanced disease, mast cell tumors can metastasize to the liver. Primary visceral mast cell tumors are more common in cats than dogs. The spleen is usually the primary site with metastasis to the liver and bone marrow, and the survival time with splenectomy alone can be a year or more.[71] The overall prognosis for disseminated mast cell tumor in the dog is grave. The median survival time reported in one study was 43 days despite therapy with various chemotherapy agents.[72] Canine mastocytoma involving the liver can be controlled with cyclophosphamide, vinblastine, and prednisone.[73] Recently, tyrosine kinase inhibitors have shown some promise and CCNU has been shown to be active against feline mast cell tumors.[49,74]

Hepatic Nodular Hyperplasia

Hepatic nodular hyperplasia is a common benign lesion observed in the liver of older dogs that can occasionally be observed in some cats. It is characterized by a discrete accumulation of hyperplastic hepatocytes arising as either macroscopic or microscopic hepatic nodules. It reportedly occurs in 70% of dogs older than 6 years and 100% of dogs over 14 years.[75-77] The WSAVA standards for clinical and histologic diagnosis of canine and feline liver diseases include hepatic nodular hyperplasia in its classification system of hepatocellular neoplasia so that it may be differentiated from true neoplasia.[78]

Etiology

The etiology of hepatic nodular hyperplasia is unknown. It has been suggested to be a preneoplastic lesion,[76] but this has not yet been reported in the dog.[77] Because of hepatocyte microscopic changes, it is suggested that nutritional and metabolic disorders play a role in the pathogenesis of this lesion.[77]

Pathophysiology

Hepatic nodular hyperplasia is characterized microscopically by well-differentiated hyperplastic hepatocytes with increased mitotic activity.[75-77] Hyperplastic nodules may be accompanied by concurrent focal intrahepatic cholestasis, mechanical compression on

surrounding hepatic parenchyma, as well as alterations in the microvascular circulation. Vacuolar changes are seen frequently, suggesting a reactive or metabolic condition such us hyperadrenocorticism, lipidosis, or hypothyroidism.[77]

Clinical Examination

Nodular hyperplasia affects older dogs with a mean age of 11 years without gender or breed predisposition. Hepatic nodular hyperplasia does not appear to cause clinical signs or illness.[77]

Laboratory findings may include mild to marked increases in serum alkaline phosphatase activity and, less commonly, increases in serum ALT activity. Liver function tests are usually normal with hepatic nodular hyperplasia.[77]

Diagnosis

Hepatic nodular hyperplasia is usually discovered as an incidental finding during a diagnostic workup for other medical problems. Nodular hyperplasia is clinically important because it may easily be confused with primary or metastatic hepatic neoplasia during abdominal ultrasound or at surgery. Even microscopically, it may be impossible to differentiate hepatic nodular hyperplasia from hepatocellular adenomas, and a large sample (wedge rather than needle biopsy) may be required to confirm hyperplasia from well-differentiated HCCs.[75-77]

Routine abdominal radiographs are generally unremarkable and ultrasonographic features are inconsistent because of the varied hepatocellular morphologic characteristics and size of the nodules.[79] Multiple nodules varying in size, distributed randomly among the liver lobes, being superficial or deep within the parenchyma are found in most cases.[77]

Hyperplasic nodules of hepatocytes need to be differentiated from regenerative nodules. Hyperplasic nodules develop in livers of normal mass, whereas regenerative nodules arise as a result of compensatory hyperplasia of surviving hepatocytes in a background of hepatic injury, atrophy, and fibrosis.

Treatment

No treatment is usually required. Rupture of large nodules may require emergency mass removal and blood transfusion (rare).

Prognosis

Hepatic nodular hyperplasia has no significance in the morbidity of affected patients.[77]

METABOLIC DISORDERS

Deborah S. Greco

Metabolic disorders of the liver are commonly encountered in companion animal practice. This section focuses on the metabolic liver disease induced by concurrent endocrinopathies (hyperthyroidism, hypothyroidism, diabetes mellitus, and hyperadrenocorticism), lipid disturbances (lipoproteinemias, feline hepatic lipidosis, and hyperlipidemias), and metabolic infiltration (amyloidosis). Hepatic lipidosis and hyperthyroid hepatopathy are the primary metabolic hepatopathies in cats. In dogs, steroid (or glycogen vacuolar) hepatopathy is the most frequent metabolic liver disorder; diabetic hepatopathy and hyperlipidemic hepatopathies (lipoproteinemias, hypothyroidism) occur less commonly.

Box 61-4 Factors Predisposing the Domestic Cat, an Obligate Carnivore, to Fat Mobilization and Hepatic Lipidosis

- Essentiality of dietary arginine[6]
- Low levels of hepatic ornithine[7]
- High dietary protein requirements[7]
- Lack of hepatic enzyme adaptation to low protein[8]
- Insufficiency of hepatic glutamate reductase[7]
- Insufficiency of intestinal ornithine transcarbamylase[7]
- Diversion to orotic acid metabolism[9]
- Differences in lipoprotein metabolism (HDLs)[10,11]

Feline Hepatic Lipidosis

Etiology

Feline hepatic lipidosis (HL) is a metabolic syndrome found in obese, middle-aged cats that undergo a period of acute anorexia and catabolism. Morbidly obese cats are at increased risk and more than 85% of cats with HL suffer from an underlying disorder that contributes to the initial anorectic event. [1-5]

Pathophysiology

Although the underlying pathogenesis of hepatic lipid accumulation in cats has not yet been completely elucidated, several unique biochemical and nutritional features place this obligate carnivore at risk for fat mobilization and fatty infiltration of the liver during periods of anorexia or starvation (Box 61-4).[2,6-11] There is a general consensus that reduced caloric intake and protein-calorie malnutrition are important predisposing factors. The result is a rapid mobilization of peripheral fat culminating in fatty accumulation in the liver.[1] Intracellular processing of fats is an important function of the hepatocyte. During fasting or starvation, fatty acid metabolism becomes deranged in an obligate carnivore as a result of obesity, catabolism, chronic overnutrition, impaired fatty acid oxidation or VLDL secretion, and enhanced hepatic fatty acid synthesis (Figure 61-29).[1,6-11]

Clinical Examination

HL is a disorder of middle-aged to older cats; domestic short-haired cats are more commonly affected. Cats with HL often present with a history of acute stress and/or near-complete anorexia of several days duration.[1-3] Icterus is a variable feature of HL. When serum bilirubin concentrations exceed 1.5 mg/dL, clinical icterus can be observed on the pinnae, mucous membranes, sclera, and hard palate in the cat. In general, most cats with HL are obese at the time of presentation, with many cats being 20% to 30% over ideal body weight prior to an episode of HL. Other physical features of HL include hepatomegaly, dehydration, vomiting, and weakness. If HE develops as a consequence of HL, neurologic abnormalities such as ptyalism, stupor, coma, ataxia, and seizures may be observed.[1-3]

A minimum database, including complete blood cell count, serum chemistry, and urinalysis, almost always reveals severe liver enzyme elevation and other abnormalities such as nonregenerative anemia, stress leukogram, poikilocytosis, and bilirubin crystalluria.[1] The pattern of liver enzyme elevation is typically cholestatic in nature and characterized by marked increases in serum ALP activity, followed by smaller increases in serum ALT and serum AST activities. Serum GGT activity is often normal in affected cats. Increased serum bile acids and bilirubin are often observed in cats with HL, and electrolyte abnormalities, such as hypophosphatemia and

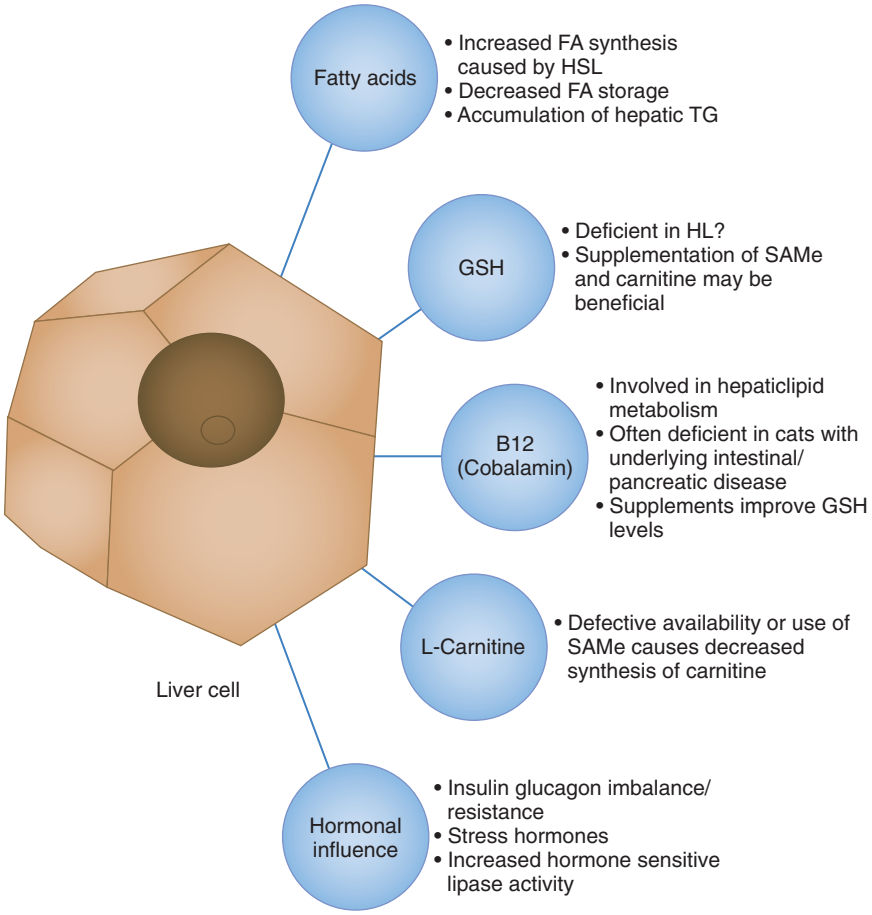

Figure 61-29 Fat metabolism in the feline hepatocyte during hepatic lipidosis.

hypokalemia, may be frequently observed. In particular, the presence of hypophosphatemia should alert the clinician to the possibility of refeeding syndrome.[12]

Diagnosis

Presumptive diagnosis of feline HL can be made on the basis of clinical history, physical examination, clinicopathologic features, ultrasound examination, and liver aspirates.[1,13-15] Ultrasound examination of the liver often reveals hepatic parenchyma that is hyperechoic to that of falciform fat, but a thorough ultrasound evaluation of the gallbladder, pancreas, intestines, kidneys, bladder, and other abdominal structures is essential to rule out other primary disorders, such as acute pancreatic necrosis, which may be the basis of the anorectic event precipitating an episode of HL. Definitive diagnosis is best achieved through liver biopsy[16]; however, anesthesia and biopsy may not be possible in acutely ill patients because of the presence of coagulopathies from vitamin K deficiency.[17] A liver aspirate that reveals more than 80% fatty infiltration of the hepatocytes may be used for presumptive diagnosis of HL. If there is no response to treatment after 3 to 5 days, liver biopsy may be necessary to rule out other underlying hepatobiliary conditions such as cholangitis.

Treatment

A catabolic state develops quickly in the anorexic cat and prompt measures should be taken to place an enteral feeding tube (Table 61-9). Nasoesophageal, esophageal, and gastrostomy tubes can be used for this purpose. The caloric needs should be approximately 60 to 90 kcal/kg body weight in most cats.[1,18] Unless HE is present, dietary protein should not be restricted (ideal is 35% to 45% protein on a dry matter basis) and even then protein restriction is controversial as protein is needed to support hepatic regeneration. Feeding multiple small frequent meals may help to maintain euglycemia and lessen the metabolic impact on the liver. The protein content of the diet should be considered when HE is present (see Chapter 32). Dairy and vegetable-based proteins are higher sources of branched-chain amino acids than meat-derived proteins and may lessen the signs of HE. Diets high in fiber generally should be avoided because they decrease the nutrient density of the diet.

Cats with HL occasionally may experience a refeeding syndrome, a condition that results in metabolic and electrolyte disturbances.[12] With the reintroduction of food, insulin secretion promotes intracellular uptake of phosphorus, potassium, and magnesium. Hypophosphatemia can result in muscle weakness and hemolytic anemia. Gradual reintroduction of food and correction of electrolytes diminishes the risk of refeeding syndrome.

Glucose intolerance and hyperglycemia are common in cats with HL and can be addressed by decreasing the carbohydrate content of the diet. Canned low-carbohydrate, high-protein formulations without added fiber are ideal for the treatment of feline HL as they provide amino acids, limited carbohydrates, and water, and are easily administered through a feeding tube. Small amounts of food should be administered via the feeding tube after residual gastric fluid contents have been removed. Trickle feeding can be performed by placing liquefied food into an empty fluid bag and allowing gravity to force flow into the feeding tube. Alternatively, a large-bore

Table 61-9 Nutritional and Therapeutic Support of Cats with Hepatic Lipidosis

Feeding Tubes	General Tips	Diet to Feed	Fluid Therapy and Supplements	Drugs and Supplements
Nasogastric Nasoesophageal	Trickle feed 60 kcal/kg/day	Liquid high-protein, low-carbohydrate diet	Crystalloid fluids Avoid dextrose and lactate KCl, KPO_4 B vitamins	Maropitant 1-2 mg/kg SC, PO, IV q24h Ondansetron 0.1 to 1.0 mg/kg q12-24 h Vitamin K_1 0.5 to 1 mg/kg SC q12h for 3 transfusions
Esophagostomy or gastrostomy	Multiple times daily 60 to 90 kcal/kg/day	Canned high-protein diet*		L-Carnitine 250 to 500 mg/day Taurine 250 to 500 mg/day SAMe 20 to 40 mg/kg/day Vitamin E 10 IU/kg/day PO

*Less than 10% carbohydrate, >40% protein on dry matter basis.

syringe attached to a syringe pump may be useful in delivering the food through the feeding tube.

Crystalloid fluids supplemented with fortified B vitamins, including thiamine, riboflavin, niacinamide, D-panthenol, pyridoxine, and cyanocobalamin, should be used.[1] Nutritional supplements to enhance antioxidant function, such as vitamin E and glutathione precursors (e.g., SAMe) may also be beneficial. Amino acid supplements that support hepatic regeneration and metabolism include carnitine and taurine.[1,18-20] Carnitine functions in the transport of fatty acids into hepatic mitochondria for energy production. Taurine is an essential nutrient for cats and is involved in CNS, cardiac, and biliary functions. Signs of taurine deficiency may be similar to those associated with HE.

Antiemetic therapy is necessary to control vomiting and facilitate feeding of an appropriate type and quantity of diet (see Chapters 23 and 35). Injectable antiemetics, such as maropitant (Cerenia, Pfizer Animal Health, Kalamazoo, MI), a selective NK-1 receptor antagonist, at a dosage of 1 mg/kg SC or IV on a daily basis, is preferred.[21] Oral maropitant at the same dosage or oral ondansetron, a 5-HT_3 receptor antagonist at a dosage of 0.1 to 1.0 mg/kg q12-24 h may be used in cats with larger-bore feeding tubes. Persistent vomiting should be investigated to identify feeding tube occlusion or other undiagnosed disease.

Prognosis

The prognosis depends upon duration of illness, and the time frame of resolution of hepatic enzyme elevation, hyperbilirubinemia, and other biochemical changes. Cats that survive an episode of HL have a greater than 50% reduction in liver enzyme and bilirubin concentrations within 10 days of therapy, whereas cats that die usually do so within 7 days of hospitalization.[1] Long-term prognosis for recovery is good with the majority of cats having resolution of HL as long as the underlying disease process (e.g., pancreatitis) is identified and treated.

Hyperthyroid Hepatopathy

Etiology

Hyperthyroidism in cats is caused by adenomatous hyperplasia of the thyroid gland resulting in increased circulating concentrations of thyroxine and triiodothyronine.[22,23] Hyperthyroxinemia increases hepatic metabolism without proportionate increases in hepatic blood flow with the overall consequence of reduced oxygen delivery to hepatocytes.[24]

Pathophysiology

Increases in serum AST and ALT activities have been reported in approximately 80% of hyperthyroid cats.[22,23] Liver enzyme elevation has been attributed to increased liver metabolic activity compared to blood flow. Long-term untreated hyperthyroidism in human beings can ultimately lead to cirrhosis.[24-26]

Clinical Examination

Middle-aged to older cats are typically affected, and there is no breed or sex predilection. Because hyperthyroidism is characterized by hypermetabolism, polyphagia, weight loss, PD, and PU are prominent features of the disease.[22,23] Hyperactivity, tachycardia, pupillary dilation, and behavioral changes are also characteristic of the disease and are associated with activation of the sympathetic nervous system. Long-standing hyperthyroidism leads to hypertrophic cardiomyopathy, high-output heart failure, and cachexia. Long nails, dermatologic conditions, panting, elevated body temperature, and poor grooming or overgrooming are additional clinical signs of feline hyperthyroidism.

Clinicopathologic features of hyperthyroidism include erythrocytosis and stress leukogram (neutrophilia, lymphocytosis) caused by increased circulating catecholamine concentrations. Increased catabolism of muscle tissue in hyperthyroid cats may result in increased BUN, but not serum creatinine. Most cats will have decreased urine specific gravity, particularly if they are exhibiting PU as a clinical sign. Increased metabolic rate results in liver hypermetabolism, therefore serum activities of liver enzymes (ALT, AST) are increased in more than 80% of hyperthyroid cats.[22,23]

Diagnosis

Diagnosis of feline hyperthyroidism is achieved by measurement of serum total thyroxine (TT_4) concentration. Serum thyroxine concentrations are elevated in more than 90% of hyperthyroid cats, making this a very sensitive test of thyroxine-induced hypermetabolism.[22,23] False-positive test results are rare to nonexistent, suggesting that hyperthyroxinemia is a specific test for feline hyperthyroidism.

In a clinically hyperthyroid cat, thyroid hormones still fluctuate on a daily (and hourly) basis with hormone concentration intermittently decreasing into the normal range.[27] To avoid this type of diagnostic error the clinician should repeat blood sampling 1 to 2 weeks after the first test. Nonthyroidal disease can have a significant effect on circulating thyroid hormone concentrations.[28-30] In the case of persisting nonthyroidal illness (e.g., renal disease), the

measurement of unbound thyroxine (T_4) or free T_4 may be preferable to repeated TT_4 measurements.

Free T_4 concentrations are a very sensitive test for the diagnosis of hyperthyroidism with 98% of hyperthyroid cats exhibiting elevated serum free T_4 concentrations. The specificity of free T_4 is not as good as its sensitivity; as many as 12% of euthyroid cats with concurrent illness will have high free T_4 concentrations for reasons that remain unclear.[29] As a result, free T_4 should not be used as a screening test, and free T_4 values should be interpreted in light of the TT_4 concentrations. The combination of a high free T_4 with a low TT_4 is indicative of nonthyroidal illness; however a high free T_4 with a high-normal TT_4 is suggestive of hyperthyroidisim.[31]

Treatment

Methimazole (Tapazole) is the antithyroid drug most often recommended (2.5 to 5 mg q12h). It is available as a transdermal gel or as an oral tablet. Methimazole is often used to prepare the patient for surgical thyroidectomy or radioiodine therapy. Antithyroid drugs have several side effects. Anorexia and vomiting are common side effects of methimazole, whereas rare side effects include self-induced excoriation of the face, thrombocytopenia, bleeding diathesis, agranulocytosis, development of serum antinuclear antibodies, and cholangitis. Bleeding, jaundice, and agranulocytosis necessitate immediate withdrawal of the drug. Hepatic injury related to antithyroid therapy such as methimazole is well documented in humans and reported in the cat.[22,32] Mild histologic changes are common, but cases of fulminant hepatic failure with central lobular necrosis have been described.[33]

Prognosis

Prognosis is excellent with definitive therapy of the hyperthyroidism (surgery or radioactive iodine). Hepatic reactions to methimazole will necessitate discontinuation of therapy.

Diabetic Hepatopathy (Hepatocutaneous Syndrome, Superficial Necrolytic Dermatitis)

Etiology

The etiology is unknown, but hypoaminoacidemia may play a role in the development of diabetic hepatopathy.[34,35] Fatty acid, niacin, and zinc deficiencies also may be involved in the pathogenesis. Increased serum glucagon, originally thought to be the cause of diabetic hepatopathy, is found in only one-third of the reported cases. A much stronger association between the skin lesions of superficial necrolytic dermatitis and glucagonoma, hyperglucagonemia, and poorly regulated diabetes mellitus have been observed in both humans and dogs.[34,35]

Pathophysiology

Hepatopathy is thought to occur secondary to the metabolic abnormalities associated with diabetes mellitus, glucagonoma, or nutritional deficiencies.[34-37] Hepatic features include vacuolar hepatocyte degeneration, hepatic parenchymal collapse, and hepatic nodularity.

Clinical Examination

The disorder is seen most frequently in middle-aged male dogs, and has been reported in one cat.[34-37] Acute presentations may include clinical signs such as vomiting, diarrhea, lethargy, weight loss, PD, PU, icterus, and lameness because of dermatopathy of the footpads. In some cases clinical signs are mild or nonexistent. Physical examination may reveal poor body condition, lethargy, and characteristic lesions of superficial necrolytic dermatitis (hard, cracked foot pads and elbows). Painful feet caused by footpad lesions are common.

Clinicopathologic features include mild nonregenerative anemia, microcytosis (with advanced liver dysfunction), increased serum liver enzyme (ALP and ALT) activities, hypoproteinemia, hypoalbuminemia, and fasting hyperglycemia. Serum bile acids are usually increased. Serum glucagon is inconsistently elevated, but plasma amino acid concentrations are often less than 50% of normal.[34,37]

Diagnosis

Abdominal ultrasonography may reveal small, normal or increased liver size; however, there usually is a characteristic "Swiss cheese" appearance of the hepatic parenchyma as a result of hepatic degeneration, nodularity, and collapse.[36,38] Pancreatic imaging and biopsy are indicated if a glucagonoma is suspected.

Treatment

Symptomatic palliative therapies may be beneficial and include high-protein diets with egg white (approximately 2 to 4 egg whites/day for a 25-kg dog), zinc (2 mg/kg q24h PO) niacinamide (250 to 500 mg/dog q24h PO), ursodeoxycholic acid (10 to 15 mg/kg/day PO), vitamin E (10 IU/kg daily PO), SAMe (20 mg/kg/day PO 2 hours before feeding), and fatty acid supplementation. Some patients will respond to 10% parenteral amino acid solutions (Aminosyn, Abbott Laboratories, Chicago) given at a dose of 500 mL over 8 to 12 hours intravenously through a large-bore central venous catheter. If no response is observed following the initial amino acid infusion, therapy should be repeated every 7 to 10 days for a total of four treatments.

Prognosis

Prognosis is poor for most cases; however, remissions of longer than 2 years have been reported with intensive amino acid and hepatic support therapy.[37]

Steroid Hepatopathy

Etiology

Steroid hepatopathy develops following exogenous corticosteroid therapy, or from endogenous hyperadrenocorticism of pituitary or adrenal origin. The dog liver is uniquely susceptible to both glucocorticoid- and sex steroid–induced liver enzyme elevation, glycogen accumulation, and vacuolar degeneration.[39,40]

Pathophysiology

In healthy dogs, glucocorticoid administration results in significant liver enzyme (ALP and ALT) elevation in 2 to 3 days. Increased ALP and GGT activities develop in parallel as the enzymes undergo induction and release from sinusoidal and canalicular membranes. Within 7 days of glucocorticoid administration, the glucocorticoid-induced ALP isoenzyme increases significantly. Glycogen accumulates within the hepatocyte resulting in a vacuolar degeneration typical of the syndrome.[1,39,40]

Clinical Examination

Steroid hepatopathy occurs primarily in the dog. There is only one reported case of steroid hepatopathy in the cat.[41] A history of corticosteroid administration or signs consistent with endogenous steroid overproduction (Cushing syndrome) are usually evident, for example, PD, PU, panting, potbellied appearance, bilaterally symmetric alopecia on the trunk, and polyphagia. In dogs affected with

atypical hyperadrenocorticism caused by sex steroid overproduction, dermatologic changes (alopecia, poor hair coat) and reproductive manifestations (perianal adenoma in a castrated male or female dog) are often the only signs suggestive of sex steroid imbalance. Atypical hyperadrenocorticism with sex steroid excess may present with no clinical signs except increased serum liver enzyme activities.[1]

Diagnosis

Diagnosis of steroid hepatopathy should be based on a history of exogenous steroid administration or endocrine function testing with or without liver biopsy. Classically, liver enzyme elevations consist of moderate to marked increases in ALP and GGT, and mild to moderate increases in ALT and AST. Bile acids may also be increased.[40]

The low-dose dexamethasone suppression (LDDS) test is considered the screening test of choice for endogenous canine hyperadrenocorticism.[42,43] The LDDS test has a high sensitivity at 92% to 95%. Only 5% to 8% of dogs with PDH will exhibit suppressed cortisol concentrations at 8 hours. In addition, 30% of dogs with PDH will exhibit suppression at 3 or 4 hours followed by "escape" of suppression at 8 hours. This pattern is considered diagnostic for PDH, making further testing unnecessary.[43] The major disadvantage of the LDDS test is the lack of specificity in dogs with nonadrenal illness.[44]

The corticotropin (ACTH) stimulation test is used to diagnose a variety of adrenopathic conditions, including endogenous or iatrogenic hyperadrenocorticism, as well as spontaneous hypoadrenocorticism.[42,45,46] As a screening test for the diagnosis of naturally occurring hyperadrenocorticism, the ACTH response test has a diagnostic sensitivity of approximately 80% to 85% and a higher specificity than the LDDS test.[45,46] In a study by Kaplan and Peterson, only 15% of dogs with nonadrenal disease exhibited exaggerated response to ACTH stimulation.[44] I prefer the ACTH response test over the LDDS test as the ACTH response test is more accurate for the diagnosis of iatrogenic hyperadrenocorticism (if the history is incomplete) and sex steroid imbalance in addition to PDH or adrenal-dependent hyperadrenocorticism.

The urine cortisol-to-creatinine ratio (UCCR) is highly sensitive in separating normal dogs from those with hyperadrenocorticism; however, the test is not highly specific for hyperadrenocorticism because dogs with moderate to severe nonadrenal illness also exhibit elevated ratios.[47-49] An elevated UCCR should always be confirmed with an LDDS test. In the UCCR test, urine is collected for 2 days for a baseline UCCR. The animal then is given three doses of dexamethasone (0.1 mg/kg, PO q6-8 h) and the final UCCR is collected 24 hours after the first dose of dexamethasone. Failure of the UCCR to suppress into the normal range is diagnostic for hyperadrenocorticism.

Treatment

Treatment for exogenous hyperadrenocorticism consists of discontinuation of exogenous steroids by slowly weaning the patient to prevent the development of addisonian crisis. Treatment for endogenous hyperadrenocorticism can be achieved with chemotherapy (o,p′-DDD, or trilostane) or surgery (hypophysectomy or adrenalectomy). Treatment of sex steroid imbalance can be achieved with mitotane or trilostane.

Prognosis

Prognosis for steroid hepatopathy is good to excellent if diagnosed early and if corticosteroid injury can be abated by discontinuation of steroid therapy or treatment of the underlying disorder.

Miscellaneous Metabolic Hepatopathies

Lipoproteinemias

Etiology

Genetic abnormalities in lipid metabolism lead to diffuse vacuolar hepatopathy and biliary mucoceles.[1]

Pathophysiology

Increased circulating cholesterol and triglyceride cause a vacuolar hepatopathy associated with excess lipid accumulation and/or hepatocyte glycogen synthesis and storage. Chronic hypercholesterolemia increases biliary cholesterol content and predisposes to cystic hyperplasia, dysmotility of gallbladder smooth muscle, and biliary mucocele.[1]

Clinical Examination

Familial hypercholesterolemia and other hyperlipidemias are found in certain breeds of dogs including the Miniature Schnauzer, Shetland Sheepdog, Briard, West Highland White Terrier, Scottish Terrier, Cairn Terrier, and Beagle. Mixed-breed dogs may also be affected. Clinical signs are usually associated with necrotizing cholecystitis and may include icterus and cranial abdominal pain. More often, dogs are asymptomatic and biliary mucoceles are identified serendipitously during ultrasound evaluation for some other medical problem (such as pancreatitis). Clinical pathology findings usually include hypercholesterolemia or hypertriglyceridemia, and elevated liver enzyme activities, particularly ALP. Necrotizing cholecystitis may be accompanied by leukocytosis, neutrophilia, and hyperbilirubinemia.

Diagnosis

Diagnosis may be made by characteristic ultrasound findings of nongravitational gallbladder sludge, increased gallbladder wall thickening, "kiwi"-shaped mucosal image, and bi- or trilaminar appearance of the gallbladder wall. The hepatic parenchyma may have a pattern of multifocal hyperechogenicity and hypoechoic nodules.[1]

Treatment

The best treatment for biliary mucoceles is surgical removal of the mucocele and/or cholecystectomy and may become an emergency procedure if the clinical signs of necrotizing cholecystitis are severe. Medical therapy following surgical removal is usually necessary and includes a fat-restricted diet and lifelong treatment with ursodeoxycholic acid (15 mg/kg PO q24h).

Prognosis

Prognosis is good for patients undergoing successful removal of the mucocele as long as lifelong medical therapy is continued.

Amyloidosis

Etiology

In dogs and cats, amyloid deposition is usually secondary to sustained systemic inflammatory response, for example, chronic infection, chronic inflammation, immune disorders, and malignancy.[50] Amyloidosis is a familial disorder in the Chinese Shar-Pei dog, and in Abyssinian, Oriental, and Siamese cats.[51-54] Hepatic amyloidosis has also been reported secondary to vitamin A toxicity in cats.[55]

Pathophysiology

Deposition of amyloid fibrils within and between hepatic sinusoids results in progressive organ dysfunction. Light deposits are found in the space of Disse and heavier deposits are often found in the

sinusoidal lumen. Amyloid fibrils are readily detected on routine hematoxylin and eosin or Diff-Quik staining. Amyloidosis is confirmed on examination of Congo red–stained aspirates or biopsies under polarized light where the extracellular material shows characteristic green birefringence.[50] Concurrent amyloid deposition in the kidneys, liver, spleen, and adrenal glands can occur, but clinical manifestations of liver failure are most common.

Clinical Examination

Chronic progressive liver failure with clinical signs of anorexia, weight loss, and lethargy, is the typical clinical course in many cases. Some animals may instead present with acute collapse following hepatic rupture and intraabdominal hemorrhage.[50] Pallor of mucous membranes, hypothermia, and hepatomegaly are the most frequently recognized physical examination findings. Typical laboratory findings include regenerative anemia, leukocytosis, thrombocytopenia, marked elevations in serum ALT and AST, and marked prolongations in aPTT and PT times.

Diagnosis

Radiography is useful in detecting free peritoneal fluid, hepatomegaly, and irregular hepatic borders. Ultrasonography reveals a diffuse, heterogeneous echogenicity with highly echogenic ("sparkling") areas and hypoechoic foci.[50] Definitive diagnosis requires tissue biopsy and Congo red staining.

Treatment

There are no specific treatments for this disorder. Colchicine has been recommended because it may block formation of amyloid in the early stages of the disease, but it is of unproven benefit and has been associated with significant side effects. Dimethyl sulfoxide has been recommended because it may promote resorption of amyloid. As there are no specific therapies for this disease, treatment is instead largely symptomatic and supportive.

Prognosis

With progressive amyloidosis lesions, the prognosis for long-term survival is poor.

Lipoprotein Lipase Deficiency

A familial hyperlipoproteinemia has been reported in cats that is characterized by fasting hyperchylomicronemia, elevated circulating concentrations of VLDLs, and hypertriglyceridemia.[56,57] Serum cholesterol is only minimally elevated. The underlying biochemical lesion is a reduction in the activity of lipoprotein lipase, and the disorder is transmitted as an autosomal recessive gene. Xanthomas accumulate in the soft tissues, including the liver, but clinical signs are more often related to involvement of the peripheral nerves. Dietary fat restriction improves clinical signs in some affected animals.[58]

Hypothyroid Hepatopathy

Etiology

Decreased circulating thyroid hormone concentration affect hepatic metabolism and cholesterol turnover in the liver. Liver function tests are mildly disturbed in almost 50% of patients with hypothyroidism despite normal histologic findings.[59]

Pathophysiology

Decreased hepatic metabolism in hypothyroidism is reflected by reduced oxygen consumption.[33,59,60] Patients with a common bile duct stone and gallbladder stone have, respectively, sevenfold and threefold increases in the frequency of hypothyroidism.[61] The pathogenesis of stone formation in hypothyroidism is believed to involve hypercholesterolemia, gallbladder dysmotility, and bilirubin retention.[61]

Clinical Examination

The most common clinical symptoms of hypothyroidism are lethargy, weight gain, depression, hypothermia, and bradycardia. GI signs such as reflux esophagitis, gastric atony, constipation, diarrhea, and hepatopathy with mucocele formation are rare clinical signs of hypothyroidism in dogs.[62] Symmetric truncal or tail-head alopecia are a classic findings in hypothyroid animals.[62] Hyperkeratosis, hyperpigmentation, secondary pyodermas, and demodicosis are also observed.

Clinicopathologic findings such as normocytic normochromic anemia, hypertriglyceridemia, and hypercholesterolemia are seen in the majority of hypothyroid animals because of altered lipid metabolism and binding proteins (increased HDLs), decreased fecal excretion of cholesterol, and decreased conversion of lipids to bile acids.[63]

Diagnosis

Total serum T_4 concentration and endogenous thyroid-stimulating hormone (TSH) may be used to confirm the diagnosis of hypothyroidism. This combination of tests has been shown to have the highest specificity, sensitivity, and lowest overall cost. If the TT_4 is in the low normal or below normal range and the TSH is high, the animal is suffering from primary hypothyroidism.[64,65] If the TT_4 and TSH are both low, free T_4 by dialysis should be determined to distinguish euthyroid sick syndrome (normal free T_4) from true secondary hypothyroidism (low canine thyroid stimulating hormone [cTSH] resulting from pituitary TSH deficiency).[66]

Treatment

Synthetic thyroid hormone supplementation is the treatment of choice for hypothyroidism. Levothyroxine sodium therapy is started at a dosage of 0.02 mg/kg given orally twice daily.[66] Thyroid function should be monitored every 6 to 8 weeks for the first 6 to 8 months of treatment and then once or twice yearly thereafter. In stable well-controlled animals, the total treatment may be given once daily with excellent clinical results, as long as adequate peak hormone concentrations are achieved.[67]

Prognosis

With thyroid hormone replacement therapy in hypothyroid dogs, the prognosis is excellent.

INTRAHEPATIC BILIARY DISORDERS

Mark P. Rondeau

Cholangitis

Inflammatory disease involving the intrahepatic bile ducts is commonly encountered in veterinary practice. Cholangitis is recognized more commonly in cats than in dogs, but both species can be affected. The WSAVA Liver Standardization Group suggests that cholangitis be considered in the following four groups: neutrophilic cholangitis (NC), lymphocytic cholangitis (LC), chronic cholangitis associated with liver fluke infestation, and destructive cholangitis.[1]

Feline Cholangitis Complex

Cholangitis is a common hepatobiliary disorder of cats, second only to HL.[2] Although varying terminology has created some confusion regarding this syndrome, it is clear that feline cholangitis includes a spectrum of disease processes, including forms displaying neutrophilic inflammation and those lacking neutrophilic inflammation.

Neutrophilic Cholangitis

Histologically, NC is characterized by the presence of neutrophils in the lumen and/or epithelium of the bile ducts.[1] The disease is recognized to occur in acute and chronic forms. In acute neutrophilic cholangitis (ANC) edema and neutrophilic inflammation are seen in the portal areas, with occasional extension of inflammation to the hepatic parenchyma. In chronic neutrophilic cholangitis (CNC) there is a mixed inflammatory infiltrate consisting of neutrophils, lymphocytes, and plasma cells. Varying degrees of bile duct hyperplasia and fibrosis will be present depending on the chronicity of disease.

Etiology. Although the true etiology remains unknown, NC is largely suspected to be caused by ascending bacterial infection from the intestine.[1-3] Rates of bacterial isolation using traditional methods have varied greatly, from less than 20% to more than 60% in affected cats.[3,4] Recently, fluorescence in-situ hybridization (FISH) with a 16S rDNA probe that recognizes bacteria in general has been used to identify and localize bacteria in cats with cholangitis.[5] Combining traditional culture and FISH, bacteria were isolated in three of three (100%) cats with ANC and eight of 13 (61%) with CNC. The localization of the bacteria identified using FISH supports translocation of enteric bacteria as the cause of infection. Although it appears that bacteria play an important role in the etiology of NC in many cases, it is important to note that they are not identified in all affected cats. Some authors theorize that NC, and CNC in particular, may have an immune-mediated etiology with persistent inflammation following an initial bacterial infection or other unknown initiating factor.[3,6]

Pathophysiology. NC in cats is commonly associated with inflammatory bowel disease and pancreatitis.[3,4,7] The pathophysiology underlying the relationship of these diseases is unknown, but rational theories revolve around the unique anatomy of the feline biliary and pancreatic duct systems. In the cat, the common bile duct and pancreatic duct merge prior to entering the duodenum at the major duodenal papilla.[7] Cholangitis may develop secondary to reflux of ascending bacteria from the duodenum during vomiting. Pancreatitis may result from bacterial reflux into the pancreatic duct, or from pancreatic duct obstruction secondary to cholangitis.[7] In most reported cases, the inflammatory bowel disease associated with cholangitis is moderate or severe, whereas the pancreatitis tends to be mild chronic interstitial disease.[7]

NC is also commonly associated with extrahepatic bile duct obstruction (EHBDO). EHBDO has been identified in 40% of cats with ANC and 76% of cats with CNC.[4] Cholangitis and/or pancreatitis are the most common cause of EHBDO in the cat.[8] In one study, 64% of cats with EHBDO had cholangitis, representing 93% of cats that did not have a neoplastic cause.[8] It is unknown whether cholangitis is the cause or the result of EHBDO. Histologic changes consistent with CNC have been seen in the livers of cats with EHBDO secondary to pancreatic carcinoma, cholelithiasis and surgical occlusion of the common bile duct.[8] In contrast, cholangitis has been implicated as the sole cause of EHBDO resulting from proliferation of mucosa within the common bile duct.[8] Bacterial infection of bile has been commonly identified in cats with EHBDO,[4,8] but whether that infection is a cause or effect of EHBDO remains unknown.

Clinical Examination. Previous literature has highlighted differences in clinical presentation between cats with different forms of cholangitis. However, we have recognized few differences between the various forms[4,9] and suggest that any statistically significant differences cited previously hold little clinical relevance given the large degree of overlap within data ranges. NC can occur in cats of any age, breed, or sex. Clinical signs are nonspecific and include anorexia, lethargy, vomiting, and weight loss. The duration of these clinical signs ranges from a few days to a few months and may be shorter in cats with ANC than in those with CNC,[3] but this is not a consistent finding.[4,9] Physical examination findings commonly include dehydration and icterus. Fever is present in 19% to 37.5% of cases.[4,10] Some reports suggest that fever is more commonly associated with ANC than CNC,[10] while others recognize no difference.[4,9] Hepatomegaly is seen in fewer than half of the cases. Abdominal pain is noted occasionally.[3,4,9]

Diagnosis. Definitive diagnosis is made by examination of liver biopsy specimens, with ancillary diagnostics providing supportive information. Hematologic findings are variable and may include poikilocytosis, neutrophilia, and left shift, although these abnormalities are present in fewer than one-third of cases.[3,4,9,10] Biochemical analysis commonly reveals increased activity of ALT, AST, ALP, and GGT ranging in severity from mild to severe. However, increased liver enzyme activity may be absent in some cases. Serum total bilirubin is increased in most cases. Serum cholesterol may become increased in cases with EHBDO. Imaging findings are nonspecific for cholangitis, but may provide useful information regarding concurrent disease. Abdominal radiographs are rarely helpful. Ultrasonographic appearance of the liver in cats with NC can vary greatly, with the most common abnormality being a diffuse change in echogenicity ranging from hypo- to hyperechoic.[11] Dilation of intra- and/or extrahepatic bile ducts, gallbladder distention, increased gallbladder sediment, and thickening of the gallbladder or bile duct walls may be seen. Gallbladder distention and bile duct dilation may indicate EHBDO, but these changes may occur in cats with cholangitis lacking obstruction. Ultrasonography will also provide information regarding the presence of concurrent disease, such as pancreatitis and inflammatory bowel disease.

Wedge liver biopsy during laparotomy is the optimal method for obtaining a definitive diagnosis. Other biopsy techniques that may be considered include laparoscopic and ultrasound-guided Tru-Cut needle approaches. Tru-Cut needle biopsy diagnoses correlate with wedge biopsies in fewer than 50% of cases.[12] Diagnostic accuracy of laparoscopic liver biopsies compared with wedge biopsies have not been evaluated. Laparotomy and laparoscopy provide the additional benefit of evaluation and sampling of extrahepatic structures. Laparotomy should be performed in any cat suspected of having EHBDO. While the optimal sampling strategy is unknown, biopsies should be obtained from multiple liver lobes, as we have recognized wide ranges of severity between different lobes in the same cat. In patients that are not stable enough for liver biopsy, such as those with hypotension, coagulopathy or HE, fine-needle aspiration with cytology offers a less-invasive diagnostic approach as it can usually be performed quickly with light sedation. However, liver cytology correlates with biopsy results in only 39% to 60% of cases.[13,14] Cytology is sensitive for identifying the presence of HL, however this is the most common misdiagnosis when using cytology.[14] Cytology is

insensitive for identifying cholangitis in cats, diagnosing fewer than 30% of cases.[14] Cytologic examination of bile may prove more sensitive for the diagnosis of NC in cats. In five of seven cats with CNC evaluated at this institution, bile cytology revealed neutrophilic inflammation, presence of bacteria, or both. Techniques have been described for safely obtaining bile via ultrasound-guided percutaneous cholecystocentesis in lightly sedated cats.[15]

Samples for aerobic and anaerobic bacterial cultures should be obtained in any cat suspected of having cholangitis. Gallbladder bile is preferred to liver tissue as the culture source. In a group of 58 cats suspected of having hepatobiliary disease, bile cultures isolated pathogens in 36% compared with only 14% of liver cultures.[16] In the same study, 22 dogs and cats had both liver and bile cultured and none had a positive liver culture in the absence of a positive bile culture.[16] In a group of cats with cholangitis, bile cultures were more likely to isolate pathogens (75% vs. 33%) and less likely to yield contaminants (4% vs. 29%) than liver cultures.[4] In a small study comparing bile versus liver cultures in 22 cats with various hepatobiliary diseases, bile culture was positive in five (four had CNC) while liver culture was positive in only two. In the two cats with positive liver cultures, the same organism was isolated from bile.[17]

It is important to recognize that many cats with NC (and other hepatobiliary diseases that mimic it clinically) are not stable enough to tolerate diagnostic testing. In such patients, the risk of aggressive diagnostics may outweigh the benefits of obtaining a definitive diagnosis. In these cases, the diagnosis may be suspected based on clinical response to supportive care, including broad-spectrum antibiotic therapy.

Treatment. Optimal treatment protocols for cats with NC are unknown and the recommendations herein are based solely on anecdotal clinical experience. Antibiotics are the mainstay of treatment. Drug selection is ideally based on results of bacterial culture and susceptibility testing. In cases where cultures are not performed, or while results are pending, broad-spectrum coverage should be provided. The most commonly isolated pathogens are aerobic and anaerobic bacteria of enteric origin,[16] including *E. coli*, *Enterococcus* spp., and *Clostridium* spp., among others.[3,4,16] Effective empiric antibiotic combinations would include a penicillin, a fluoroquinolone, and metronidazole. The optimal duration of antibiotic therapy is unknown, but we recommend a 4- to 6-week course for initial treatment.

Supportive care and treatment of specific sequelae of liver disease should be included as indicated. Nutritional support is required in many cats and is best accomplished by use of enteral feeding tubes. We recommend placement of esophageal feeding tubes in cats with cholangitis if they are anorexic and stable enough for general anesthesia. In unstable patients, nasoesophageal feeding tubes offer a less-invasive method of providing short-term support.

Several medications and nutritional supplements (including ursodeoxycholic acid [UDCA], SAMe, milk thistle, vitamin E, vitamin C, carnitine, taurine, and phosphatidylcholine) have been suggested for treating cats with cholangitis. While most of these compounds have theoretical benefits, a clinical benefit has not been proven. To optimize client compliance and avoid adverse drug reactions, I prefer to minimize the number of medications given to feline patients. Because most cats with ANC respond well to antibiotic therapy, I rarely include other medications in our treatment protocol. However, in cats with ANC that do not quickly respond to antibiotics and in many cats with CNC, I like to use UDCA. Among its theoretical benefits, UDCA has immunomodulatory and choleretic properties that make it a rational choice for treating cholangitis.

Because of the possibility of immune-mediated mechanisms in the perpetuation of NC, particularly with CNC, corticosteroids may be appropriate in some cases. Initial treatment should always involve antibiotics in cats with NC. Failure to improve within 2 weeks of antibiotic therapy, or clinical deterioration prior to that time, warrants initiation of corticosteroid therapy. Prednisolone at 1 to 2 mg/kg twice daily is given initially and gradually tapered to the lowest effective dose. Antibiotics should be continued concurrently with corticosteroids for a minimum of 4 weeks. The duration of corticosteroid therapy varies between individual patients. Many cases can be gradually tapered off of corticosteroids over 4 to 6 months, while others require lifelong therapy.

Surgical intervention is required in cats with EHBDO; however, the optimal surgical procedure is unknown. Biliary diversion (cholecystocholedochostomy, choledochoduodenostomy, or cholecystojejunostomy) and choledochal stenting are the most common procedures. Surgery in cats with EHBDO is associated with significant perioperative morbidity. In many cases, profound hypotension develops intraoperatively after 45 to 60 minutes as a result of decreased vascular responsiveness and decreased myocardial contractility and is often refractory to interventions such as fluid or vasopressor therapy.[8,18,19] Whichever surgical procedure is chosen, it is clear that anesthesia time should be minimized and long-term medical management will be necessary. Biliary diversion is associated with short-term mortality rates of 36% to 57%[8,18] and is associated with long-term complications.[8,19] In a small case series describing choledochal stenting in cats with pancreatitis and cholangitis, five of seven experienced long-term survival (≥7 months), but reobstruction occurred in two of seven and chronic vomiting and recurrent cholangitis were reported.[19]

Prognosis. The prognosis for cats with NC is typically good.[3,4,10] Survival to discharge was reported in 72% of all cats with cholangitis in one study.[4] Median survival time of 29.3 months has been reported in cats with NC, with no difference between ANC and CNC.[10] Prognostic factors have not been identified. Given the high rate of perioperative morbidity and mortality, it seems likely that cats with EHBDO have a worse prognosis than those without EHBDO. Thirty percent to 40% of cats with EHBDO secondary to inflammatory disease die within a week of surgery.[8,18] However, in those that survive to discharge, long-term survival has been reported.[18]

Lymphocytic Cholangitis

The WSAVA Liver Standardization Group describes LC as a common, slowly progressive, chronic disease of cats characterized histologically by infiltration of small lymphocytes (and occasionally plasma cells or eosinophils) restricted to the portal areas associated with varying degrees of fibrosis and bile duct hyperplasia.[1] They remark that inflammation centered on the bile ducts may be present, but is not a hallmark of the disease. It is also stated that well-differentiated lymphoma may be difficult to differentiate from LC. Based on the existing literature regarding LC in cats, the description from the WSAVA group includes several clinically and histopathologically different subsets that may or may not revolve around a common pathogenesis. Recognition of these different subsets within the umbrella of LC may have therapeutic and prognostic ramifications.

Several investigators describe a group of cats with LC where inflammation is confined to portal regions and there is a lack of targeting of bile ductules or biliary epithelium.[2,20,21] This has been

referred to as *lymphocytic portal hepatitis*.[2,21] The connection between this histopathologic finding and clinical disease in cats is unknown, as it may represent a common change associated with aging. It was identified in 82% of cats older than 10 years of age and 96% of cats older than 15 years of age from a necropsy population that did not have primary liver disease.[21] It is also possible that this lesion represents a response to inflammation at a distant site, as it is similar to the lesion of nonspecific reactive hepatitis associated with chronic extrahepatic disease.[1] Although clinical signs have been described in cats with lymphocytic portal hepatitis,[10] the common occurrence of concurrent disease in these cats makes it difficult to know if the clinical signs are attributable to the lesions in the liver.

In another subset of cats, LC is marked by inflammation targeting bile ductules and infiltrating biliary epithelium, leading to progressive ductopenia.[20,22,23] These cases seem more likely to have clinical disease attributable to their liver pathology, although side-by-side comparisons of cases with and without bile duct targeting have not been performed. Cats with this form of LC in the United States have a similar clinical picture to cats with NC.[9] In the United Kingdom, this lesion has been associated with ascites, icterus, and hyperglobulinemia in young cats and termed *progressive lymphocytic cholangitis*.[22,23]

Etiology. Although the etiology of LC is unknown, theories suggest that it is an immune-mediated or infectious phenomenon. Genetic factors may also play a role, as Persian cats are overrepresented in the United Kindgom.[22,23] Immunohistochemistry in affected cats has provided evidence for an immune-mediated pathogenesis, although the inciting antigen is unknown.[20,23] Bacteria have been identified in the liver or bile of fewer than 20% of cats with LC.[3-5,17,20] Although *Helicobacter pylori* has been isolated from the liver and bile of cats with cholangitis, the evidence for this organism playing an important role in feline cholangitis is not compelling at this time.[24,25]

Pathophysiology. As with NC, concurrent inflammatory bowel disease and pancreatitis appear to be common in cats with LC,[3,4] although some authors report it to be uncommon.[23] The theory that reflux of duodenal bacteria into the biliary and pancreatic ducts incites inflammation may hold true for cats with LC, although a common immune mechanism must be considered.

Clinical Examination. The clinical picture of cats with LC varies widely and has significant overlap with other forms of hepatobiliary disease in cats, including NC.[4,9] Although some studies describe a predominance of older cats,[3] others describe more younger cats.[22,23] Nonspecific clinical signs, including anorexia, lethargy, vomiting, and weight loss, may be chronic and intermittent.[3,6,22] Physical examination findings may include icterus, hepatomegaly, or ascites, but none are consistent findings. Signs of HE (dullness, ptyalism, seizure) may develop in severely affected cats.

Diagnosis. Definitive diagnosis is made by liver biopsy. As discussed for NC, ancillary diagnostics will provide information to support hepatobiliary disease, but are not specific for LC. Hematology results may be unremarkable, even though marked lymphocytosis has been described in some cases.[3] Activity of serum liver enzymes is increased in many, but not all cases and varies in severity. Hyperglobulinemia has been described.[3,6,22] Abdominal radiographic and ultrasonographic findings are nonspecific, but may aid in the recognition of concurrent disease.

Distinction between LC and well-differentiated (small cell) lymphoma can be a challenge even for experienced pathologists. Preliminary data using immunohistochemistry and PCR for T-cell receptor clonality has not proven useful in differentiating between the two conditions. Surprisingly, cats with both LC and lymphoma had monoclonal T-cell receptors, oligoclonal T-cell receptors, and polyclonal T-cell receptors.[20] Using light microscopy, the following features were unique to LC and not present in cats with lymphoma: ductopenia, bile duct targeting by lymphocytes, and the presence of lipogranulomas within portal regions (representing a residual marker of cell death).[20] Until more studies are done evaluating molecular techniques, these features may prove useful in differentiating the two conditions. Interestingly, bile duct hyperplasia and fibrosis were present in cats with LC and those with lymphoma. This may suggest that an inflammatory state precedes the development of lymphoma,[20] which has been reported anecdotally.

Treatment. The therapeutic approach to cats with LC should be similar to that described for cats with NC in regards to supportive care and symptomatic treatment of the sequelae of liver disease. Because bacteria have been isolated from some cats with LC, I recommend treatment with broad-spectrum antibiotics while awaiting results of bacterial cultures. In contrast to NC, long-term treatment of culture negative cats with antibiotics is not warranted. Immunomodulation and immune suppression are the major components of treatment based on a presumed immune-mediated etiology. Cats that are culture negative, or that have failed to respond to antibiotics within a few days, should be treated with prednisolone at 1 to 2 mg/kg twice daily. Responders should be tapered gradually over 4 to 6 months to the lowest effective dose. Other drugs that are useful for immunomodulation include metronidazole and UDCA. Cats that fail to respond completely to corticosteroids and/or other immunomodulators, or who relapse while being treated, may require additional immunosuppressive drugs. Although these drugs have not been well evaluated in cats with LC, chlorambucil and methotrexate are suggested by some authors.[3] Cats with small cell lymphoma often respond to combination therapy with prednisolone and chlorambucil, but they may require a multidrug weekly sequential chemotherapy protocol.

Prognosis. Cats with LC have a variable prognosis,[3,6] likely a result of being diagnosed at different stages of a chronic disease process. Survival of greater than 5 years has been reported, and many cats that die appear to succumb to disease unrelated to the liver.[22] Other cases have been reported that fail to respond to treatment and die more acutely,[6] though this is uncommon in my experience. This is a disease that likely requires lifelong management and monitoring with relapse of illness possible as medication doses taper.

Chronic Cholangitis Associated with Liver Fluke Infestation

Trematode parasites of the families *Dicrocoeliidae* and *Opisthorchiidae* may inhabit the gallbladder and bile ducts of cats and rarely dogs.[26] There are multiple species with worldwide distribution. The most commonly identified species include the dicrocoelid *Platynosomum concinnum* and the opisthorchid *Amphimerus pseudofelineus*.[27-29] *P. concinnum* is mainly found in tropical and subtropical areas, including the southeastern United States.[26] *A. pseudofelineus* has a wider area of distribution throughout North and South America.[26] The life cycle is similar for both dicrocoelids and opisthorchids.[26] Parasite eggs are ingested by a land snail (*Subulina octona* or *Eulota* [*Bradybaena*] *similaris*), develop into cercariae and enter a second

intermediate host.[26,27,29] The dicrocoelids tend to use an arthropod, while opisthorchids utilize fish. Typically cats acquire infection by ingesting the second intermediate host. In the case of *P. concinnum*, the sporocysts leaving the snail intermediate host may be eaten by a paratenic terrestrial isopod host (pill, sow, or dung bugs).[26,29] Cats are infected by ingesting this form in a variety of lizard or amphibian intermediate hosts. Cercariae migrate from the cat intestine to the gallbladder and bile ducts, where they develop into adults. Eight weeks or more after infection eggs are passed in the feces to complete the life cycle.[27]

Clinical signs are proportional to parasite burden. Cats with light infections are often asymptomatic.[27,28] Clinically ill cats may present with nonspecific signs such as anorexia, lethargy, vomiting, or diarrhea. Severely affected cats present with signs of EHBDO such as icterus and acholic feces.[27-30] Preliminary diagnostics are nonspecific for fluke infestation. Eosinophilia proportional to the parasite burden may be present.[29] Serum liver enzyme activity may be mildly to moderately increased, although it is normal in many cases.[28-30] Abdominal ultrasound often reveals evidence of EHBDO.[28-30] Definitive diagnosis by identification of flukes or fluke eggs in the feces is difficult as small numbers of eggs are shed daily, the eggs have varying morphology at different stages of development, and the eggs are quite small.[27] Fecal concentration-sedimentation using the formalin-ether technique is the most reliable method of identifying eggs in stool.[27,29] Eggs may also be identified in cytologic preparations of bile.[28,30] Eggs or adults may be seen in liver biopsy specimens, but they are inconsistently identified.[1,27,28,30] Histopathologic changes seen in the liver are characterized by dilation of larger intrahepatic bile ducts associated with papillary projections and marked periductal and portal fibrosis. Mild to moderate inflammation may be present within the ducts (neutrophils and macrophages) and in the portal areas (neutrophils, lymphocytes, plasma cells). Eosinophils may be present in limited numbers.[1] Rarely, chronic cholangitis associated with liver flukes can result in the development of cholangiocarcinoma.[1,29]

Optimal treatment protocols have not been established, but praziquantel at 10 to 20 mg/kg daily for 3 days appears to be the most effective.[26-30] Doses as high as 40 mg/kg daily have been used successfully,[28] but this dose has also been fatal in cats.[26] Sporadic resumption of egg shedding following praziquantel has been reported, suggesting that it does not completely eliminate infection.[26,27] For this reason, continued treatment at 12-week intervals has been recommended.[29] Symptomatic and supportive therapy should be tailored to the individual patient. Cats with EHBDO require surgical decompression. Glucocorticoids and UDCA may have some benefit in controlling inflammation and providing choleresis. Although infected cats may remain asymptomatic, patients with EHBDO appear to have a grave prognosis. Long-term survival has only been reported in rare cases.[28,30]

Canine Cholangitis

Cholangitis is rarely reported in dogs. Reports of cholangitis in dogs include two distinct entities: destructive cholangitis and NC.

Destructive cholangitis is characterized histopathologically by a loss of bile ducts (ductopenia) within the smaller portal areas, associated with cholestasis, portal inflammation consisting primarily of macrophages, neutrophils, and occasionally eosinophils, and progressive portal fibrosis.[1,31,32] This is a rarely reported lesion of unknown etiology. It has been postulated that the lesion represents an idiosyncratic drug toxicity. However, of the eight cases reported in the literature only three had a prior drug history: two having received potentiated sulfonamides and the other having received amoxicillin-clavulanate, milbemycin oxime, and amitraz prior to the onset of clinical signs.[31,32] The proposed toxic etiology is based on these case histories and histopathologic similarity to humans with idiosyncratic drug toxicity. Other toxic insults and viral infection, such as canine distemper, can also result in destructive cholangitis.[1] Affected dogs typically present for signs referable to cholestasis, including anorexia, icterus, vomiting, and acholic feces.[31,32] Activities of serum liver enzymes and total bilirubin are moderately to markedly increased. Abdominal ultrasound may be unremarkable, showing only mild dilation of intrahepatic bile ducts.[32] Definitive diagnosis is made by liver biopsy. Optimal treatment options are unknown, but should undoubtedly involve discontinuation of any medications that preceded illness. Corticosteroids for immune suppressive and antiinflammatory effects and UDCA for immunomodulatory and choleretic effects would be rational treatments options, but their efficacy has not been documented. The prognosis appears to be poor, as six of the eight reported cases were euthanized within 6 weeks and the remaining two had only short-term followup (<6 months).[31,32]

NC, as described in the cat, has been rarely reported in dogs.[33-37] Bacteria have been isolated from the majority of cases reported, including *E. coli*, *Klebsiella* spp., *Proteus mirabilis*, *Streptococcus* spp., and *Clostridium* spp.[34-37] Although the bacterial species would support ascending infection from the intestine, the literature is too sparse to make conclusions about the pathophysiology of this disease in dogs. Bacterial infection could also spread hematogenously or via translocation from the portal circulation. The clinical presentation and diagnostic findings are similar to those reported for cats with NC. Affected dogs present with lethargy, anorexia, vomiting, and icterus usually of acute onset. Fever is reported in approximately half of the cases.[33-37] Neutrophilia with or without a left shift is common. Activity of serum liver enzymes is typically increased and most dogs have mild to moderate elevation of serum total bilirubin. Ultrasonography is nonspecific, with the liver varying from normal to hyperechoic with some heterogeneity.[34,36] Thickening and hyperechogenicity of the gallbladder wall is common.[36] Definitive diagnosis is made by liver biopsy with changes similar to those reported in cats with NC. Most dogs have some degree of mixed inflammatory infiltrate, similar to CNC.[33-37] This infiltrate extends into the hepatic parenchyma in the majority of cases. Aerobic and anaerobic culture of bile or hepatic tissue should be performed, though bile has been the source of bacterial isolation in most cases. Treatment involves antibiotic therapy guided by culture and susceptibility results. Duration of treatment should be prolonged, as antibiotic courses of 8 to 12 weeks or greater have been required to completely eliminate bile infections. Clinical improvement precedes bacterial eradication.[36] The prognosis appears to be good in most cases, although dogs with concurrent disease may have a worse prognosis.

Congenital Disorders

Cystic Disease

Liver cysts arising from the intrahepatic bile ducts are rarely encountered in veterinary practice. Although cysts may be acquired secondary to trauma, neoplasia, inflammation, or biliary obstruction,[1,38] the vast majority of cases described in the literature are congenital in origin. Congenital cystic liver diseases result in dilation of various segments of the intrahepatic bile ducts, and they are associated with varying degrees of hepatic fibrosis and cysts in other organs (most commonly the kidneys). Little is known about inheritance patterns of cystic disease in dogs and cats. The various morphologic patterns of cystic disease likely represent abnormalities of bile duct

development at different stages of their formation. The WSAVA Liver Standardization group suggests that cystic disorders be classified into one of the following groups: congenital dilation of the large and segmental bile ducts; juvenile polycystic disease/congenital hepatic fibrosis; and adult polycystic disease.[1]

Congenital dilation of the large intrahepatic bile ducts (i.e., the hepatic ducts and segmental ducts) has been described in dogs.[39-41] The lesion is similar to that of Caroli disease in humans and it is thought to represent an early defect in the formation of the intrahepatic bile ducts.[1,40] The disease is marked by extreme, diffuse, grossly evident dilation of the extrahepatic portion of the large intrahepatic bile ducts containing pale-yellow viscous fluid. The gallbladder and common bile duct are normal, as these have a separate embryologic origin from the intrahepatic bile ducts. The liver is normal to mildly increased in size, with diffuse cysts of varying sizes throughout. Histologically there are areas of marked bridging portal fibrosis containing multiple dilated bile ducts. The lobular architecture of the liver is normal. Although concurrent ascending cholangitis commonly occurs in humans, this is rarely reported in dogs.[39-41] In addition to the hepatic lesions, affected dogs have fusiform, radially arranged renal cysts with moderate to marked fibrosis throughout the renal cortex and medulla.[39-41] Affected dogs are presented early in life, ranging from 13 weeks to 3.5 years.[39-41] Clinical signs include vomiting, weight loss/failure to thrive, decreased appetite, lethargy, ascites, and rarely icterus and neurologic signs. The clinical signs are typically chronic in nature. GI signs, neurologic signs, and ascites are likely a result of portal hypertension caused by pressure of the cysts on the portal vein. Hepatomegaly may be noted on physical examination. Activity of serum liver enzymes is typically normal to mildly increased, although marked increases in activity of ALT and ALP have been reported.[40] Renal azotemia is present in some patients. Ultrasonographically, cystic dilations of the intrahepatic ducts (most with associated calcification) are easily recognized, even though the renal cysts are not always apparent. Definitive diagnosis is made on the basis of the gross and histologic findings described above. Rational treatment options and prognosis are unknown, as only one dog in the literature has been treated. This dog was doing well on a low-protein diet at 5 months of followup.[40] Most of the affected dogs have been fairly stable, and supportive care may be warranted despite the appearance of severe cystic disease.

Juvenile polycystic disease/congenital hepatic fibrosis has been described in litters of Cairn Terriers, West Highland White Terriers, and cats.[42-44] This form is analogous to autosomal recessive polycystic kidney disease in humans, and the inheritance appears to be autosomal recessive in the few families of veterinary patients that have been described.[42,43] The liver cysts are thought to represent an intermediate defect in the development of the intrahepatic bile ducts.[1,40] The liver involvement is primarily microscopic including fibrotic portal areas containing abnormally structured, dilated small bile ducts. The result is a grossly enlarged and firm liver.[40] Renal cysts are present and are identical to those described for dogs with dilation of the large and segmental bile ducts.[40] Affected animals are usually presented at less than 8 weeks of age for abdominal distention because of renomegaly and hepatomegaly.[42,43] However, one 12-year-old cat with similar lesions has been reported.[44] Most affected animals are ill or have died at the time of presentation.[42,43] Liver enzyme activity has been increased in the few animals in which it was evaluated.[43] Abdominal ultrasound may identify cysts and definitive diagnosis is made based on histologic findings as described. Treatment has not been attempted, and the prognosis appears to be grave.

Adult polycystic disease is most commonly recognized as polycystic kidney disease in Persian cats.[44,45] It has also been reported in cats of other breeds and in dogs.[39,43] This is similar to autosomal dominant polycystic kidney disease in humans. Inheritance in Persian cats is autosomal dominant.[45] Liver cysts are thought to represent a late defect in the development of peripheral intrahepatic bile ducts. The liver may contain multiple cysts ranging from less than 1 mm to greater than 12 cm in diameter. These cysts typically contain clear, colorless fluid. Discrete fibrotic areas containing small, irregularly formed bile ducts, referred to as *Von Meyenburg complexes*, may be present.[1] In the kidneys, multiple cysts may form in any segment of the kidney but may involve only a small percentage of the nephron population. This is in contrast to the diffuse cysts seen with congenital dilation of the large and segmental bile ducts and juvenile polycystic disease.[1,40] Hepatic cysts are present in 10% to 40% of cats with polycystic kidney disease, while hepatic fibrosis is recognized in up to 48%.[44,45] The hepatic cysts are usually incidental findings and the animals are not clinically ill unless they develop renal failure secondary to cysts in the kidneys, which happens in adulthood.

Biliary Atresia

Biliary atresia is an extremely rare congenital disorder, having been reported in only one dog and one cat.[46,47] In both cases, the common bile duct was not patent because of atresia. In the dog, the occluded segment of bile duct was histologically comprised of fibrous tissue with minimal inflammation.[47] The etiology is unknown, but this lesion likely represents an embryologic nonfusion of the cranial (hepatic) and caudal (cystic) anlages of the bile ducts during development.[1] Other possible explanations include ischemic, toxic, traumatic, or infectious insults occurring pre- or postnatally.[47] Affected animals have presented at 4 to 6 months of age with clinical signs of depression, anorexia, vomiting, or lameness associated with rickets because of inadequate vitamin D absorption.[46,47] Affected animals show icterus, hepatomegaly and acholic feces. Serum biochemistry abnormalities are consistent with EHBDO. Definitive diagnosis is made at exploratory laparotomy. Surgical biliary diversion is a viable treatment option depending on the location of atresia, but it was unsuccessful in the one case reported.[47] A guarded prognosis should be given as for any animal undergoing a biliary diversion procedure (see discussion under "Neutrophilic Cholangitis").

Intrahepatic Cholestasis

Cholestasis is impaired bile flow resulting in the accumulation of bile components in the blood.[1] Intrahepatic cholestasis occurs secondary to a variety of primary or secondary hepatobiliary diseases.[1,48,49] Increased activity of serum liver enzymes, particularly ALP and GGT, is common with intrahepatic cholestasis but is not specific for the condition. Clinically patients may appear jaundiced, but the predominant clinical sign will be related to the underlying disease process. Cholestasis is marked by the presence of bile plugs in canaliculi, phagocytosed bile in Kupffer cells, and bile granules within hepatocytes. These changes are easily recognized in cytologic and frozen preparations, but are less apparent in paraffin-embedded specimens, particularly in cats.[1] When cholestasis is identified, EHBDO should be ruled out. This should be easily accomplished by abdominal ultrasonography as animals with intrahepatic cholestasis lack the dilation of intra- and extrahepatic bile ducts that is typical of EHBDO.[48] However, exploratory laparotomy should be considered in highly suspicious cases for confirmation.

Intrahepatic cholestasis is associated with extrahepatic bacterial infection in dogs.[49] This syndrome is well characterized in humans and may occur in other species such as the cat. It represents an important differential diagnosis for hyperbilirubinemia in animals without primary liver disease, as over 40-fold increases in total bilirubin have been reported. The physiology behind this mechanism is incompletely understood, but it is thought to result from reduction of bile salt–dependent and –independent bile flow caused by bacterial toxins and/or inflammatory mediators.[49]

Neoplastic Disorders

Tumors of biliary origin in dogs and cats include cholangiocellular adenoma, cholangiocellular carcinoma, and carcinoid.[50] They are uncommon, representing less than 1% of all canine and feline neoplasms.[51-54] The tumors of epithelial origin, cholangiocellular adenoma and carcinoma, are the most common, comprising 40% of all hepatic neoplasms in dogs[51-53] and 56% to 80% of all hepatic neoplasms in cats.[54-56] Tumors showing characteristics of both hepatocellular and cholangiocellular carcinoma have been reported rarely.[50,52] In dogs, 70% to 100% of biliary epithelial tumors are malignant,[51,52] while in cats 35% to 43% are malignant.[54-56] Cholangiocellular adenomas commonly contain cystic components, especially in cats, and have been referred to as biliary or hepatobiliary cystadenomas in this species.[57,58] Cholangiocellular tumors arise predominantly from intrahepatic bile ducts in both species. Extrahepatic location is more common in cats than in dogs and is always associated with malignancy.[51-54,56] In both species, cholangiocellular carcinomas are more likely to present as multiple or diffuse tumors than are adenomas.[51,52,54] Carcinomas are highly metastatic (70% to 90% rate) with local lymph nodes, peritoneum, and lung being the most common sites of metastasis.[51,52,54] The etiology of biliary neoplasia is unknown. Affected dogs and cats are typically middle-aged to older, although animals with malignancy may present at a younger age than those with benign disease.[52,56] Clinical signs are usually vague (such as anorexia and lethargy) and somewhat chronic. Malignant tumors are more likely to cause clinical signs, as many benign tumors are incidental findings not associated with illness.[51,56-58] Hepatomegaly or the presence of a cranial abdominal mass may be identified on physical examination. Increased activity of serum liver enzymes is more commonly associated with malignancy, often being absent with benign tumors.[51,56,58] Even though abdominal radiographs will often identify the presence of hepatomegaly or an hepatic mass, ultrasonography is the preferred imaging method for identification of biliary neoplasms. This modality allows for determination of the cystic nature of the tumors[58] and for the evaluation of metastatic potential. Fine-needle aspiration and cytology are of limited utility for diagnosis of biliary epithelial tumors. Carcinoma was correctly identified via liver mass aspiration in only 20% of cases in one study.[14] However, cytology is recommended as it likely exhibits high specificity, especially for metastatic lesions. Surgical excision and biopsy is the optimal diagnostic and therapeutic technique for tumors confined to one or two liver lobes. Surgical excision appears to be curative in cats with benign tumors,[56,57] but malignant tumors carry a poor prognosis in both dogs and cats with many cases not surviving to discharge and survival greater than 6 months not reported in any case.[56,59] Adjunctive chemotherapeutic protocols have not been reported.

Carcinoids, also referred to as neuroendocrine tumors, are far less prevalent in dogs and cats than the tumors of biliary epithelial origin.[52,54,55] These tumors are thought to develop from neuroendocrine cells in the epithelium of bile ducts or gallbladder or from hepatic progenitor cells.[50] They may be identified at intrahepatic or extrahepatic locations. They appear to have a more aggressive course than cholangiocellular carcinomas, with the majority being present in multiple lobes and greater than 90% having metastasized at the time of diagnosis.[52,54,55]

EXTRAHEPATIC BILIARY DISORDERS

Michael D. Willard and Theresa Fossum

Etiology

The major pathogenetic mechanisms of canine and feline extrahepatic biliary tract disease are obstruction, inflammation, and exudation. The major causes of extrahepatic biliary tract obstruction (EHBO) are pancreatitis, gallbladder mucoceles (in dogs), cholelithiasis, parasitic infections (in cats), and tumors. EHBO is more common in dogs than cats. Biliary tract inflammation (e.g., cholecystitis, cholangitis) is primarily caused by bacterial infection, but can be nonseptic or parasitic, especially in cats. Gallstones may be associated with biliary tract disease (e.g., infection, obstruction), but the majority of them appear to be clinically silent. Stones in the gallbladder are termed *choleliths* while stones in the biliary tract are termed *choledocholiths*. Biliary tract exudation or leakage can be caused by traumatic (primarily of the bile ducts) or spontaneous rupture (primarily of the gallbladder). The latter is caused by necrotizing cholecystitis, which can be caused by sepsis (e.g., infectious cholecystitis), pressure necrosis (e.g., mucocele), or infarction. Biliary tract *tumors* are rare and of uncertain cause.

Pathophysiology

Extrahepatic Biliary Tract Obstruction

The common bile duct passes through the lesser omentum and the pancreatic parenchyma before entering the mesenteric wall of the duodenum. In the dog, it empties near the opening of the minor pancreatic duct at the major duodenal papilla, whereas in the cat it joins with the major pancreatic duct before emptying into the duodenum. Inflammation and edema with pancreatitis may be sufficient to cause compression and obstruction of the bile duct. This is probably the most common cause of canine EHBO.[1] There is, however, no consistent relationship between clinical severity of the pancreatitis and likelihood of EHBO, possibly because pancreatitis can affect different regions of the pancreas. Pancreatitis is a rare cause of EHBO in the cat. Chapter 60 discusses the breeds at increased risk for pancreatitis and causes.

Gallbladder mucoceles occur primarily in dogs. In such cases, the gallbladder is filled with inspissated, semisolid mucus that may extend into the bile ducts causing obstruction. Mucoceles can exceed the storage capacity of the gallbladder thereby causing pressure necrosis on the wall of the gallbladder. They can also spontaneously rupture (often at the fundus)[2,3] causing bile peritonitis. The cause of gallbladder mucocele is unknown, but might include dysfunction/hyperplasia of mucus-secreting cells in the gallbladder mucosa. Mucoceles may become secondarily infected.[2]

Gallstones are often clinically silent and observed incidentally only at the time of abdominal imaging. They can be associated with cholecytitis,[4] but they rarely cause EHBO because they must be small enough to enter the cystic bile duct but large enough to lodge there.

Parasites occasionally cause obstruction. *Platynosomum fastosum* (i.e., *P. concinnum*) is a fluke that inhabits the gallbladder and/or bile ducts of cats that are infected by eating lizards or toads.[5] Natural infections are found primarily in Florida, Hawaii, and the Caribbean. It may be asymptomatic or may cause obstruction or fibrosis. They are rare causes of cholecystitis.

Tumors may cause obstruction, and may be one of the more common causes in cats.[6,7]

Inflammation and Necrosis

Cholecystitis is most commonly caused by bacterial infection, ostensibly from bacterial migration up the bile duct. Various Gram-positive, Gram-negative, aerobic, and anaerobic bacteria (e.g., *Clostridium*, *Staphylococcus* spp., *Enterococcus* spp., *Streptococcus* spp., *Klebsiella* spp., *E. coli*, *Helicobacter* spp.) have been reported.[8-11] Infections caused by gas-producing bacteria can produce emphysematous cholecystitis. Because of a shared biliary and pancreatic ductal system in the cat, hepatobiliary disease is a well-established risk factor for pancreatitis in the cat. Aseptic infection of the gallbladder (necrotizing cholecystitis) has been reported, and infarction is one such cause.[11,12]

Exudation

Leakage of bile into the abdomen can be a result of mechanical forces (e.g., automobile trauma) that cause a shearing effect resulting in transaction of the common bile duct or one of the other bile ducts. Mechanical rupture has also been reported following gunshot trauma. Necrosis of the gallbladder raises the risk for rupture of the gallbladder and occasionally the bile ducts.

Gallstones

Canine and feline gallstones are typically composed of cholesterol, bilirubin, or may be mixed (as opposed to human gallstones which are usually caused by cholesterol).[4] Feline gallstones are typically calcium carbonate or mixed stones.[13]

Clinical Examination

Biliary tract diseases can cause severe clinical signs (e.g., anorexia, depression, vomiting, icterus, abdominal pain) or they may be relatively asymptomatic. Most symptomatic patients have serum biochemical abnormalities (e.g., increased serum ALT, ALP, and serum bilirubin). Hypercholesterolemia is common in patients with EHBO. Hyperbilirubinemia by itself does little besides cause icterus; therefore, patients with extremely high serum bilirubin concentrations can be relatively asymptomatic. Renal failure has been attributed to excessively high serum bilirubin concentrations, but it is unclear that bilirubin is the cause or that this is common. Shetland Sheepdogs[14] appear to have an increased risk for biliary tract disease, and Cocker Spaniels might also (see Chapter 62).

Besides icterus, clinical signs in patients with EHBO are primarily a result of the cause of the obstruction, not the obstruction itself. Canine pancreatitis in particular may cause severe clinical signs (e.g., anorexia, vomiting, abdominal pain—see "Complications of Liver Disease" section). However, not all patients with pancreatitis-induced EHBO have severe pancreatitis. Causes of EHBO that are insidious (e.g., mucoceles, tumors, and stones) are often unsuspected until the patient becomes icteric.

Biliary tract inflammation such as septic cholecystitis is well-documented in dogs and cats. Shetland Sheepdogs appear to be at a greater risk of inflammatory biliary tract disease than most other breeds.[14] Clinical signs vary, but most animals are clinically ill with anorexia and vomiting as more prominent symptoms. Fever is uncommon, icterus inconsistent, and leukocytosis is often insignificant, even with marked bacterial infections of the biliary tract.

Gallstones are generally asymptomatic. They can be associated with cholecystitis or EHBO.

Bilious abdomen can be a clinically mild condition, or it can be associated with life-threatening signs. Septic bilious abdomen causes extremely severe peritonitis with systemic inflammatory response syndrome (e.g., anorexia, vomiting, abdominal pain, poor perfusion, fever, and death). These patients may be in the initial hyperdynamic state (e.g., red mucus membranes, bounding pulse, fever, or hypothermia) or, if initially undiagnosed, can be in the late hypodynamic state (e.g., pale mucus membranes, weak pulse, and hypothermia). Intraperitoneal bile seems to make septic peritonitis more severe. In contrast, some animals with sterile bilious abdomen (e.g., as a consequence of automobile trauma) are essentially normal except for ascites and icterus.

Diagnosis

Plain radiography is occasionally diagnostic of biliary tract disease. Some gallstones are radiopaque (Figure 61-30).[4] Finding air in the gallbladder or in the wall of the gallbladder (i.e., emphysematous cholecystitis; Figure 61-31) is diagnostic of infection with a gas-producing bacterium. "Porcelain" gallbladder (i.e., a radiopaque gallbladder because of intramural mineralization of the gallbladder) is associated with carcinoma.[15]

Ultrasound is generally accepted as the most important and sensitive method for diagnosing extrahepatic biliary tract diseases.[7] Many patients that are not suspicious for biliary tract disease are fortuitously diagnosed when ultrasound or radiographs are requested for various reasons.[14] In difficult cases (e.g., partial EHBO versus complete EHBO), nuclear scintigraphy techniques can be used[16]; however, this seems to be rarely required.

Diagnosis of EHBO generally relies upon the use of ultrasound. Dilation of the bile ducts (normal canine bile ducts are ≤3 mm; normal feline bile ducts are ≤2 to 2.5 mm) is primarily caused by EHBO, and is generally seen by 3 days postobstruction. If one is unsure whether the ducts are dilated, repeating the examination in 3 days should be helpful. Enlargement of the gallbladder is not diagnostic of EHBO because anorexia and starvation of any cause may do the same thing. However, failing to find a dilated gallbladder

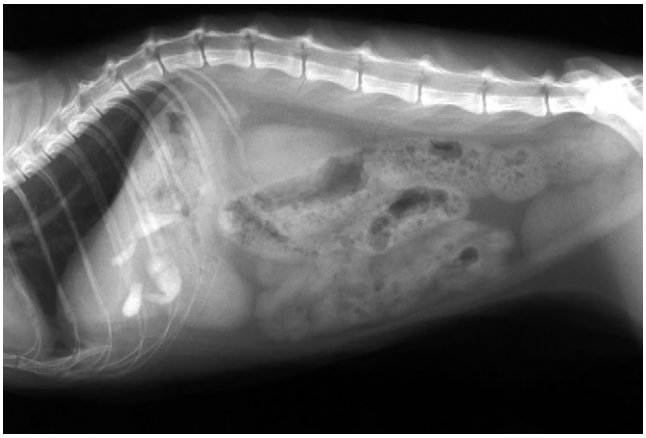

Figure 61-30 A lateral radiograph of a cat. There are several radiodense choleliths. These were serendipitous findings; the cat had no signs referable to abdominal disease. The cat was not treated for the stones and did well.

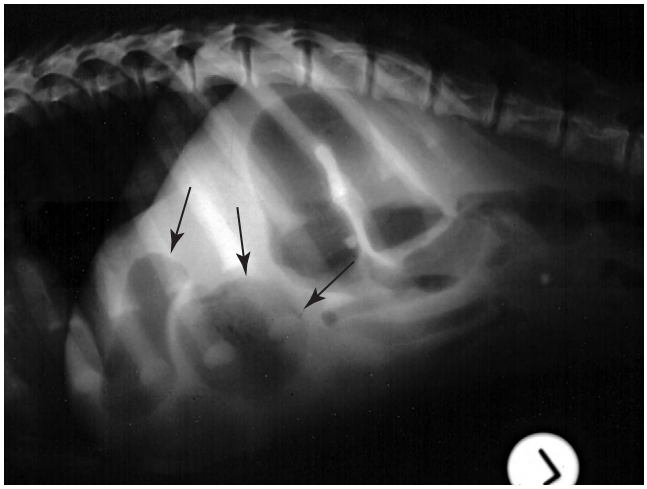

Figure 61-31 A lateral radiograph of a dog with emphysematous cholecystitis. The air-filled structure pointed out by *small arrows* is the pylorus; the air-filled structure pointed out by *larger arrow* is an air-filled gallbladder.

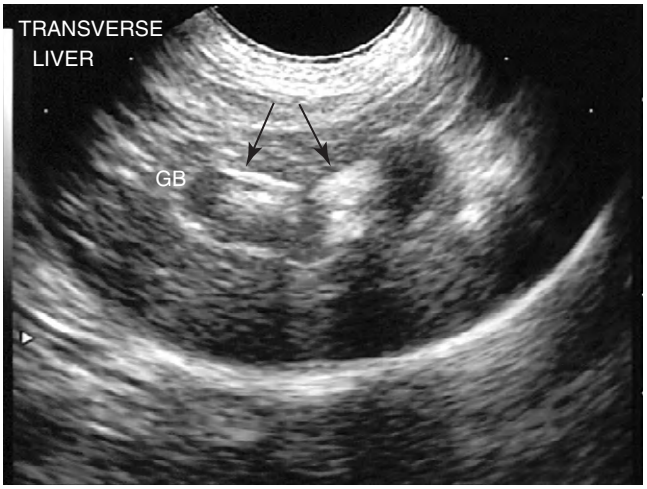

Figure 61-33 An ultrasonographic image of the gallbladder of a dog with gallstones (*arrows*). The stones were found fortuitously during an abdominal ultrasound; there was no evidence that they were causing any clinical signs.

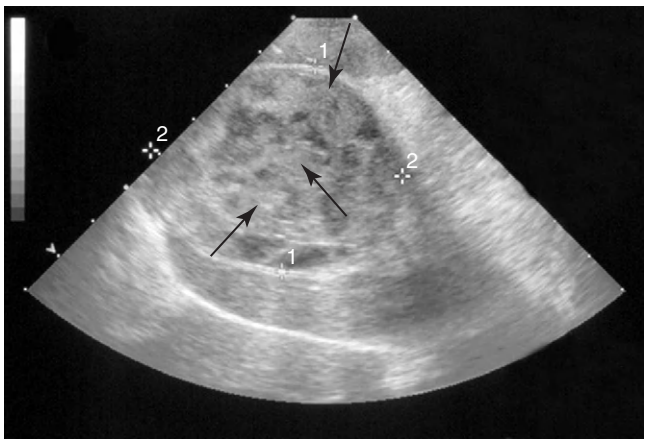

Figure 61-32 An ultrasonographic image of a Dachshund's gallbladder. The gallbladder is filled with hyperechoic material (*arrows*) that was not gravity dependent. The dog was asymptomatic for biliary tract disease and was still in good health without therapy for the gallbladder 10 months after this image was taken.

in a patient with clearly dilated bile ducts suggests biliary tract inflammation or prior EHBO. Any dog with EHBO should be suspected of having acute pancreatitis until proven otherwise. Chapter 60 details the diagnosis of pancreatitis. If acute pancreatitis is eliminated in a patient with EHBO, then one should look for gallstones and tumors, first by imaging and then by exploratory surgery or laparoscopy if imaging fails to provide a diagnosis.

Mucoceles are readily diagnosed by ultrasound, although there is some debate about what constitutes a mucocele. "Classic" mucoceles are described as producing a "kiwi fruit" appearance without gravity-dependent bile movement. "Sludge" in the gallbladder is a common finding (and it has gravity-dependent movement), but is not clinically significant.[17] The gallbladder of clinically normal dogs may appear abnormal on ultrasound examination (Figure 61-32), while patients with significant biliary tract disease may appear essentially normal. Whether or not patients with ultrasonographic abnormalities of the gallbladder will become symptomatic cannot be reliably predicted.

Cholecystitis is often diagnosed by ultrasound-guided percutaneous aspiration of gallbladder bile for cytology and culture. This is a relatively sensitive and specific procedure for diagnosing biliary tract infection.[2,18] The finding of a dilated bile duct coincident with a normal-size gallbladder suggests cholecystitis, prior EHBO, or a rare congenital problem such as Caroli disease.[19] It is important to note that patients with bacterial cholecystitis may have no ultrasonographic or gross abnormalities. Ultrasound may be suggestive, but is relatively insensitive for cholecystitis.[8,20] Consequently, it is probably best to routinely aspirate bile for cytology and culture in patients with hepatobiliary disease.

Gallstones are relatively easy to diagnose, most of them are easy to find by radiographs, more so by ultrasonography (Figure 61-33).

Treatment

With EHBO, the underlying cause is always the primary concern. EHBO in and of itself is not the primary consideration when deciding upon therapy. Pancreatitis, for example, is primarily a medical disease (see Chapter 60). Surgery is rarely appropriate in the management of pancreatitis even when it is causing EHBO. If deemed necessary, EHBO caused by pancreatitis can be relieved by percutaneous aspiration[21] or placement of a biliary tract stent.[22] If absolutely necessary, a cholecystoduodenostomy may be performed, but this surgery should be avoided if possible. These procedures are seldom necessary because almost all patients with EHBO caused by pancreatitis will experience resolution of the obstruction with medical therapy.

Gallstones should be removed only if they are causing obstruction or cholecystitis. It is usually better to perform a cholecystectomy[4,13] as opposed to a cholecystotomy; the former has a lower morbidity and mortality rate in people and presumably in dogs and cats as well. Biliary tract tumors can seldom be cured surgically.

If a patient has EHBO caused by something that cannot be treated medically (e.g., mucocele, tumor, pancreatic stricture, traumatically torn bile duct), then a biliary bypass procedure can be performed. Cholecystoduodenostomy can relieve the obstruction, although the surgery requires special surgical skills. This surgery can predispose the patient to recurrent, ascending cholecystitis or other complications[10,23] and should only be performed in patients that

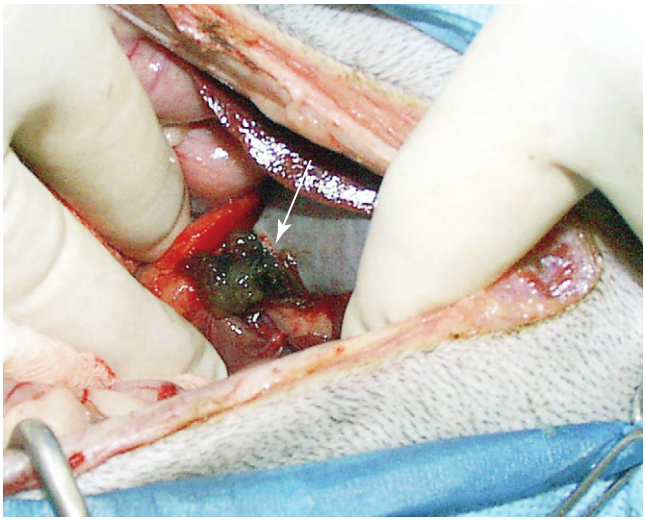

Figure 61-34 A photograph taken at surgery. The abdomen has just been opened, and bile has just begun to escape from a spontaneous rupture of the gallbladder wall (*arrow*) caused by necrotizing cholecystitis.

absolutely require it. Generally speaking, EHBO caused by pancreatitis that is not resolving as quickly as desired is not necessarily a good indication for this procedure; patience and medical therapy generally resolve the problem. In fact, pancreatitis can be a complication of surgery in this region.[24]

Many animals with hepatic disease are concurrently treated with antioxidants and other hepatoprotectants. Although most of these drugs will not hurt patients with biliary tract disease (in fact, they may be beneficial if the disease is extending into the hepatic parenchyma, such as cholangitis/cholangiohepatitis), care must be taken before administering UDCA. UDCA is a choleretic agent that stimulates bile flow. This could be disadvantageous in a patient with complete EHBO.

Mucoceles usually need to be removed surgically.[2,3,14] Medical management may be attempted (e.g., fat-restricted diet plus UDCA), but there is a substantially increased mortality rate for patients that experience gallbladder rupture (Figure 61-34); consequently, surgery is probably the safest course. Most patients are not at risk of immediate rupture. As long as ultrasonography does not suggest impending rupture, one should make sure the patient is an optimal anesthetic risk.

Bacterial cholecystitis, uncomplicated by EHBO or stone, should generally first be treated with antibiotics, usually for 4 to 6 weeks. However, some patients with bacterial cholecystitis cannot be cured with antibiotic therapy, ostensibly because the infection has localized in the gallbladder mucosa. These patients consistently relapse after discontinuation of antibiotics, and therefore a cure may be achieved only with antibiotics plus cholecystectomy. When performing this surgery, great care should be taken to avoid causing a stricture or obstruction of the common bile duct. Postcholecystectomy bile duct obstruction may prove fatal. It is also very important to be avoid traumatizing the pancreas to avoid severe pancreatitis.[24]

Biliary tract leakage is treated based upon the underlying cause. If the gallbladder has ruptured, cholecystectomy is usually most appropriate. If the bile duct has ruptured, it is very difficult to successfully anastomose the two ends. In that instance, one generally must perform a cholecystoduodenostomy and ligate both ends of the torn bile duct. It is important to avoid biopsying the gallbladder as that has a risk of dehiscence. In general, one should either remove the gallbladder, aspirate gallbladder bile, gently express the gallbladder, or leave it undisturbed. If the leakage is associated with septic peritonitis, then that is a true emergency and requires immediate, aggressive medical and surgical therapy.

Gallstones may be monitored if the patient is asymptomatic.

Tumors can rarely be resected; they are generally inoperable when found. Rare examples exist of patients with biliary tumors being cured surgically.

Biliary flukes can be treated with praziquantel (20 to 40 mg/kg SQ for 3 days).

Prognosis

Chapter 60 discusses pancreatitis in greater detail. Biliary mucoceles that have not ruptured often have a good prognosis; however, one report found a 32% mortality rate in patients without a rupture versus 68% mortality in patients with bile peritonitis.[14] The report authors recommended a more preemptive approach (i.e., versus waiting until the patent is symptomatic). Another group found no difference in mortality between rupture and nonruptured mucoceles (i.e., 21%).[3] Gallstones generally are innocuous, and even when they are causing signs have a good prognosis as long as rupture has not occurred. Bacterial cholecystitis has a good prognosis as long as the gallbladder is intact and not at risk for rupture. Septic bilious peritonitis has a very guarded to poor prognosis, depending upon the severity of the peritonitis. Gallstones are usually asymptomatic, but can occasionally cause a problem. They are usually easily removed and resolved. Biliary tumors are usually a poor prognostic finding[6,7] because of late diagnosis. Flukes can be treated, but without early recognition, extensive tissue injury may or may not resolve after therapy.

COMPLICATIONS OF LIVER DISEASE

Penny Watson

The liver serves many important functions including metabolism (carbohydrate, protein, lipid, nucleic acid, xenobiotics, porphyrins, vitamins, minerals, glutathione, endogenous hormones), coagulation factor synthesis, biliary secretion, and immune surveillance (see Chapter 1). It is not surprising, therefore, that animals with liver disease experience a broad range of complications reflecting perturbations in one or more of these functions.

Portal Hypertension and Its Consequences

The hepatic portal venous system accounts for up to 75% of the total hepatic circulation and serves to transport nutrients from the GI tract to hepatic sinusoidal capillaries (and hepatocytes) before coalescing once again into central veins, hepatic veins, and caudal vena cava. In health, the multiple branching of the main portal vein, venules, and capillaries reduces the overall resistance to blood flow (circuits in parallel reduce resistance), and therefore the pressure required to perfuse these capillaries is maintained at a low level of less than 5 to 6 mm Hg.[1,2] Disease processes that obstruct flow through the intrahepatic branches of the portal vein or sinusoids elevate this pressure and result in significant portal hypertension. Hepatocyte swelling impedes portal flow in acute pathophysiologic states, and fibrosis further impedes this flow in

chronic pathophysiologic states. Sustained portal hypertension is associated with many, but not all, of the complications of liver disease.

Portal hypertension is an important, potentially life-threatening complication of liver disease in the dog. It is rare or poorly documented in the cat. Portal hypertension develops most often in dogs with chronic liver disease and cirrhosis. It is occasionally recognized as a congenital lesion in young animals with arteriovenous fistulas,[3] or as a hypoplastic disorder of the intrahepatic portal vein branches resulting in a condition referred to as *noncirrhotic portal hypertension*.[4,5] Prehepatic portal hypertension can develop secondary to portal vein thrombosis or congenital hypoplasia of the extrahepatic portal vein, but these are less common. Sustained portal hypertension may progress to splanchnic congestion, GI ulceration, ascites, and encephalopathy.

Gastrointestinal Ulceration

Portal venous hypertension produces vascular stasis and venous congestion and increases the risk of GI ulceration, particularly in conjunction with other risk factors such as anorexia and steroidal and nonsteroidal antiinflammatory drug usage. Portal hypertension–related ulceration in the dog is typically duodenal although bleeding esophageal varices, similar to those reported in humans, are occasionally observed.[3] Glucocorticoids should be used only with great caution in dogs with portal hypertension.

Ascites

Reduced systemic blood pressure is another consequence of portal hypertension and splanchnic venous congestion. Changes in systemic blood pressure activate the renin–angiotensin–aldosterone system (as described in Chapter 8) and renal sodium retention, and thus increase total circulating fluid volume. The increase in circulating fluid volume (the "overfill" hypothesis) is believed to be the triggering event for the development of ascites in animals with portal hypertension.[6] This is why aldosterone antagonists are the initial treatment of choice in ascites caused by portal hypertension (for more details see Chapter 8). Ascites is a negative prognostic indicator in dogs with chronic hepatitis,[7] although individual animals with chronic hepatitis and ascites can be managed and maintained for many months.

Acquired Shunts

With sustained portal hypertension, multiple acquired PSSs develop and serve as a conduit for portal blood flow directly into the systemic circulation. Shunts serve to dissipate some of the increased portal pressure thus reducing the risk of adverse complications such as venous congestion, GI hemorrhage, and ulceration. They do, however, raise the risk of yet another complication of liver disease—hepatoencephalopathy.

Hepatoencephalopathy

HE is a syndrome of potentially reversible brain dysfunction resulting from impaired liver function. It results from either severe hepatocyte dysfunction or more commonly the presence of portosystemic collateral circulation, either congenital or acquired, where a variable combination of shunting of portal blood and hepatocyte dysfunction contributes to the clinical signs. It can be acute or chronic in presentation. Acute HE is most often a result of acute fulminating liver failure (see "Consequences of Hepatocyte and Biliary Tract Injury" section) and carries a poor prognosis. More chronic HE is usually a result of congenital or acquired PSSs.[2]

Table 61-10 Clinical Signs Attributed to Pathophysiology

Clinical Sign	Dysfunction
Anorexia, weight loss	Decreased metabolism; hepatic inflammation
Icterus	Biliary obstruction (intra- or extrahepatic) or dysfunction
Melena, hematuria	GI ulceration as a consequence of portal hypertension; coagulopathy
Ascites	Portal hypertension; hypoalbuminemia (reduced production in liver)
Polyuria/polydipsia	Multifactorial and poorly understood; may be contributions from hepatoencephalopathy; decreased urea cycling; increased antidiuretic hormone and cortisol and other factors
Hepatoencephalopathy	Hyperammonemia and other triggers (see text)
Depression, weakness	Hypoglycemia, anemia, hepatoencephalopathy
Vomiting, diarrhea	Portal hypertension (GI congestion); ascites; hepatic inflammation; hepatoencephalopathy; decreased xenometabolism

Clinical signs associated with HE in dogs and cats include depression, behavioral changes, circling/head-pressing, ataxia, apparent blindness, abnormal swallowing or salivation, stupor, seizures, and coma (Table 61-10). Salivation is much more common in cats than dogs with HE.

Brain dysfunction in HE was historically considered to be a neurotransmitter dysfunction but current evidence suggests low-grade cerebral edema caused by astrocyte swelling is the predominant pathologic change.[8] There is consensus that ammonia is the key toxin in HE but blood ammonia concentrations do not always correlate with severity of clinical signs. This is because a large number of other factors interact with the effects of ammonia to precipitate HE. Astrocytes play a central role because they express glutamine synthetase and detoxify the ammonia that reaches the CNS. Intraastrocyte accumulation of osmotically active glutamine in HE results in astrocyte swelling and thus low-grade cerebral edema.[8] This is largely reversible if the precipitating factors are treated, but edema can become severe and result in irreversible CNS changes in severe and acute HE. Precipitating factors include inflammatory cytokines, benzodiazepine-type sedatives, and disturbances in amino acid metabolism and dopaminergic neurotransmission.[8-10] The source of ammonia is primarily absorption from the gut, although other sources also exist as a result of interorgan metabolism. Gut-derived ammonia was traditionally assumed to be a by-product of intestinal bacterial metabolism in the colon. This remains an important source in some conditions such as melena. However, recent studies in other species suggest that small intestinal enterocyte metabolism of glutamine as their main energy source is the most important source of postprandial ammonia absorption in the portal vein.[9,10] This is also likely the case in most dogs on normal diets as it is very unusual for undigested protein to reach the colon, although the source of gut-derived ammonia has never been investigated in dogs. In normal dogs, ammonia is transported to the liver via the main portal vein, and further metabolized

to urea by hepatocytes in the Krebs-Henseleit cycle. With portosystemic shunting or severe hepatocyte dysfunction, ammonia accumulates in the brain (and other tissues) where it is taken up by astrocytes and results in edema as described previously. Dogs with HE also show disturbances in CNS aromatic amino acid metabolism.[11,12] The aromatic amino acids (tyrosine, tryptophan, and phenylalanine) accumulate in, the CNS in portasystemic shunting. In the brain, β-phenylalanine and tyrosine are metabolized to phenylethanolamine and octopamine, both of which can act as false neurotransmitters. However, dietary supplementation with branched-chain amino acids (e.g., leucine, isoleucine, valine) does not convincingly improve HE in either dogs or humans.[9,12] However, some dietary protein sources appear to be better than others in dogs with HE. Dogs on soya protein diets show a lower plasma ammonia concentration than those fed meat protein.[13] Dogs with HE have also traditionally been fed a protein-restricted diet. However, protein restriction is no longer advocated in humans with HE[9] and it may be the digestibility and type of protein rather than a reduced amount that are most important in dogs. More studies are needed to investigate this.

Several other metabolic alterations exacerbate clinical signs associated with HE, including acid–base disorders, electrolyte abnormalities, particularly hypokalemia, hypoglycemia, hypoxemia, and arginine deficiency (cats). An important trigger in humans and rodents is inflammation: Recent studies confirm that inflammatory cytokines are synergistic with ammonia in precipitating HE and that controlling inflammation in other organs is an important part of managing the patient with HE.[14,15] There is anecdotal evidence that this is also true in dogs.

Consequences of Hepatocyte and Biliary Tract Injury

Functional Reserve

The liver has significant structural and functional reserve capacity to support ongoing metabolic needs during mild to moderate forms of liver injury. Moreover, the liver has the ability to regenerate liver volume and cell mass during the recovery phase of most forms of liver injury. Signs of liver failure develop earlier with acute forms of liver injury than with chronic, progressive liver disease.

Zones 1, 2, and 3 hepatocytes of the hepatic acinus have differing functions. Zone 1 (periportal) hepatocytes, for example, have a high capacity to cycle ammonia through the urea cycle thereby reducing the toxicity of ammonia. Zone 3 hepatocytes (nearer the hepatic vein) have a lesser capacity for ammonia and instead convert it to glutamine.[16,17] In health, zonation permits flexibility in hepatic function such that in metabolic acidosis, for example, the liver can rapidly divert ammonia toward glutamine production, which is necessary for H+ ion excretion in the kidney. In severe acute liver injury, this becomes an important "tradeoff" because acute selective destruction of periportal (zone 1) hepatocytes more readily results in signs of encephalopathy because of the reduced ability of zone 3 hepatocytes to detoxify ammonia. In chronic liver disease, if hepatocytes undergo piecemeal necrosis at different rates in different zones, the remaining hepatocytes can assume some of those functions, so that clinical signs of deficiency are not seen until later in chronic disease processes.

Coagulopathy

Coagulopathy is a complication of both acute and chronic liver disease in dogs and cats. A recent study reported one or more coagulation abnormalities (prolongation of coagulation times, changes in platelet counts, D-dimers, fibrinogen, or protein C) in 24 (57%) of 42 dogs affected with liver disease.[18] Coagulation abnormalities are also common in cats with liver disease and one study found abnormalities in 18 (82%) of 22 cats with liver disease.[19]

Multiple mechanisms of coagulopathy are possible in liver disease patients. In ALF cases such as xylitol toxicity in dogs,[20] HL in cats,[21] and cirrhosis in dogs,[18] loss of normal hepatocyte function results in severe coagulation factor deficiency. Vitamin K deficiency has also been implicated in coagulopathy particularly in cats in which cholestasis impedes bile salt secretion, emulsification, and micellarization of fat and fat-soluble vitamins and fat-soluble vitamin absorption.[21] Concurrent inflammatory bowel disease and pancreatitis exacerbate this condition in many cats with cholangitis.[21] Finally, platelet abnormalities (cytopenia and cytopathy) may contribute to coagulopathy in dogs with liver disease.[18,22]

Regeneration

The liver has the unique ability to regulate its growth and mass. Hepatocyte loss caused by viral, bacterial, or chemical injury, or partial hepatectomy triggers hepatocyte replication.[23,24] Liver injury not only stimulates hepatocyte turnover but may also stimulate biliary proliferation and activation and proliferation of HSCs. These changes usually occur together in an orchestrated wound-healing response. In the case of hepatocyte loss, normally quiescent hepatocytes replicate to restore the liver functional capacity and mass. These are the main cells that regenerate liver mass. However, in severe injury or where hepatocyte turnover is inhibited by senescence, a progenitor cell reserve may also replicate and regenerate liver mass.[24] Although hepatocytes are capable of replication, they have very slow turnover in a normal liver and there are negative consequences of long-term increased stimulation and turnover in chronic liver disease. It has been shown that cycling hepatocytes suffer irreversible erosion of telomeres, which leads to senescence.[25] Functional capacity is a relative rather than absolute parameter. The set point for growth regulation is the ratio between liver mass and body mass rather than liver mass per se. The optimization of the ratio indicates that the liver reaches a state in which it performs the amount of metabolic work needed to meet the functional requirements of the body.[24]

Gene expression in the regenerating liver is a multistep process with at least two critical steps: the transition of quiescent hepatocytes into the cell cycle ("priming"), and the progression beyond the restriction point in the G_1 phase of the cell cycle. Hepatocytes must first be primed before they can fully respond to growth factors. As many as 70 different genes participate in the early response to hepatectomy, but TNF and IL-6 appear to be the major cytokines involved in the priming of hepatocytes.[20] The proliferative effect of TNF on hepatocytes is further influenced by reactive oxygen species, nitric oxide, and glutathione content, and at least four transcription factors (nuclear factor kappa B, STAT3, AP-1, and C/EBPβ) play major roles in the initiation of early liver regeneration.[23,24] Progression through the cell cycle beyond the initiation phase requires growth factors, primarily hepatocyte growth factor and TGF-α. The subsequent expression of cell-cycle genes, particularly cyclin D_1, establishes the stage at which replication becomes growth factor–independent and autonomous. At this point, the hepatocyte is irreversibly committed to replicate and the cell-cycle replication machinery takes over. The regenerative capacity of the residual hepatocytes may restore liver mass and function after as much as 65% to 70% hepatectomy.[23,24] Progenitor cells are only activated in severe liver injury. They appear to reside in a "niche" that is a particular regulatory environment.[24] A recent immunohistochemical

study suggests that canine and human liver progenitor cells are functionally very similar.[26] Further characterization of the molecular events regulating hepatocyte replication and liver regeneration should improve outcome in animals affected with severe liver disease.

Fibrosis and the Wound-Healing Response

The normal ECM of the liver provides cells with positional information and a mechanical scaffold for adhesion and migration. The ECM consists of collagens, glycoproteins, proteoglycans, glycosaminoglycans and molecules that are bound specifically by the ECM, such as certain growth factors, cytokines, matrix metalloproteinases, and processing enzymes such as tissue transglutaminase and procollagen propeptidases. A normal liver contains a very small amount of fibrous tissue as a percentage of its total mass.[27,28] Acute or chronic liver injury causes a dynamic wound-healing response with both production and removal of fibrosis.[29] HSCs are the major source of the collagens that comprise fibrosis and cirrhosis, as well as of the tissue inhibitors of metalloproteinases (TIMPs) that inhibit collagen degradation. It is the balance between collagen production by HSCs and its degradation by matrix metalloproteinases that determines the severity and reversibility of the fibrotic response. Following acute or chronic liver damage, HSCs are stimulated to multiply and to undergo a complete phenotypic transformation from quiescent vitamin A–storing cells to contractile myofibroblasts which synthesize large amounts of ECM.[25,29] Important stimuli for HSC transformation and multiplication in liver injury include oxidative stress; chemokines including platelet-derived growth factor; VEGF and TGF-β; adipokines; and parts of the innate immune system including Toll-like receptor ligands.[29] The role of adipokines in stimulating fibrosis is increasingly being recognized in humans, where nonalcoholic fatty liver disease can lead to fibrosis and cirrhosis. They are produced by HSCs themselves, as well as fat cells, and increased leptin and reduced adiponectin drive fibrosis.[29] Their importance in dogs is unknown and it is also unknown whether vacuolar or fatty liver diseases progress to fibrosis in dogs, but these are important questions to answer in the future given the widespread occurrence of obesity in dogs.

The contractile function of activated HSCs contributes significantly to the development of portal hypertension,[28] and increases in angiogenic chemokines such as VEGF and platelet-derived growth factor not only contribute to fibrogenesis by HSCs, but also to the development of portal hypertension, so that the two pathologic processes are inextricably linked.[29]

Activated HSCs have greatly increased production of TIMPs, particularly TIMP1 and TIMP2, which prevent the action of matrix metalloproteinases in the ECM. The degree of fibrosis and reversibility then depend on the balance between perpetuation of HSC proliferation and secretion and resolution of HSC by either apoptosis or senescence of HSCs or, indeed, their reversion to an inactive state. Many factors contribute to HSC apoptosis, senescence, or reversion, including reduction in TIMPs and nuclear factor kappa B and increased Fas and p53.[29] However, in spite of all this understanding of the molecular mechanisms of fibrosis, a truly effective treatment for hepatic fibrosis in either humans or dogs has yet to be found.[29]

It is important to remember that a normal fibrotic response (scar) is important in walling off pathogens and tissue injury and inhibiting this response without removing the inciting cause (e.g., a viral cause) could lead to spread of the pathology.[28] Future treatment strategies for fibrosis should therefore incorporate treatment of the underlying cause of disease. This is clearly a problem in dogs where the cause of chronic hepatitis is usually unknown.[30] There is increasing evidence that fibrosis and even some forms of cirrhosis in humans and rodent models are reversible if the underlying cause is removed.[28,31] The challenges are removing the cause and also defining the point at which cirrhosis moves from a reversible to irreversible state. Increased fibrous septal thickness, smaller nodule size, and reduced cellularity together with increased collagen cross-bridging have all been associated with an irreversible cirrhotic state in rodents and humans.[28]

It is unknown whether liver fibrosis or cirrhosis in dogs is reversible clinically. Cases of chronic hepatitis in dogs very rarely have sequential liver biopsies over a long period of time to assess progression of disease and noninvasive markers of fibrosis remain to be validated. Serum hyaluronic acid is increased in dogs with cirrhosis[32] as is TGF-β[33] but the usefulness of these markers in following progression in clinical cases has not been assessed. Identifying a reliable noninvasive marker of fibrosis for sequential studies in humans and dogs remains a challenge.[34]

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STRUCTURE AND FUNCTION

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CHAPTER 62

Breed-Related Diseases

GASTROINTESTINAL TRACT

Robert J. Washabau

Breed predispositions are suspected in many medical disorders of dogs and cats, not just those of the digestive system. Heritability has been established for many of these disorders, and even the specific genetic locus. Gene therapy, however is still many years away for most of these disorders. Understanding and recognizing breed associations is important for several reasons. First, known or suspected associations help guide the clinician in considering a list of reasonable differential diagnoses, and in narrowing down the list of costly or invasive diagnostic tests. Second, knowledge of breed predispositions assists veterinarians in providing advice to pet owners and aspiring pet owners. A well-educated pet owner is always a better (and happier) pet owner. Finally, although a specific genetic deficiency may not be treatable, knowledge of the underlying pathogenesis may help to develop better therapies, even if nonspecific, thereby improving the patient's long-term prognosis.

In addition to breed predispositions, the medical investigation should always include a problem-solving method. The DAMNIT system of disease diagnosis (Box 62-1) is but one of several pathogenetic methods used in disease diagnosis. The final diagnosis should always explain all of the problems on the problem list, including breed identity. If the final diagnosis is inconsistent with the problem list or breed, the diagnosis may be incorrect, or there may be more than one diagnosis.

Tables 62-1 to 62-6 outline the breed-related diseases of the primary GI tract. Disorders are outlined for each of the segments of the GI tract, for example, oropharynx, esophagus, stomach, small intestine, large intestine, and anorectum, but it is important to bear in mind that one disease process may affect several segments of the GI tract, particularly those that are contiguous. References for each of these disorders may be found in the literature citations.[1-138]

LIVER AND BILIARY TRACT

Penny Watson

The diseases of the liver and biliary tract described in this book (Chapter 61) can be found in both purebred and crossbred animals. A number of these diseases have an increased incidence in certain breeds. In some cases, the inheritance patterns and genetic loci are well understood. In most cases, however, increased breed prevalence is simply an observation in published studies and the underlying genetic basis has not yet been determined. Some breed-related disorders appear to be worldwide in their distribution, whereas others occur only in certain countries or regions, either as a result of different breed genetics in different countries or simply increased recognition in those countries.

The recognition of increased breed prevalence of any disease is important as it helps increase diagnosis in the breed, although it is important to remember that not all cases will be "typical." For example, not all Bedlington Terriers with increased serum liver enzyme activities will have copper storage disease. Breed recognition is important for the dog or cat breeder as it should ultimately permit development of a genetic test to breed the disease out of the population. Breed recognition is also important for the clinical researcher as it allows focused investigation into the genetic underpinning of these diseases.

It is important to establish clear evidence for increased breed prevalence in liver, biliary, pancreatic, or GI disease. It is all too easy for erroneous data on proposed breed-related disease to become established fact once they are published. Lobular dissecting hepatitis in Standard Poodles is an example where published reports resulted in book chapters and reviews reporting this disease as a breed-related association, even though the original report suggested it may be infectious and not inherited. To ensure that there really is an increased prevalence, and not just a bias introduced by the researcher or local conditions, the prevalence of disease in that breed should be compared to a standard control population such as the normal hospital caseload, Kennel Club, or Cat Fancy registrations in that region, pet insurance, or similar database. Box 62-2 outlines potential reasons for a falsely increased breed prevalence.

Canine Hepatitis

Canine hepatitis can be classified as acute or chronic and some cases of acute disease progress to chronic hepatitis.[1] The majority of acute hepatitis cases are infectious or toxic, but a proportion of cases of copper storage disease in dogs present acutely. Copper storage disease can also be a cause of chronic hepatitis although most other cases of chronic disease are idiopathic. The majority of breed relationships reported are for copper storage disease and chronic hepatitis, and these two conditions are considered separately.

Canine Copper Storage Disease

Pertinent Breeds

Hepatitis associated with copper storage disease in dogs can be acute, subacute, or chronic, although it is often characterized as *chronic hepatitis*. The breeds affected with copper storage disease are

Table 62-1 Breed-Related Diseases of the Oropharynx

Disease	Breed	References
Cleft palate	English Bulldog, Great Pyrenees, Foxhound, Beagles, Brittany Spaniels, Australian Shepherd dogs	1-5
Cricopharyngeal achalasia	Golden Retriever	6,7
Cricopharyngeal dysphagia	Golden Retriever	8
Eosinophilic granuloma	Siberian Husky, Cavalier King Charles Spaniel	9-12
Gingival neoplasia	Boxer, Cocker Spaniel	12,13
Oropharyngeal neoplasia	German Shepherd, Cocker Spaniel, German Shorthaired Pointer, Golden Retriever, Weimaraner	12,13
Oropharyngeal dysphagia	Bouvier des Flandres	14
Salivary gland necrosis	Jack Russell Terrier	15-17
Sialocele	German Shepherd, Miniature Poodle	18

Table 62-2 Breed-Related Diseases of the Esophagus

Disease	Breed	References
Esophageal dysmotility	Terrier breeds	19
Esophageal neoplasia	Irish Setter, Beagle, Pointer Breeds	20-24
Hiatal hernia	Chinese Shar-Pei, English Bulldog, French Bulldog	25-28
Megaesophagus	Abyssinian cat, Siamese cat, German Shepherd, Golden Retriever, Greyhound, Irish Setter, Miniature Schnauzer, Wirehaired Fox Terrier	29-39
Persistent right aortic arch	Boxer, English Bulldog, German Shepherd, Irish Setter	40-42

Table 62-3 Breed-Related Diseases of the Stomach

Disease	Breed	References
Chronic hypertrophic pyloric gastropathy	Lhasa Apso, Shih Tsu, brachycephalic breeds	43-45
Eosinophilic granuloma	Scottish Terrier	46
Gastric neoplasia	Belgian Shepherd, Chow, Collie, Staffordshire Bull Terrier, Dutch Tervueren, Lundehund	22, 47-56
Gastric dilation/volvulus	Greyhound, Irish Wolfhound, Blood Hound, Grand Bleu De Gascogne, German Longhaired Pointer, Neapolitan Mastiff, Otterhound, Irish Setter, Weimaraner, Akita, Newfoundland, large and giant breeds, Saint Bernard, Standard Poodle, Great Danes	57-66
Gastroparesis	Siamese cat	67
Hemorrhagic gastroenteritis	Newfoundland, Rottweiler	68
Hypertrophic gastritis	Basenji, Drentse Partrijshond	69-73
Pyloric stenosis	Boston Terrier, brachycephalic breeds	74,75

Box 62-1 DAMNIT System for Disease Diagnosis in Dogs and Cats

D Degenerative, developmental, drug-induced
A Anatomic, allergic, autoimmune
M Metabolic, mechanical
N Neoplastic, nutritional
I Inflammatory, infectious
T Traumatic, toxic

Box 62-2 Reasons for a "False" Impression of Increased Breed Prevalence of a Disease

- Congenital lesions—congenital, e.g., infectious, nutritional, but not inherited diseases affecting several or all dogs in a litter
- Selection bias:
  - Investigators actively recruiting cases in one breed to their research center
  - Local breeder breeding increased numbers of affected dogs which are then sent on to the local referral center
  - Purebred dogs may be more likely to be referred or investigated than crossbred dogs
  - Some breed health coordinators may be more likely to alert the veterinary profession to a perceived problem in their breed than others (some breed societies may even actively discourage reporting of the problem)

Table 62-4 Breed-Related Diseases of the Small Intestine

Disease	Breed	References
Bacterial overgrowth	Beagle, German Shepherd	76-79
Cobalamin malabsorption	Border Collie, Chinese Shar-Pei, Giant Schnauzer	80-83
Eosinophilic enteropathy	Rottweiler	84
Gluten enteropathy	Irish Setter	85-90
Lymphangiectasia	Basenji, Lundehund, Yorkshire Terrier	91-94
Lymphocytic, plasmacytic enteritis	Basenji, German Shepherd	95-102
Immunoproliferative enteropathy	Basenji	103
Inflammatory bowel disease	German Shepherd, Chinese Shar-Pei	95-102
Intestinal neoplasia	Siamese cat	104-106
Parvoviral enteritis	Rottweiler, Doberman Pinscher	107
Protein-losing enteropathy	Norwegian Elkhound, Soft-Coated Wheaten Terrier, Rottweiler, Yorkshire Terrier	108-116

Table 62-5 Breed-Related Diseases of the Large Intestine

Disease	Breed	References
Colonic neoplasia	Mixed breeds	117-119
Colonic perforation	Dachshund	120,121
Constipation	Boxer, Manx cat, Siamese cat, English Bulldog	122,123
Histiocytic ulcerative colitis	Boxer	124-128

Table 62-6 Breed-Related Diseases of the Anorectum

Disease	Breed	References
Anal sac adenocarcinoma	Domestic short hair, Cocker Spaniel	129-131
Circumanal neoplasia	Boxer, Fox Terrier, Cocker Spaniel	132
Fecal incontinence	English Bulldog, Manx cat	133-134
Perianal fistulas	German Shepherd, Irish Wolfhound	135-138

listed in Table 62-7 along with evidence of heritability. Some of these same breeds are affected by a separate idiopathic chronic hepatitis not associated with copper storage disease (Table 62-8) and there are geographical variations in the relative proportions of each of these diseases (Tables 62-7 and 62-8). Consequently, liver biopsies and copper determinations are very important for effective diagnosis and treatment of hepatitis in these breeds. Bedlington Terriers are the original, and best understood, example of canine copper storage disease, but other breeds have been more recently reported. Copper storage disease has only been reported in a small number of cats (Table 62-7).

Disease Association

Copper storage disease in dogs affects the liver and not other organs, unlike Wilson's disease in humans, which affects other parts of the body such as the eyes and basal ganglia. In one feline case report, copper was found in the epithelium of the proximal convoluted tubules and collecting ducts of the kidney, and alveolar epithelium and macrophages in the lung.[2]

Evidence of Heritability

Heritability of copper storage disease has been reported extensively in the Bedlington Terrier and to a lesser extent in the Labrador Retriever and West Highland White Terrier breeds (see Table 62-7). Evidence in other breeds is restricted to isolated case reports (see Table 62-7).

Definitive Diagnosis

In the normal liver, copper is excreted in the bile. Consequently, it can build up in the periportal area (zone 1) secondary to cholestasis. It is important to differentiate this "secondary" copper retention from "primary" copper storage disease where the degree of pathology is directly related to the amount of copper found in the centroacinar area (zone 3). Any breed of dog will show evidence of copper-associated hepatotoxicity if there is a large excess of copper in the diet. What is accepted as a "normal" hepatic copper concentration has increased over the last 30 to 40 years. Increasing reports of copper storage disease in dogs may represent an interaction between genetic susceptibility and dietary copper content. Diagnosis can only be definitively obtained with liver biopsy. Ideally, a large sample (at least 1 g of tissue) should be submitted for copper determination, and histopathology should be performed with a copper stain (rubeanic acid or rhodanine) to show copper distribution in the liver and its association with pathology. If measurement of copper content is not possible, a semiquantitative estimate of copper content can be made with histologic scoring as described by Hoffman and others.[3] A genetic screening test is now available for copper storage disease in Bedlington Terriers, but there are inconsistent results in some cases, as detailed in Table 62-7.

Therapy

Copper storage disease can be successfully managed with diet and chelating agents (see Chapter 43), particularly if diagnosed early, or, better still, it can be prevented in susceptible individuals by feeding a low-copper diet from weaning. Chapters 32, 43, and 61 describe the details of therapy.

Idiopathic Canine Chronic Hepatitis

Pertinent Breeds

Chronic hepatitis is the most common liver disease recognized in dogs, with a reported prevalence of 12% in older dogs in the United Kingdom.[4] The current prevalence in the United States is unknown. In those cases not associated with copper storage disease, the cause remains unknown. It can occur in any breed or crossbreed, but there

Table 62-7 Breed Relationships in Copper Storage Disease in Dogs and Cats

Breed	Countries Reported	Strength of Evidence for Copper Storage Disease*	Evidence of Heritability
Dogs			
Bedlington Terrier	USA,[13] UK,[14] Australia,[15] Holland[1,16]–probably worldwide	Good–copper is centrilobular in distribution; copper concentrations in liver are clearly increased and degree of copper accumulation correlates with severity of clinical signs.	Inheritance pattern is simple autosomal recessive.[17] Genetic studies initially identified a microsatellite marker[18] and subsequently the genetic defect was proposed to be causative–a deletion in the MURR1 (COMMD1) gene.[19] A genetic test is available at the Animal Health Trust in the UK (http://www.aht.org.uk/genetics_toxicosis.html). However, recent cases have been described that do *not* have the COMMD1 deletion so there appears to be more than one genetic defect predisposing to copper storage disease in Bedlington Terriers.[20,21]
Dalmatian	Only USA[22-24] and Canada[25] to date	Good–as Bedlingtons. The mean hepatic copper concentration for 9 Dalmatians was 3197 µg/g dry weight liver (dwl) (normal, <450 µg/g).[22]	None. Suspected to be inherited because of breed relationship.
Labrador Retriever	USA[26] and Holland[1,3]; seems uncommon in UK where most Labrador hepatitis cases are idiopathic and not associated with copper[27]	Good–as Bedlingtons. However, only a proportion of Labrador Retrievers with hepatitis have copper storage disease. The remainder have idiopathic chronic hepatitis (see Table 62-8)	Hoffman and others reported increased mean copper concentration in unaffected relatives of affected dogs suggesting a heritable disease; (mean hepatic copper concentrations in related Labradors 1317 µg/g dwl (range: 402 to 2576 µg/g). Mean hepatic copper concentration of unrelated normal Labradors 233 µg/g dwl (range: 120 to 304 µg/g). No breeding or genetic studies yet reported.
Doberman Pinschers	Holland[28] and probably USA.[29,30] Two types of chronic hepatitis proposed in the breed–one copper associated and the other possibly autoimmune	Dogs with proposed copper storage disease have increased hepatic copper concentrations. Chelation reduces copper concentration and histologic lesions.[31] However, the role of copper in chronic hepatitis in Dobermans has long been debated. It is likely there are at least two different diseases in the breed.	None. Suspected to be inherited because of breed relationship.
West Highland White Terriers (WHWT)	Copper storage disease in the breed only reported in the USA[32] and Holland[1] to date, although chronic hepatitis in WHWT also reported in Sweden.[7]	Only a proportion of WHWT with chronic hepatitis have copper storage disease; in those, the copper is classically distributed centrilobularly and the concentration is >2000 parts/million on a dry weight basis.[33] Other WHWT have idiopathic chronic hepatitis with no increase in copper accumulation (see Table 62-8).	Breeding studies show that affected dogs produced affected puppies.[32] No further genetic studies have been performed.
Skye Terriers	UK only to date[34,35]	Unsettled pathogenesis. Copper builds up to high concentrations in zone 3 but is not present at initiation of disease. It has been proposed that the primary defect is in membrane transport systems of zone 3 and that copper retention is secondary. Excess copper (801 to 2257 µg/g) was related to the severity of cholestasis.[34]	The original report was of 9 related dogs, suggesting a possible inherited basis.[33] Only one subsequent case report has been published in a single dog[34] and there no further studies on an inheritance pattern.

Continued

Table 62-7 Breed Relationships in Copper Storage Disease in Dogs and Cats—cont'd

Breed	Countries Reported	Strength of Evidence for Copper Storage Disease*	Evidence of Heritability
Cats			
Siamese cat	Only one individual cat in USA.[2]	Good–acute disease + other organs affected. The liver copper value was 4074 µg/g dry weight, whereas normal hepatic copper levels in cats are 148 to 180 µg/g dry weight.[2]	None.
European Shorthair cat	Only one individual cat in Holland.[36]	Good–disease was chronic and severe, no report of other organs affected. Copper was largely centrilobular and the liver copper content was elevated at 4170 µg/g dry weight. Normal controls ranged from 26 to 174 µg/g dry weight	None.

*See text. The question is: Is there clearly increased copper content in the liver and is pathology associated with amount of copper buildup, ideally with copper accumulating in zone 3?

Table 62-8 Breed Associations in Canine Idiopathic Chronic Hepatitis

Breed	Countries Reported	Any Proposed Mechanism of Disease in Breed (see Table 62-4 for Potential Causes)	Evidence of Heritability
Doberman Pinschers	USA,[37] Scandinavia,[7,38] UK[8]	Role of copper is strongly debated (see Table 62-7). A separate form of chronic hepatitis is postulated to be autoimmune based on marked female predominance and increased expression of major histocompatibility complex class II.[38]	The only evidence is increased prevalence in the breed.[7,8] No breeding or other studies have been reported.
Labrador Retrievers	USA,[37] Sweden,[7] UK,[8] and Holland[1]; most Labradors reported with hepatitis in the UK do not have copper storage disease,[27] whereas many in the USA and Holland do have copper storage disease (see Table 62-7)	A proportion have copper storage disease (see Table 62-7). In those without significant copper accumulation, cause is unknown.	The only evidence is increased prevalence in the breed.[7,8] No breeding or other studies have been reported for idiopathic chronic hepatitis in the breed, only copper storage disease (see Table 62-7).
West Highland White Terrier	USA,[33] Holland,[1] and Sweden[7]	A proportion have copper storage disease (see Table 62-7). Most have no significant copper accumulation and cause of the hepatitis is unknown.	The only evidence is increased prevalence in the breed.[7] No breeding or other studies have been reported for idiopathic chronic hepatitis in the breed.
English Cocker Spaniel	Sweden,[7] Holland,[1] UK[8]	Unknown. Early reports of accumulation of abnormal α_1-antitrypsin in liver of affected dogs[39] but blood concentrations in affected dogs were not reduced, so significance of this finding remains unknown.	The only evidence is increased prevalence in the breed.[1,7,8] No breeding or other studies have been reported.
American Cocker Spaniel	Sweden,[7] Holland[1]	Unknown	The only evidence is increased prevalence in the breed.[1,7] No breeding or other studies have been reported.
English Springer Spaniel	UK, Norway,[40] and Australia (personal communication); no reports yet in the USA	Unknown. Hypothesized to be "toxic/metabolic" or the result of an infectious agent because of histologic appearance.[40]	The only evidence is increased prevalence in the breed.[8,40] Initial pedigree analysis of UK dogs failed to reveal a clear inheritance pattern, but did identify show lines were more affected than field lines.[41]

Other breeds recently also identified in the UK as at increased risk of idiopathic chronic hepatitis in one study were Cairn Terriers, Great Danes, and Samoyeds.[8] Causes and inheritance patterns unknown. For lobular dissecting hepatitis in Standard Poodles and other breeds, see text.

Table 62-9 Potential Reasons for Genetic Susceptibility to Chronic Hepatitis in Dogs

Genetic Reason for Susceptibility	Examples in Humans	Evidence in Dogs
Susceptibility to infectious causes of chronic hepatitis and/or to chronicity of infection rather than recovery	Reported nonresponsiveness to hepatitis B vaccine and tendency to chronic carrier state and chronic hepatitis in certain human leukocyte antigen (HLA) alleles[42]	None for hepatitis; some for other diseases, e.g., increased parvovirus susceptibility reported in certain breeds[43]
Susceptibility to autoimmune disease	Strong genetic predisposition to autoimmune hepatitis in certain HLA classes[44]	None for hepatitis; some suspected for other autoimmune diseases[45]
Mutation of gene coding for protein involved in metal transport/storage/excretion	Wilson's disease (copper storage disease); also iron storage disease	Copper storage disease in Bedlington terriers; possibly also other breeds (see Table 62-7 for details)
Gene mutations resulting in hepatic accumulation of glycoprotein protease inhibitor	α_1-Antitrypsin deficiency	No examples; reported α_1-antitrypsin abnormalities in Cocker Spaniels are not true deficiency (see Table 62-8 for details)
Increased susceptibility to chronic hepatic injury with toxic causes	Genetic susceptibility to alcoholic cirrhosis[46]	No clear examples but Dobermans reportedly have impaired detoxification of potentiated sulphonamides[47]

Adapted from Watson PJ: Chronic hepatitis in dogs: a review of current understanding of the aetiology, progression, and treatment. *Vet J* 167: 228-241, 2004.

are reports of increased prevalence in certain breeds as outlined in Table 62-8. These increased prevalences provide opportunities for research in to the cause(s) of this disease, and the causes are likely to be different in different breeds. Table 62-9 outlines the potential reasons for increased breed associations in canine chronic hepatitis, and Table 62-8 details any evidence or suggestions of causes reported in breeds in the literature.

Lobular dissecting hepatitis is a histologically distinct form of chronic hepatitis reported predominantly in young dogs, particularly Standard Poodles, Rottweilers, and Mastinos.[5,6] This has led to the suggestion of a breed-related disease in Standard Poodles. However, the original authors suggested an infectious rather than inherited etiology[6] and the occurrence in litters could be because of environmental rather than inherited factors. Of course, both could interact (an inherited predisposition to an environmental trigger) but the absence of any prevalence data[1,7,8] argues more strongly for an environmental cause. Lobular dissecting hepatitis has been reported anecdotally by breeders with increased prevalence in Finnish Spitz dogs in the United Kingdom (personal communication) but no studies have yet confirmed this.

Evidence of Heritability

Most of the published breed prevalence data come from a study performed in Sweden in 1991[7] that reviewed 299 cases of histopathologically confirmed chronic hepatitis between 1984 and 1989 and compared them with a control population of Swedish Kennel Club registrations. This study found Labrador Retrievers, American Cocker Spaniels, English Cocker Spaniels, West Highland White Terriers, Scottish Terriers, and Dobermans at increased risk of disease. A recent study in the United Kingdom[8] that reviewed 4,551 cases of histologically confirmed chronic hepatitis in dogs between 2001 and 2008 compared with a control population of dogs registered by a UK microchip company (175,442 dogs in 2001 and 311,085 dogs in 2008) found overrepresentation of Labrador Retrievers, American and English Cocker Spaniels, Dalmatians, and Dobermans. In addition, English Springer Spaniels, Cairn Terriers, Great Danes, and Samoyeds were significantly overrepresented with idiopathic chronic hepatitis in the UK compared with the control population. A clinical study in Holland of 101 dogs with hepatitis identified a significantly different breed distribution involving English and American Cocker Spaniels, Labrador and Golden Retrievers, West Highland White Terriers, Jack Russell Terriers, and German Pointers.[1] The latter study did not separate acute and chronic hepatitis and copper storage disease.

Definitive Diagnosis

Definitive diagnosis of canine chronic hepatitis can only be made on the basis of hepatic histopathology as outlined in Chapters 29 and 61. Finding elevated serum liver enzyme activity and compatible signs on hepatic ultrasound is not sufficient to make a diagnosis, as these findings are very nonspecific and do not differentiate primary chronic hepatitis from other liver pathologies.

Therapy

Chapters 40, 43, 46, and 61 detail treatment for canine chronic hepatitis.

Canine Vacuolar Hepatopathies

Vacuolar hepatopathy is generally considered to be a reversible secondary disease characterized by hydropic degeneration of hepatocytes or accumulation of fat or glycogen within these cells (see Chapters 29 and 61).[9] These are recognized in a wide variety of breeds and for a variety of reasons,[10] but one specific canine breed relationship is currently recognized. There is no reported breed predilection for feline hepatic lipidosis.

Pertinent Breeds

Scottish Terriers in the United States have been diagnosed with a specific type of vacuolar hepatopathy associated with elevated serum alkaline phosphatase activity.[10a,10b]

Disease Association

The cause of vacuolar hepatopathy in Scottish Terriers is unknown. They do not have overt hyperadrenocorticism but it has been suggested that they may suffer from adrenal dysfunction.

Table 62-10 Breed Relationships in Biliary Tract Disease and Gallbladder Mucocele

Disease: Canine or Feline	Breeds Involved	Evidence of Heritability
Feline lymphocytic cholangitis	Purebred cats appear to be overrepresented.[48]	None except apparent increased prevalence in studies.
Feline polycystic disease of liver	Recognized as part of polycystic disease in Persian cats[49,50] and also probably Exotic Shorthair cats. Polycystic kidney disease (PCKD) has been reported in these breeds worldwide, including USA, UK, Australia, Italy, France, and Slovenia.	Much evidence for polycystic renal disease (PCKD), which appears to be linked to polycystic hepatic lesions. Persians have an autosomal dominant PCKD[51] that was found in 27.5% of Persian and Exotic Shorthair cats tested in one study in the UK and proposed to be the most common inherited disease in cats,[52,53] although other genetic forms of the disease are also suspected.
Canine polycystic disease of liver	Much less common than cats but reports in Cairn Terriers,[54] West Highland White Terriers,[55] and Golden Retrievers (where it was proposed to be equivalent to Caroli disease in humans).[56]	Evidence in Cairns: one case report of 3 related puppies.[54]Evidence in West Highland White Terriers from one case report of 7 dogs born from the same parents (2 matings) but none of other relatives suggested autosomal recessive.[55] Evidence in Golden Retrievers: one case report of 2 siblings.[56] Other large case series fail to show any clear breed prevalence.[57,58]
Canine gallbladder mucocele	Reported to have increased prevalence in Shetland Sheepdogs in the USA,[59] and possibly Cocker Spaniels and Miniature Schnauzers.	High numbers of Shetland Sheepdogs in one published case series.[59] Recent study demonstrated a mutation in the gene coding for a phosphatidylcholine transporter was strongly associated with mucocele in Shetland sheepdogs and also 3 dogs of other breeds. Another recent study suggests hyperadrenocorticism is a strong risk factor,[60] so some genetic predisposition may be to the underlying cause and not the mucocele itself.

Evidence of Heritability

The only evidence of heritability in the Scottish Terrier is a report of increased prevalence in the breed.

Definitive Diagnosis

Definitive diagnosis is based on liver biopsy as described in Chapter 61.

Canine and Feline Biliary Tract Diseases

Acute and chronic cholangitis can affect both cats and dogs, but are more common in cats where breed predilections have been suggested for lymphocytic cholangitis. Gallbladder mucocele is recognized in dogs with some suggested breed predispositions but is very rare in cats, where there is no recognized breed disposition. Cystic lesions in the liver in cats are usually biliary in origin and part of an inherited polycystic disease in a number of organs, particularly the kidney. Table 62-10 provides details of known breed relationships in canine and feline biliary tract disease.

Canine and Feline Congenital Hepatic Vascular Defects

The most common congenital vascular defect is the congenital portosystemic shunt (PSS) which is usually a single vessel and may be either intra- or extrahepatic in location. Microvascular dysplasia and portal vein hypoplasia are less commonly reported congenital defects. The latter two conditions may represent similar abnormalities in the development of intrahepatic smaller portal vein branches during embryonic development. Portal vein hypoplasia, noncirrhotic portal hypertension, and idiopathic juvenile hepatic fibrosis may be synonymous. Microvascular dysplasia and/or portal vein hypoplasia can coexist with a single congenital PSS in the same dog (described in greater detail in Chapter 61). It is very possible that all of these vascular defects represent a continuum of developmental abnormalities and that the final defect results from the interaction between genetic predisposition and uterine environment in that individual.

Congenital Portosystemic Shunt

Pertinent Breeds

There are well-recognized breed associations for congenital PSSs in dogs. It has long been recognized that large-breed dogs develop intrahepatic PSS primarily and small-breed dogs develop extrahepatic PSS primarily. It is also known that purebred dogs are at greater risk than crossbred dogs for congenital PSS. Some limited breeding and genetic studies have been undertaken, the details of which are outlined in Table 62-11. It is also important to note that not all breeds will have "typical" anatomic shunts and that there are some exceptions, which means that the anatomy of the PSS needs to be confirmed in each case prior to surgery. Hunt et al.[11] reported that PSS found in breeds not at risk for PSS were significantly more likely to be unusual or inoperable compared with those in dogs from breeds at risk.

Congenital PSS is less common in cats than dogs, and intra- and extrahepatic PSS is found in approximately equal proportions in cats.[12] There may be some breed predispositions to PSS in cats, but these are less-well investigated than predisposition in dogs (see Table 62-11).

Evidence of Heritability

Table 62-11 outlines the evidence of heritability for congenital PSS.

Table 62-11 Breed Relationships in Canine Congenital Hepatic Vascular Abnormalities

Type of Congenital Vascular Abnormality	Breeds Involved	Evidence of Heritability
Canine congenital portosystemic shunt (PSS)	Large-breed dogs tend to develop intrahepatic PSS and small breed dogs develop extrahepatic PSS.[11,61] Irish Wolfhounds usually (but not always[62]) have patent ductus arteriosus.[11] Cairn Terriers, Yorkshire Terriers, West Highland White Terriers, Maltese, Havanese, other Terriers, and Miniature Schnauzers were reported to have increased risk in a large study of PSS in the USA.[61] Maltese, Silky Terrier, Australian Cattle Dog, Bichon Frise, Shih Tzu, Miniature Schnauzer, Border Collie, Jack Russell Terrier, and Irish Wolfhound are reported to be at increased risk of intra- and extrahepatic PSS.[11]	Evidence in most breeds is confined to increased prevalence in published studies. Pedigree analysis and breeding studies in Holland in Irish Wolfhounds with PSS are supportive of a familial disorder that is likely genetic and suggests a digenic, triallelic trait.[63,64] A breeding study in Cairn Terriers with PSS in Holland suggests an autosomal inheritance that is most likely polygenic, or monogenic with variable expression.[65]
Feline congenital portosystemic shunt (both intra- and extrahepatic)	Purebred cats are overrepresented, but any breeds, including mixed breeds, can be affected.[11,12,66,67] In one study in Australia, Himalayan cats were overrepresented.[11] There is no reported association between breed and shunt types (unlike in dogs) although in one study in the UK, 6 of 13 cats with an intrahepatic PSS were Siamese.[12]	No evidence apart from increased prevalence in published studies.
Canine microvascular dysplasia	Increased prevalence reported in small-breed dogs, particularly Yorkshire Terriers[68] and Cairn Terriers.[69]	Pedigree analysis in a family of affected Cairn Terriers suggested an autosomal inheritance pattern.[69] Evidence in other breeds confined to increased prevalence in published studies.
Canine noncirrhotic portal hypertension/portal vein hypoplasia	Increased prevalence suggested in large breeds in some studies, particularly in Dobermans.[70,71] A Dutch study reported portal vein hypoplasia in a variety of small and large breeds, including 6 related English Cocker Spaniels.[72] It is also likely that an early report of idiopathic hepatic fibrosis in young German Shepherd dogs was a similar condition.[73]	Evidence limited to small published cases series. Three of 4 Dobermans reported in one study were littermates.[70] Six of 6 English Cocker Spaniels in another study were from the same breeding colony.[72]

Microvascular Dysplasia and Portal Vein Hypoplasia

Table 62-11 summarizes breed relationships and evidence for heritability of these conditions.

PANCREAS

Elias Westermarck

Exocrine Pancreatic Insufficiency in Dogs

Canine exocrine pancreatic insufficiency (EPI) is a disease characterized by inadequate synthesis and secretion of digestive enzymes by pancreatic acinar cells. This is almost without exception the result of pancreatic acinar atrophy (PAA), and the abbreviations EPI and PAA are often used synonymously in the literature.[1] Affected dogs show typical clinical signs, including polyphagia, weight loss, yellowish poorly digested loose feces, increased fecal volume, and defecation frequency.[2] In German Shepherd dogs and Rough-Coated Collies, the disorder has been shown to be an autoimmune disease.[3] Although EPI may occur at any age, signs of maldigestion appear before the age of 4 years in most dogs (93%).[2] Cavalier King Charles Spaniels have been reported to be at an older age at the time of diagnosis (mean 6 years), and it has been suggested that a different pathogenesis may be involved in this breed.[4] Male and female dogs are usually equally affected,[1,5,6] although a stronger association between EPI and female gender has been reported.[4] A number of tests have been developed to aid in the diagnosis of EPI. Serum canine trypsin-like immunoreactivity has been reported to be 100% sensitive and specific in the diagnosis of canine EPI.[7] When clinical signs of maldigestion appear, enzyme replacement therapy is almost always indicated. Various pancreatic enzyme extracts are available and the highest enzyme activity in the duodenum has been obtained with noncoated enteric supplements, for example, raw chopped pancreas and lyophilized enzyme powder.[8] Lifelong enzyme treatment is usually needed, and the response to treatment is variable. In 50% to 60% of dogs, GI signs are almost always completely controlled, but in approximately 20% of dogs a variable to poor response is obtained.[9-11]

The earliest reports of EPI in dogs provided no indication of breed predisposition.[12-15] Since the 1960s, however, almost all reports assert that the disease is found more frequently in German Shepherd dogs than in other breeds (Table 62-12). Hence, EPI has been postulated to be a hereditary disease in this breed.[1,16-18] Freudiger reported that the morbidity of EPI is 8% in German Shepherd dogs and only 0.3% in all other breeds.[18] The incidence of EPI in German Shepherd dogs in Finland has been estimated as approximately 1%.[1] In other studies, the incidence in German Shepherd dogs as compared with all clinically diagnosed EPI dogs has varied

Table 62-12 Breed-Related Diseases of the Exocrine pancreas

Disease	Breed	References
Exocrine pancreatic insufficiency	German Shepherd, Rough-Coated Collie, Cavalier King Charles Spaniel, Chow	1-22,24,25
Acute pancreatitis	Miniature Schnauzer, Yorkshire Terrier, Cocker Spaniel	26,27
Chronic pancreatitis	Cavalier King Charles Spaniel, Collie, Boxer, Cocker Spaniel	27
Pancreatic carcinoma	Airedale Terrier	28

between 50% and 70%.[1,4] In the United Kingdom, a retrospective study of more than 1000 dogs with EPI revealed that German Shepherd dogs, Rough-Coated Collies, Cavalier King Charles Spaniels, and Chows are at risk for the development of EPI.[4] To date, genealogic studies have only been performed in German Shepherd dogs and Rough-Coated Collies.

In 1977, the first inheritance study of EPI in German Shepherd dogs was conducted by Weber and Freudiger.[19] They analyzed a pedigree comprising 19 German Shepherd dogs with EPI and 33 unaffected German Shepherd dogs. All 19 affected dogs were found to have a common ancestor born in 1918. Eighteen of the dogs were inbred more than once with a descendant of this common progenitor. On the basis of the degree of inbreeding within this pedigree, Weber and Freudiger hypothesized that EPI was an autosomal recessive trait.

Westermarck studied the hereditary nature of EPI in two kindreds, which included 59 German Shepherd dogs.[20] The male progenitors were the same in both kindreds. In the four litters of the first kindred, the incidence of EPI was 24%, and there was at least one affected dog in each litter. In the second kindred, when an EPI-affected bitch and a clinically healthy male (suspected carrier) were mated, two of the resultant six offspring were found to suffer from EPI. The results of the study indicated that EPI is a disease inherited as an autosomal recessive trait, although the possibility of dominant inheritance with incomplete penetrance could not be excluded.

Moeller et al.[21] assessed the heritability of EPI in German Shepherd dogs in the United States. The study included two pedigrees consisting of 135 dogs. Of 102 dogs that were tested, 19 were definitively diagnosed with EPI. The first family consisted of 59 dogs, and nine (18.8%) of the 48 tested dogs were affected. The second family consisted of 76 dogs, and 10 (18.5%) of the 54 tested dogs were affected. Several litters from parents of which at least one parent was affected had unaffected individuals. Conversely, there were several litters with affected individuals from unaffected parents. This provides evidence that the putative trait for EPI is recessive, although the rate of affected dogs is slightly lower than would be expected (25%) for a simple autosomal recessive inheritance. The study concluded that EPI is inherited as an autosomal recessive trait in German Shepherd dogs in the United States. The same pedigree material was used in a study to identify the gene and the mutation causative for EPI.[22] Five genes of interest were found, and these were further assessed by quantitative real-time reverse-transcription polymerase chain reaction. One gene, *gp25L*, was downregulated by more than 500-fold in affected pancreas and was further investigated as a candidate gene. Sequence data did not reveal a mutation in the coding sequence that segregates with EPI.

The preliminary results of a test mating between two German Shepherd dogs with EPI revealed that only two of the six offspring were affected.[23] The dogs were studied for 11 years, and pancreatic biopsies were obtained four to six times from each dog during their lifetimes. This study showed that EPI is not a single-gene disease but likely a polygenic disease, where environmental factors may also have a role. Only one survey has examined the role of different environmental factors, including feeding, housing, and training, in the development of EPI in dogs.[2] This study failed to identify any common factors in the histories of the dogs with EPI. Such factors as stress and viruses are difficult to evaluate, however, and require further research.

Besides German Shepherd dogs, EPI has also often been diagnosed in Rough-Coated Collies in Finland. Of all dog breeds diagnosed with clinical EPI, approximately 20% of the cases have been reported in Rough-Coated Collies. The Smooth-Coated Collies appears to be unaffected. The prevalence of EPI in the Rough-Coated Collies breed is estimated to be approximately 1%.[1] In a study including 51 Rough-Coated Collies with EPI, 44 could be placed in one composite pedigree.[24] An affected dog in that pedigree had, on average, 17 affected relatives distributed over 11 different litters. Thus clustering strongly suggested that EPI is a hereditary disease in Rough-Coated Collies. The pedigree data indicated that EPI could be an autosomal recessive trait, although the estimated proportion of affected offspring within litters (0.13) was lower than the expected mendelian frequency (0.25).

Pancreatitis in Dogs

The high prevalence of acute pancreatitis in the Miniature Schnauzer suggests a possible hereditary component; however, no pedigree studies have been published, and a recent study failed to identify any mutations in the cationic trypsinogen gene in this breed.[25] The Yorkshire Terrier breed has been reported to be at increased risk for acute pancreatitis, and the Labrador Retriever has been reported to be at reduced risk.[26] In another study, the Cavalier King Charles Spaniel, Collie, and Boxer breeds were reported to be at increased for chronic pancreatitis.[27] The Cocker Spaniel breed was found to be at increased risk for both acute and chronic pancreatitis (see Table 62-12).[27]

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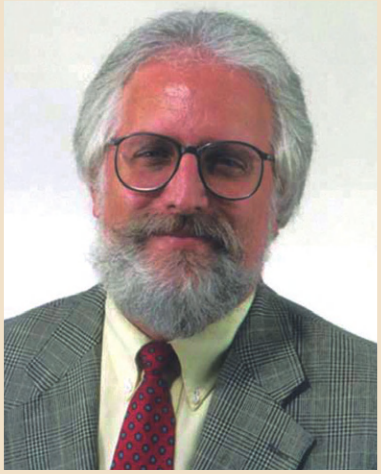

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I dedicate this work to my parents, Brady and Anna Washabau; my wife, Rosalie Stoner Kreider; and my children, Ethan and Noah Washabau, all of whom gave me inspiration, insight, and abiding love.

Robert Washabau

I dedicate this work to my children, Christopher and Natalie Day.

Michael Day

Preface

Profile

The book was planned as a comprehensive reference standard for the discipline of canine and feline gastroenterology. It has an international focus, including 85 authors from 17 different countries, reflecting the latest in clinical practice and research. The content covers the breadth and depth of gastroenterology from biology to pathobiology, diagnosis, and treatment of disease of the gastrointestinal (GI), pancreatic, and hepatobiliary systems. An initial basic overview of the GI system in health provides up-to-date information on microflora, immunology, cellular growth, and systems integration as a foundation for understanding and treating clinical problems. Disease coverage spans the digestive system from the oral cavity to the esophagus, stomach, small and large intestine, anorectum, liver and biliary tract, exocrine pancreas, peritoneum, and associated vasculature. Our focus on patient management examines the full range of procedures and techniques essential to diagnosis and treatment—from clinical signs and diagnosis to nutritional support, and pharmacologic management of disease. A stand-alone section on pharmacologic approach to GI disease also serves as an easy drug reference. Clear explanations of current diagnostic modalities include laboratory tests, molecular methods, diagnostic imaging, endoscopy, and histopathology, showing how to interpret and utilize results. Practitioners will appreciate the emphasis on need-to-know information for managing the common and not-so-common GI clinical problems of every day practice. Problem-based algorithms are included for diagnosing every GI clinical problem from A to Z. The text is supplemented by full-color photographs and illustrations that depict concepts, conditions, and procedures. An evidence-based medicine perspective reflects the latest research as well as the modern practice of veterinary medicine. Logical, coherent, and consistent internal organization makes this a reader-friendly edition, and a necessary and essential reference standard for veterinary students, practitioners (clinicians, clinical pathologists, and histopathologists), educators, and biomedical researchers.

Format

The book contains 62 chapters organized into six sections. Each section provides a unique perspective on the function and dysfunction of the digestive system.

Section I: Biology of the Gastrointestinal Tract

The book opens with a proposed model for understanding the complexities of the digestive system. The components of this system—food intake, motility, secretion, digestion, absorption, blood flow, and defecation—and their regulation are described in some detail, including the neural, endocrine, and paracrine regulatory elements that coordinate and integrate these functions. The first three chapters (physiology, GI microflora, and immunology) highlight the digestive system in health, whereas the last two chapters (inflammation and cellular growth) highlight the digestive system in disease. The practitioner who masters the basic precepts of Section I will have a firm foundation upon which to move on to clinical problem-solving (Sections II to VI).

Section II: Approach to Clinical Signs in Gastrointestinal Disease

This section contains 19 chapters describing the history, physical examination findings, laboratory data, imaging findings, pathophysiology, differential diagnosis, treatment, and management of the major digestive system clinical presentations including abdominal pain, anorexia, ascites, coagulopathy, constipation, diarrhea, dyschezia, dysphagia, fecal incontinence, gas, hemorrhage, hepatoencephalopathy, icterus, polyphagia, polyuria, polydipsia, regurgitation, salivation, vomiting, and weight loss. This section illustrates the use of clinical algorithms in problem-solving GI clinical signs.

Section III: Diagnostic Approach to Gastrointestinal Disease

This section contains five comprehensive chapters on laboratory testing, diagnostic imaging, endoscopy, laparoscopy, and histopathology, all provided by international experts in the field.

Laboratory Testing

This chapter reviews laboratory tests (hematology; serum chemistry; serum enzymology; serology; serotyping; PCR, RT-PCR, fluorescence in situ hybridization; fecal parasitology; fecal microbiology; cytology; and GI, pancreatic, and liver function) and how to interpret test results.

Diagnostic Imaging

This chapter illustrates the use of imaging technology in the diagnosis of GI pathology, including those techniques used in every-day practice (e.g., survey and contrast radiography, ultrasonography) and those used more often in secondary and tertiary referral centers (e.g., scintigraphy, CT, MRI, and PET-CT). Each chapter outlines the indications and contra-indications for each of the imaging modalities. Each of the chapters includes multiple examples of normal (e.g., size, shape, volume, density) and abnormal conditions.

Endoscopy

The chapter on endoscopy contains an introduction to basic endoscopic equipment, care and cleaning, indications for endoscopy, patient preparation, specific procedures (esophagus, stomach, intestine, colon), interventional procedures, and complications.

Laparoscopy

As with endoscopy, this chapter contains an introduction to basic laparoscopic equipment, care and cleaning, indications for

laparoscopy, patient preparation, and specific procedures (liver, biliary tract, pancreas).

Histopathology

The histology and histopathology of the stomach, intestine, colon, pancreas, liver, and biliary tract are summarized in great detail in this chapter. Internationally recognized scholars from the WSAVA Gastrointestinal and Liver Standardization groups were recruited to write these chapters.

Section IV: Nutritional Approach to Gastrointestinal Disease

This section opens with a chapter on the nutritional assessment and management of the GI patient, including mechanisms of malnutrition and obesity, followed by chapters on pathophysiology of adverse food reactions, nutritional strategies for adjunct therapy, and advances in enteral and parenteral nutrition.

Section V: Pharmacologic Approach to Gastrointestinal Disease

This section has a comprehensive discussion of drug therapies used in the treatment of GI disease, including drug classifications and mechanisms of action, commonly used examples within drug classifications, formulations and doses, rational use in the diagnosed and undiagnosed patient, and contra-indications and side effects. Specific pharmacologic therapies described in this chapter include anti-diarrheal agents, anti-emetic agents, anti-fungal agents, anti-helmintic agents, anti-inflammatory agents, anti-microbial agents, anti-oxidant agents, anti-spasmodic agents, behavioral modification, chelating agents, chemotherapy, cytoprotective agents (gastric), cytoprotective agents (hepatobiliary), enzyme supplementation, fluid therapy, immunosuppressive drugs, laxative agents, probiotic agents, prokinetic agents, and vitamins and minerals.

Section VI: Diseases of the Gastrointestinal Tract

Each of the chapters of this Section opens with structure and function, followed by diagnostic evaluation, and finally diseases of that part of the digestive system. Mechanisms of disease included in each of these chapters cover inflammation, infection, obstruction, dysmotility, neoplasia, ulceration, metabolic, congenital/genetic, and vascular disorders. Each of the diseases is discussed in a standard format, including etiology, pathophysiology, clinical examination, diagnosis, treatment, and prognosis.

Intended Audiences

The book has several intended audiences—practicing veterinarians (clinicians, clinical pathologists, and histopathologists), veterinary students, residents in training, and biomedical researchers—and was tailored accordingly.

General and specialty practice veterinarians, particularly those wanting to practice at a high level of expertise and confidence, will uniquely benefit from this book, and were seen as our first intended audience. The utilization of an evidence-based medicine approach to reflect the latest science and research, complemented by principles of problem-solving, algorithms to improve clinical diagnoses, and extensive full-color illustrations should make this a required reference on the bookshelf of every serious practitioner. Residents in training will also find this to be a very useful resource in their study of the discipline and in preparation for general and specialty certification examinations. The book should also become a major reference source for clinical pathologists and histopathologists. Chapters are devoted to full explanation of current and future laboratory diagnostic tests, and the histology and histopathology of each region of the alimentary tract are described in individual chapters that present a library of supportive histopathological images.

Veterinary students are our second intended audience. We aimed to produce a high-quality reference standard for the discipline that would be used by students as a supplement to their studies of physiology, pharmacology, biochemistry, and pathology in the pre-clinical years of the veterinary curriculum, and as a primary reference in their studies of GI medicine and surgery in the clinical years of the curriculum. Foundation material on GI immunology, microflora, inflammation, cellular growth, and systems integration, for example, should serve to more readily bridge the student from basic to clinical concepts.

Biomedical researchers are seen as our third intended audience. The biomedical researcher will appreciate the extensive literature citation; scientific rigor; emphasis on the histologic, immunologic, and molecular basis of disease; summary of breed-related diseases; and, relevance to animal models of human disease.

Acknowledgments

I wish to acknowledge three Veterinary School Deans (Drs. Bob Marshak, Ed Andrews, and Alan Kelly) at the University of Pennsylvania who, during the formative years of my training, emphasized the importance of science and discovery thereby setting a standard to emulate in veterinary medicine.

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Dr. Ken Bovée was an outstanding mentor to me during my internship, graduate training, and early faculty years at the University of Pennsylvania. Ken epitomized the role of the *sempai* in a mentor-protégé relationship, and he helped me to understand the importance of focus and resilience.

Dr. Bruce Blazar, physician-scientist and principal investigator of the NIH Clinical and Translational Science Award (NIH CTSA) at the University of Minnesota, was an early advocate of the Comparative Medicine program who supported us in the development of spontaneous animal models of human disease, in gastroenterology especially, as well as in other disciplines.

Great textbooks require great publishing firms, editors, and editorial staff. With Elsevier, we were blessed with all three. I would particularly like to thank (in alphabetic order) Celeste Clingan, Kate Dobson, Brandi Graham, Lauren Harms, Whitney Noble, Penny Rudolph, and Tony Winkel, all of whom contributed time, expertise, and hard work to the production of this book.

The book was a grand undertaking with the recruitment of an extensive international authorship. Our task could not have been accomplished without the engagement of an elite group of Section Editors: Marge Chandler (Nutrition), Jörg Steiner (Diagnostic Techniques), Rebecca Syring (Therapy), David Twedt (Biology), and Michael Willard (Clinical Problem-Solving). Effusive thanks to all.

In addition to the dedication, I wish to further acknowledge Rosalie Stoner Kreider: wife, mother of our children, attorney-at-law, university professor, and guiding light. I couldn't have accomplished any of it without her.

Robert Washabau

My interest in small companion animal gastroenterology has been sparked and fostered by two colleagues and friends with whom I have been privileged to work over the past 20 years. Professor Ed Hall first introduced me to the complexities of canine chronic enteropathy and Professor Tim Gruffydd-Jones to the equivalent feline disorders. Together, we have unraveled some of the incredible immunopathology of the alimentary tract of the dog and cat in a perfect clinicopathological partnership. We have been fortunate to have worked with a series of talented postgraduate students, postdoctoral fellows and visiting scientists including Drs Alex German, Iain Peters, Andrea Lynch, Eshan Esfandiari, Jurgen Zentek, Nashwa Waly and Ross Harley.

From 2004 to 2008 it was a pleasure to work with Robert Washabau and colleagues on the WSAVA Gastrointestinal Standardization Group. The outcomes from this very worthwhile project repeatedly appear throughout the pages of this book. It was therefore an honour and pleasure to accept Robert's invitation to join him as co-editor of *Canine and Feline Gastroenterology* in what has proven to be a further example of the benefit of clinical and pathological collaboration. The book has had a long gestation, but the finished product should serve as a standard reference for clinicians and pathologists alike.

I can only re-iterate Robert's acknowledgments to our ever-patient Section Editors and the Elsevier production team. It has been a pleasure working with all of you.

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