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To the many pets I have known and loved, for they have enriched my life immeasurably.

To my students and professional peers, who have challenged and inspired me to continue to ask questions and seek answers.

To my family, for their encouragement and enduring love.

PREFACE

The importance of dermatology in veterinary medicine is readily apparent: one out of every four patients in a typical small animal practice is seen for a skin disorder. As the largest and most visible organ of the body, the skin reflects the internal health of the animal in addition to influences from the environment and genetically determined reaction patterns unique to the skin. An understanding of small animal dermatology is fundamental to building a successful veterinary practice.

The unique question-and-answer format of the *Secrets* series of books promotes understanding of subject material. As veterinarians, we are constantly asking questions and applying the answers to guide us in solving our patients' problems. As humans, we have been programmed from infancy to learn by asking questions. The Socratic method of teaching through questioning helps us to maintain an inquiring, probing mind and is highly effective in self-assessment and learning. The contributors to this book share my excitement in presenting *Small Animal Dermatology Secrets* to you in this Socratic format.

Dermatology is a rapidly growing specialty. The American College of Veterinary Dermatology has increased from 24 diplomates in 1982 to more than 150 in 2003 With this increase in "critical mass" of specialists has come increased knowledge of the pathogenesis of dermatologic diseases, as well as the recognition of many new diseases. The overriding objective of this book is to provide practitioners and students with concise and up-to-date information regarding small animal dermatology. The question-and-answer format will foster self-assessment of the reader's understanding of each topic. Additionally, the contributors have shared many "practice tips" that readers can apply to improve their management of dermatology patients.

Dermatology is a visual specialty, and therefore we are excited to bring this *Secrets* book to you with more than 270 color illustrations. The book is divided into nine sections: general principles of dermatology, dermatologic therapy, inherited disorders, parasitic skin diseases, infectious skin diseases, inflammatory skin diseases, endocrine and metabolic disorders with cutaneous manifestations, miscellaneous dermatoses, and tumors of the skin.

I am indebted to the contributing authors—professional colleagues who have taken time from busy schedules to prepare their chapters and share excellent illustrative materials. A special thanks also to William Lamsback, who initiated this project, and to Jolynn Gower, John Casey, Liz Fathman and numerous others at Elsevier who brought it to completion.

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Section I
General

1. STRUCTURE AND FUNCTION OF THE SKIN

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1. **Name the three layers of the skin. List the principal components of each layer** (Figure 1-1)**.**
   - Epidermis—includes keratinocytes, melanocytes, Langerhans cells, Merkel's cells, and intracellular lipids.
   - Dermis—composed of collagen fibers, elastin fibers, ground substance; adnexal structures including hair follicles, sebaceous glands, and apocrine sweat glands; and cutaneous blood vessels, lymphatics, and nerves.
   - Subcutaneous layer of adipose fat tissue, blood vessels, and nerves (also known as the subcutis or panniculus).

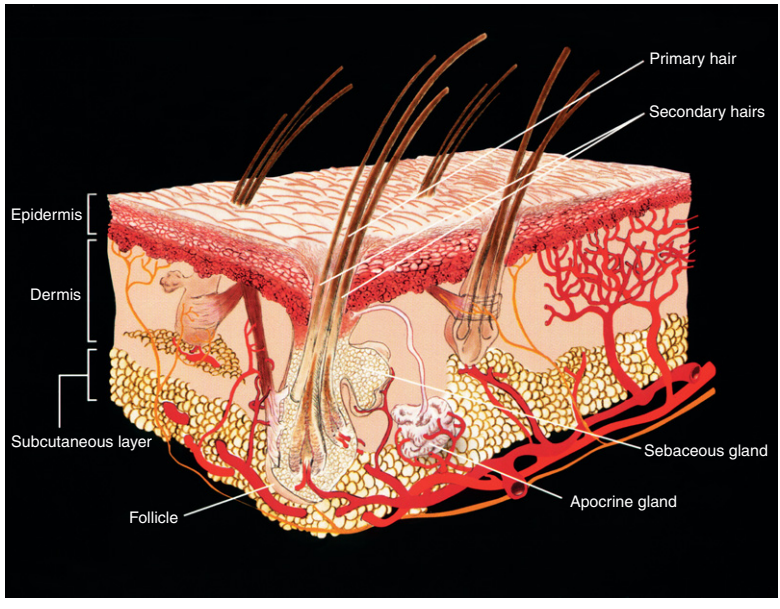

Figure 1-1 Structure of canine skin. (Courtesy DVM Pharmaceuticals, Miami.)

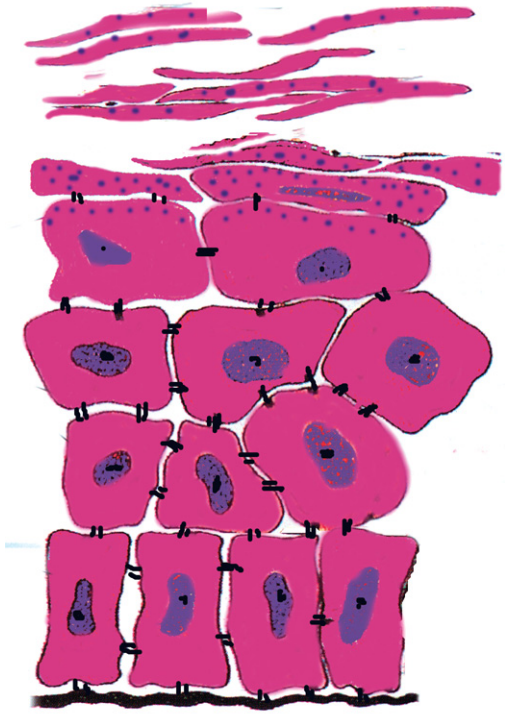

Figure 1-2 Schematic of canine epidermis. Note that the stratum spinosum is shown as being three layers thick, the stratum basale and stratum granulosum each consist of a single cell layer, and the cells of the stratum corneum are exfoliating from the skin surface.

2. **Cells of the epidermis are divided into layers based on their degree of differentiation. List the layers of the epidermis and the characteristics of each of these layers** (Figure 1-2)**.**
   - Stratum basale (basal cell layer): these are the germinative cells of the epidermis; they are in direct contact with the basement membrane. Melanocytes, Merkel's cells, and Langerhans cells are also present in the stratum basale.
   - Stratum spinosum (prickle cell layer): the high concentration of desmosomes and keratin filaments gives this layer a "spiny" appearance when the cells are fixed in formalin. An occasional Langerhans cell may also be found in this layer.
   - Stratum granulosum (granular layer): cells in this layer have changed from cuboidal to flattened and contain numerous keratohyalin granules in their cytoplasm.
   - Stratum lucidum (clear layer): this is a fully keratinized hyaline-like layer containing refractile droplets and a semifluid substance called eleidin rich in protein-bound lipids; in dogs and cats this layer is only found in the footpads and nasal planum.
   - Stratum corneum (horny layer): this is the fully keratinized outer layer of the epidermis; in normal skin, these cells are anuclear, flattened, eosinophilic cells (corneocytes) that are constantly being shed into the environment.

3. **What is the cell renewal time (CRT) for the viable epidermis (also referred to as epidermal turnover time)? List factors influencing the CRT of the skin.**

   The CRT is the time it takes for a cell to move from the stratum basale to the stratum granulosum. It is approximately 22 days for normal canine skin.

CRT is influenced by many factors including:
- epidermal growth factor
- epidermal chalone (inhibitor of proliferation)
- arachidonic acid and its metabolites (leukotrienes, prostaglandins, thromboxanes, hydroxyeicosatetraenoic acids)
- calcium ions
- cyclic nucleotides
- glucocorticoids
- ultraviolet light
- vitamins (1,25-dihydroxyvitamin D_3, vitamin A, retinoids)

Minor trauma such as clipping of the hair coat can shorten the CRT to 15 days.

The CRT in disorders of keratinization (e.g., primary seborrhea in Cocker Spaniels) may be as short as 7 days.

4. List the barrier functions of the skin.
- Prevent loss of water.
- Prevent loss of electrolytes.
- Prevent loss of cells.
- Protect from environmental insults.
- Protect from environmental toxins.
- Protect from ultraviolet light.

5. What is transepidermal water loss (TEWL) and how does this affect the hydration of the skin? What factors control TEWL and the barrier function of the skin?

TEWL is the amount of water vapor evaporating from the surface of the skin. In healthy skin, TEWL is directly proportional to skin hydration. Many skin diseases have inverse ratios of TEWL and skin hydration (i.e., increased TEWL with decreased skin hydration, as is seen in atopic dermatitis and disorders of keratinization.) The barrier function of the skin has been compared to a wall made up of bricks and mortar. The keratinized cells of the stratum corneum are the "bricks" and the intracellular lipids are the "mortar."

6. What are the principal components of epidermal lipids in dogs?
- Sphingolipids rich in linoleic acid
- Diester waxes
- Ceramides
- Hydroxyceramides
- Cholesterol
- Cholesterol esters
- Sterol esters
- Free fatty acids

7. What is the role of the skin in temperature regulation?
- Hair coat provides important insulation.
- Arrector pili muscles control piloerection; piloerection increases the insulating properties of the hair coat.
- Cutaneous circulation is not as important in regulation of body temperature in dogs and cats as in pigs and humans due to the absence of extensive arteriovenous shunts within the dermis of canine and feline skin.
- The epitrichial (apocrine) sweat glands of dogs and cats are not directly innervated and are not thought to be important in thermoregulation.
- Subcutaneous fat is an efficient insulator.

8. Describe the antimicrobial functions of the skin, including components protecting the animal from cutaneous infections.

Many factors are involved in protecting animals from cutaneous infections; these include:
- Physical barrier (shedding of stratum corneum)

- Dryness of the stratum corneum
- Fatty acids ("lipid seal," disrupt the cell wall of some microbes)
- Inorganic salts (secreted in sweat)
- Immunoglobulins and complement (secreted in sweat and in serum)
- Cutaneous pH
- Cutaneous immune system (Langerhans cells, keratinocytes, lymphocytes)
- Resident microflora (compete for nutrients, secrete antimicrobial metabolites including antibiotics, acetic acid, propionic acid, ammonia, and lipases)

9. In the past, the skin has been referred to as having "an acid mantle." Is this true for dogs and cats? What are the factors contributing to the pH of the skin?

Human skin has an average pH of 4.8, however the reported average pH of the skin of dogs is 7.4 and of cats is 6.4. Canine skin tends to have the highest pH of any mammalian species. Factors contributing to the cutaneous pH include:

- Filaggrin breakdown products (urocanic acid, pyrrolidine, carboxylic acid)
- Amino acids (from sweat, sebum, keratinocytes)
- Fatty acids (from sebum, keratinocytes)
- Alpha-hydroxy acids (e.g., lactic acid, from sweat, cutaneous microbes)
- Carbon dioxide
- Bicarbonate (from sweat)

10. Differentiate between bacterial residents, nomads, transients, and pathogens of the skin.

- Bacterial residents are organisms living and multiplying on normal skin.
- Bacterial nomads are organisms that can colonize and reproduce on the skin for short periods.
- Bacterial transients are organisms that are contaminants from the environment and do not reproduce on the skin.
- Bacterial pathogens are organisms that become established and proliferate on the skin surface and deeper, causing cutaneous inflammation. They are deleterious to the normal physiology of the skin.

11. What are the functions of the Langerhans cells of the skin?

- Langerhans cells are bone marrow–derived dendritic cells which function in antigen presentation in association with MCH II and thus are of importance in immune surveillance.
- Langerhans cells have Fc-IgG and C3 receptors and also high affinity receptors for IgE.

12. What are the functions of Merkel's cells in the skin? Where are these cells located?

- Merkel's cells are slow-adapting mechanoreceptors.
- Merkel's cells may also have roles in controlling hair follicle activity, cutaneous blood flow, sweat production, and keratinocyte proliferation.
- Merkel's cells are located in the stratum basale, in tylotrich pads, and in hair follicle epithelium.

13. What is the origin of the melanocytes in the skin? What is an epidermal melanin unit?

- Epidermal melanocytes originate in the neural crest and migrate to the skin during embryogenesis.
- Each epidermal melanocyte transfers pigment-containing melanosomes to a finite number of neighboring keratinocytes (typically 20-36). An epidermal melanin unit is a melanocyte plus its associated keratinocytes.

14. What is the distribution of melanocytes in the body?

- Stratum basale of the skin
- Retinal pigment epithelium
- Leptomeninges
- Mucous membranes

- Uveal tract
- Stria vascularis of the ear
- Hair matrix

Melanocytes are found in each of the above locations; together, these are termed the melanin pigmentary system.

15. List the different types of melanins and the hair coat color associated with each.

- Eumelanin—dark brown to black (metabolites of tyrosine)
- Pheomelanin—reddish (rich in sulfur-containing pigments)
- Oxymelanins—yellow to reddish-brown (do not contain sulfur, properties are similar to bleached eumelanin)
- Trichromes—reddish (rich in sulfur, different synthesis pathway from that of pheomelanin)

16. List the functions of melanins of the skin.

- Photoprotection
- Scavenging free radicals
- Coloration

17. Define constitutive pigmentation and facultative pigmentation. What hormones affect pigmentation?

- Constitutive pigmentation is genetically determined.
- Facultative pigmentation is influenced by stimuli (ultraviolet radiation, inflammation, cytokines, hormones, etc.).
- Hormones affecting pigmentation include α-MSH and β-lipotropin from the pituitary gland.

18. Describe the structure of the basement membrane zone (BMZ).

The BMZ is an extremely complex structure with many components functioning to anchor the basal cell layer to the dermis. Uppermost in the BMZ are cytoplasmic tonofilaments of the basal cells, which attach to the basal plasma membrane of the cells at the hemidesmosome. The hemidesmosome is attached to the lamina lucida and the lamina densa of the BMZ via anchoring filaments. The BMZ is anchored to the dermis by anchoring filaments that intercalate between collagen fibers of the dermis. Hemidesmosomes contain plaque proteins including BP230 and plectin (BP is a target in many autoimmune blistering diseases; plectin is deficient in some forms of congenital epidermolysis bullosa). Hemidesmosomes also contain the transmembrane proteins BP180 and $\alpha_6\beta_4$-integrin, which have roles in anchoring cells to extracellular matrix. Anchoring filaments also contain BP180, $\alpha_6\beta_4$-integrin plus laminin-5 and laminin-6. Other important components of the BMZ include collagen IV, nidogen, perlecan, and collagen VII. Defects or deficiencies of any of these molecules can result in blister formation in the skin.

19. List the functions of the hair coat.

- Thermal insulation
- Sensory protection
- Barrier against chemical, microbial, and physical injury to the skin
- Coloration—camouflage, photoprotection, and sexual roles

20. What are the differences between primary hairs and secondary hairs?

Primary hairs or guard hairs are usually larger than secondary hairs and each emerges through its own hair follicle orifice (pore).

Secondary hairs form the undercoat of dogs and cats. In cats and most breeds of dogs, secondary hairs outnumber the primary hairs (ratios of 5:1 to 25:1 are common). The secondary hairs generally emerge through the same pore as a primary hair.

21. List the stages of the hair growth cycle and what occurs in each stage.

- Anagen—growing period, follicle is actively producing hair.
- Catagen—transitional period, constriction occurs at the hair bulb.
- Telogen—resting stage, the dermal papilla separates from the old "club" hair.

22. List factors influencing the hair growth cycle. Which one is most important?

- Photoperiod—this is the most important factor. In the Northern Hemisphere, the increasing photoperiod in the spring results in new hair growth, while the short days of winter are associated with minimal hair follicle activity.
- Ambient temperature.
- Nutrition—hairs are 65% to 90% protein; with protein deficiency dull, dry, brittle hairs and a thin hair coat will be seen.
- Hormones—anagen is initiated and hair growth rate is accelerated by thyroxine. Conversely, excessive amounts of glucocorticoids inhibit anagen and suppress hair growth.
- Genetics.
- Other environmental factors.
- Intrinsic factors—each hair follicle has an inherent rhythm of cyclical activity; although the length of each stage of the hair cycle can be altered by extrinsic factors, the sequence cannot be changed. Cytokines, such as epidermal growth factor, can also influence the hair cycle and hair growth rates.

23. What are the functions of the sebaceous glands?

- Sebaceous glands are holocrine glands that open through a sebaceous duct into the infundibulum of primary hair follicles.
- Sebaceous glands secrete an oily emulsion called sebum. Sebum spreads over the hair shafts and the surface of the skin, providing a glossy sheen and helping to keep the skin and hairs soft and pliable.
- Sebum contributes to the permeability barrier of the skin and helps to retain moisture in the skin.
- Sebum contributes to the chemical barrier of the skin protecting it from potential pathogens.
- Sebum may also have pheronome properties.

24. What types of sweat glands do dogs and cats have in their skin? What are their functions?

Epitrichial (also referred to as apocrine) sweat glands are located throughout the haired skin of dogs and cats. These glands are located below the sebaceous gland and open into the infundibulum of the pilary canals of primary hair follicles. Epitrichial sweat functions together with secretions of the sebaceous glands to form an antimicrobial emulsion on the surface of the skin. Epitrichial sweat contributes inorganic salts and IgA to the surface emulsion. Epitrichial sweat also has pheronome properties.

In dogs and cats, atrichial (also referred to as eccrine, although functionally closer to being merocrine) glands are only found in the footpads. These glands are located in the deep dermis and subcutis of the footpads. The ducts of atrichial glands open directly onto the surface of the footpads. Atrichial sweat is alkaline and hypertonic. It contains inorganic salts that contribute to a chemical barrier against microbial proliferation.

25. What is the cell type of canine circumanal (perianal) glands?

These glands are composed of cuboidal cells arranged in lobules resembling the lobules of the liver; thus the cells are called hepatoid cells. The function of these gland is unknown. These glands are located in the perianal region and may be found in the skin of the prepuce and on the dorsal and ventral surfaces of the tail.

26. Why are the cells of the tail glands also referred to as hepatoid cells? What are the proposed functions of these glands?

There are actually two cell types in these glands: (1) cuboidal cells forming lobules identical in appearance to the hepatoid cells of the circumanal glands and (2) sebaceous glands.

The sebaceous gland ducts open into hair follicles; the secretions from the tail gland may serve pheronome functions.

27. List the functions of cutaneous nerves.

- Sensory perception (touch, heat, cold, pressure, pain, itch)
- Modulation of inflammation, proliferation, wound healing via neuropeptide activation of target cells (keratinocytes, mast cells, endothelial cells)
- Control vasomotor tone
- Control piloerection
- Influence secretory activities of glands

28. List neuropeptides produced by cutaneous nerves.

- Substance P
- Neurokinin A
- Calcitonin gene-related peptide
- Vasoactive intestinal peptide
- Neuropeptide Y
- Somatostatin
- Pituitary adenylate cyclase activity peptide

29. List the types of mechanoreceptors found in the skin.

- Pacinian corpuscle units—these are extremely sensitive to vibrations and pressure.
- Meissner's or Ruffini corpuscles—these are sensitive to the velocity of skin movement or touch.
- Afferent units sensitive to hair movement—some are affected only by movement of guard (G) hairs or tylotrich (T) hairs, others are affected by movement of secondary hairs (D for "down" hairs), and others are activated by movement of vibrissae.
- Slow-adapting type I endings from Merkel cell complexes are activated by steady pressure.
- Slow-adapting type II units are associated with Ruffian endings and are activated by skin stretch.
- δ High-threshold mechanoreceptor units have A δ axons and respond to painful stimuli and carry signals for spontaneous itch (well-localized, prickling); these are myelinated and conduct rapidly (10-20 m/sec).
- Polymodal nociceptor units with C axons are involved with hyperalgesia and itch; these are slow-conducting (2 m/sec), unmyelinated, and transmit a diffuse burning itch sensation.

30. What are the differences between sinus hairs and tylotrich hairs? (Table 1-1)

Table 1-1 ***Sinus Hairs vs. Tylotrich Hairs***

CHARACTERISTIC	SINUS HAIRS (VIBRISSAE, WHISKERS)	TYLOTRICH HAIRS
Location	Muzzle, lip, eyelid, face, throat, palmar aspect of carpus in cats (pili caralis)	Scattered among ordinary body hairs, associated with a tylotrich pad (synonyms include: haarsheiben, touch corpuscle, touch dome, hair disk, tactile hair disk, tactile

Continued

Table 1-1 *Sinus Hairs vs. Tylotrich Hairs—Cont'd*

CHARACTERISTIC	SINUS HAIRS (VIBRISSAE, WHISKERS)	TYLOTRICH HAIRS
		pad, herediform ending, Pinkus corpuscle, Iggo dome, Iggo-Pinkus dome and Eimer's organ)
Unique features	These hairs are thick and stiff and are characterized by an endothelium-lined blood sinus located between the external root sheath of the follicle and an outer connective tissue capsule. Pacinian corpuscles are located close to the sinus hair follicle.	These hair follicles are larger than surrounding ones and contain a single stout hair. An annular complex of neurovascular tissue surrounds the follicle at the level of the sebaceous glands. These hairs are located on a tylotrich pad consisting of the hair follicle and an underlying convex area of fine highly vascularized connective tissue. Unmyelinated nerve fibers ending as flat plaques (touch plaques) in association with Merkel's cells are also located on the pad.
Function	Slow-adapting mechanoreceptors	Tylotrich hairs are rapid-adapting mechanoreceptors; the touch plaques serve as slow-adapting touch receptors

31. Give the locations of the three major vascular plexuses of the skin and the structures supplied by each.

- The superficial plexus is located immediately below the epidermis; capillary loops from this plexus supply the epidermis and the upper portions of the hair follicles.
- The middle plexus is located at the level of the sebaceous glands; it gives off branches to the arrector pili muscles, ascending branches that supply the superficial plexus, and ascending and descending branches that supply the middle portion of the hair follicles and the sebaceous glands.
- The deep plexus is found at the interface of the dermis and the subcutis. Branches from this plexus descend into the subcutis and ascend to supply the lower portions of the hair follicles and the epitrichial sweat glands; the ascending vessels continue upward to supply the middle plexus.

32. List the functions of cutaneous lymph vessels.

- Return protein, fluid (H_2O), and cells from interstitial spaces to the bloodstream.
- Remove material that has penetrated the epidermis and dermis (solvents, medications, vaccines, other antigens).
- Link the skin and regional lymph nodes and thus function in immunoregulation.

33. How is the subcutis organized?

The subcutis (subcutaneous fat, panniculus) is arranged in fat lobules divided by fibrous septae. The fibrous bands of the septae are continuous with dermal collagen on the top and with fascial sheets on the bottom. Thus these fibrous bands serve to anchor the skin to underlying muscles and periosteum. Blood vessels, nerves, and lymph vessels are also found in the septae. The fat lobules are composed of lipocytes (adipocytes or fat cells) and function as (1) an energy reserve, (2) in thermogenesis and insulation, (3) as protective padding, and (4) to maintain surface contours.

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2. THE VOCABULARY OF DERMATOLOGY

Karen L. Campbell, DVM, MS, DACVIM, DACVD
Carol A. Lichtensteiger, DVM, PhD, DACVP

1. Why do dermatologists use words that no one else understands?

Each discipline has its own unique vocabulary—whether it is a medical discipline or a technical one. Dermatologists use many terms that are rarely used in the other medical specialties. The use of the correct dermatologic terms is important to accurately describe skin lesions when talking or corresponding with other clinicians or pathologists. A good description of a skin lesion will enable others to picture the problem and formulate differential diagnoses. To complicate matters, terminology is dynamic and sometimes controversial—particularly when the terms have been "borrowed" from human medicine and human dermatopathology—there may be subtle but significant differences between the cutaneous reaction patterns of different species. You should consult with your veterinary dermatologist or pathologist if you are uncertain of the significance of a term being used.

2. Why are so many terms used?

The use of detailed terminology, including the description and distribution of lesions, assists the listener or reader in visualizing the lesions. This is important in recognizing patterns of disease and formulating differential diagnoses.

33. How is the subcutis organized?

The subcutis (subcutaneous fat, panniculus) is arranged in fat lobules divided by fibrous septae. The fibrous bands of the septae are continuous with dermal collagen on the top and with fascial sheets on the bottom. Thus these fibrous bands serve to anchor the skin to underlying muscles and periosteum. Blood vessels, nerves, and lymph vessels are also found in the septae. The fat lobules are composed of lipocytes (adipocytes or fat cells) and function as (1) an energy reserve, (2) in thermogenesis and insulation, (3) as protective padding, and (4) to maintain surface contours.

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2. Why are so many terms used?

The use of detailed terminology, including the description and distribution of lesions, assists the listener or reader in visualizing the lesions. This is important in recognizing patterns of disease and formulating differential diagnoses.

3. How can I learn to use the language of dermatology?

First learn the basic definitions of terms used in dermatology. Then follow this simple template when describing skin lesions to systematically describe different types of skin lesions.

- Level of the lesions (e.g., flat, elevated or depressed)
- Color or additional descriptive terms (e.g., pigmentation, shape, size)
- Type of primary, secondary, or special skin lesions present
- Arrangement of the lesions (e.g., linear, annular, serpiginous, grouped)
- Distribution of the lesions (e.g., localized, facial, pedal, truncal, multifocal, generalized, symmetric, or asymmetric)
- Duration of the lesions (e.g., acute or chronic)

4. Give examples of lesions that are flat, elevated, or depressed relative to the plane of the skin (Table 2-1)

Table 2-1 ***Types of Lesions Relative to Plane of Skin***

FLAT (IN THE PLANE OF THE SKIN)	ELEVATED (ABOVE THE PLANE OF THE SKIN)	DEPRESSED (BELOW THE PLANE OF THE SKIN)
Macule	Cyst	Atrophy
Patch	Lichenification	Erosion
Telangiectasia	Nodule	Excoriation
	Papule	Necrosis
	Plaque	Scar
	Pustule	Sinus
	Scales and crusts	Ulcer
	Vesicle and bullae	
	Wheal	

5. What is a primary skin lesion?

A primary lesion is the initial eruption that develops as a direct result of the disease process. It has not been altered by trauma (scratching) or natural regression over time. Examples include bullae, cysts, macules, nodules, papules, patches, plaques, pustules, vesicles, and wheals.

6. How are each of the primary lesions defined? List examples of diseases associated with each type of primary lesion (Table 2-2)

Table 2-2 ***Diseases Associated with Primary Lesions***

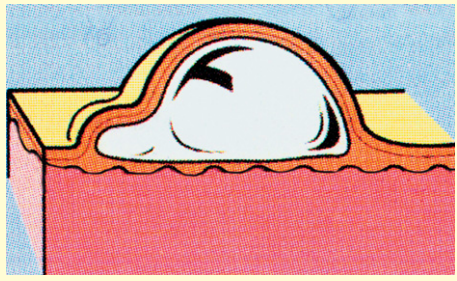
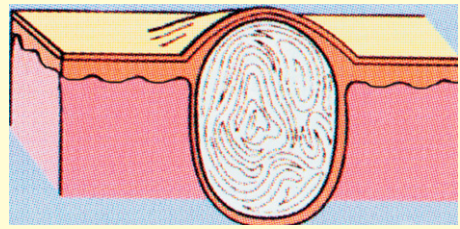
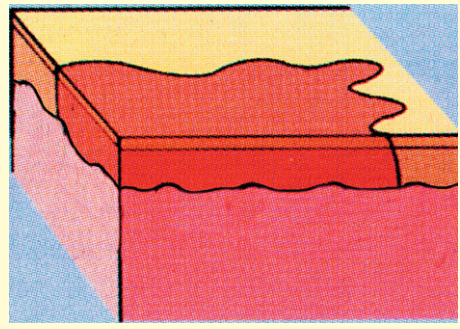
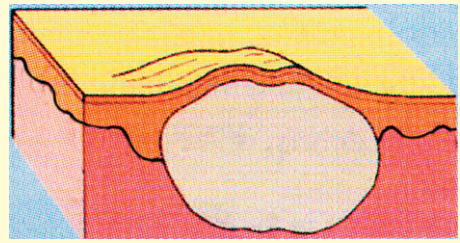
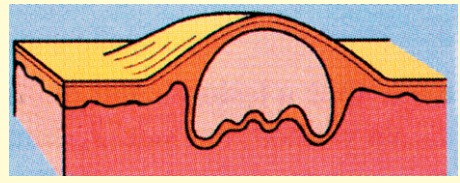
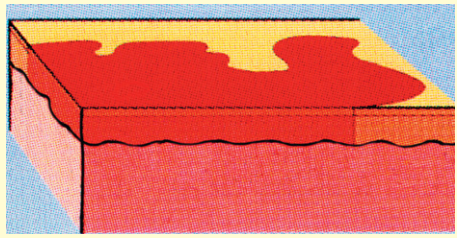
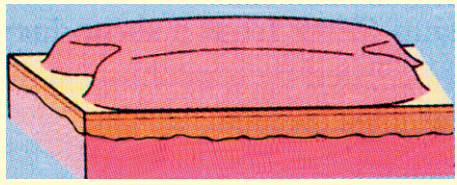
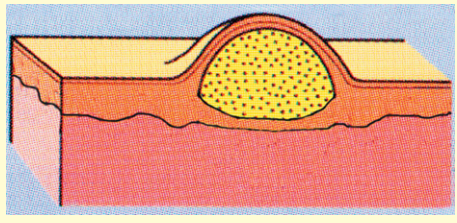
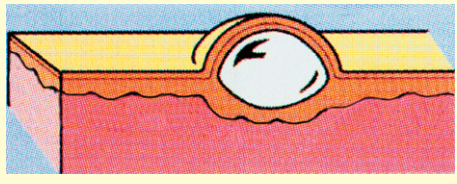
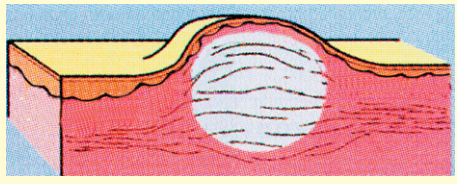
PRIMARY LESION	DEFINITION AND EXAMPLES	MORPHOLOGY
Bulla	Localized collection of fluid, >0.5 cm in diameter, larger than vesicles. Autoimmune diseases Epidermolysis bullosa	

Table 2-2 ***Diseases Associated with Primary Lesions—Cont'd***

PRIMARY LESION	DEFINITION AND EXAMPLES	MORPHOLOGY
Cyst	A nodule that contains fluid or semisolid material. Epidermal inclusion cyst Follicular cyst Acne	
Macule	Flat, circumscribed skin discoloration, <1 cm, lacks surface elevation or depression. Pigmented nevi Lentigo Purpura Petechiae Acute erythema Vitiligo	
Nodule	A circumscribed, solid elevation. Usually greater than 1 cm and usually extends into the dermis. Large nodules may be referred to as masses. Neoplasia Granulomas Deposits of collagen	
Papule	Small, solid elevation of the skin up to 1 cm in diameter, feels solid, is due to infiltration of inflammatory cells and edema and epidermal hyperplasia. Flea bites Sarcoptes Superficial bacterial Folliculitis	

Continued

Table 2-2 ***Diseases Associated with Primary Lesions—Cont'd***

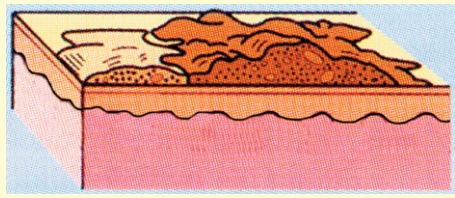
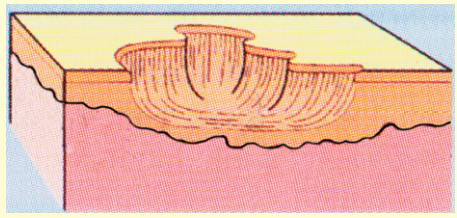
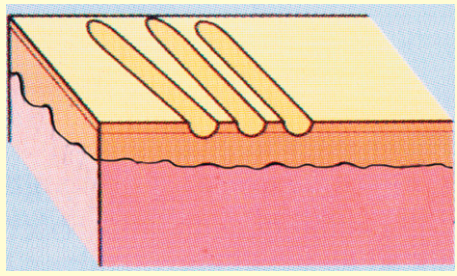
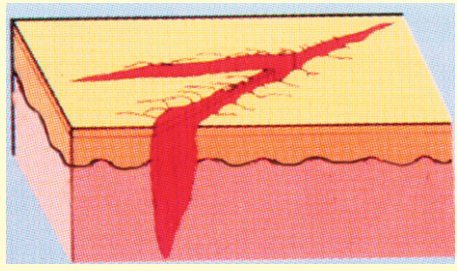
PRIMARY LESION	DEFINITION AND EXAMPLES	MORPHOLOGY
Patch	A localized flat change in skin pigmentation, larger than 1 cm in diameter. Ecchymoses Leukoderma Postinflammatory hyperpigmentation	
Plaque	A flat-topped elevation > 0.5 cm formed by coalition of papules. Eosinophilic plaques	
Pustule	A small, circumscribed elevation of the epidermis filled with purulent material. Bacterial infections Eosinophilic folliculitis (allergic, parasitic) Pemphigus foliaceus Acne Impetigo	
Vesicle	A sharply circumscribed elevated lesion that contains fluid, < 0.5 cm in diameter. Viral diseases Irritants Autoimmune diseases Epidermolysis bullosa	
Wheal	A sharply circumscribed, raised lesion consisting of edema, usually appears and disappears within minutes to hours. Urticaria Insect bites	

7. What is a secondary skin lesion?

Secondary lesions may be created by scratching, chewing or other trauma to the skin; as a result of infections; or may evolve from regressing primary lesions. Examples include crusts, erosions, excoriations, fissures, scales, scars, and ulcers.

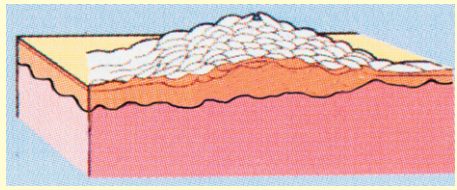
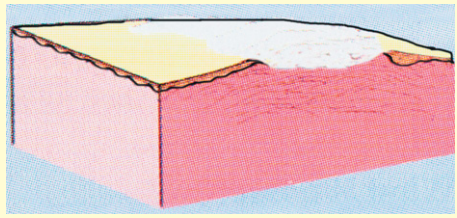
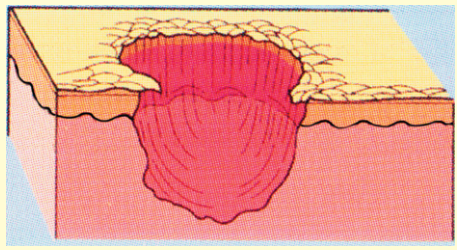
8. How are the secondary skin lesions defined? (Table 2-3)

Table 2-3 ***Characteristics of Secondary Skin Lesions***

SECONDARY LESION	DEFINITION	MORPHOLOGY
Crust	A collection of cellular debris, dried exudates of serum, inflammatory cells or blood; antecedent primary lesions include pustules, vesicles and bullae.	
Erosion	A partial focal loss of epidermis; does not penetrate the basement membrane and heals without scarring.	
Excoriation	Linear erosion induced by scratching or trauma.	
Fissure	Vertical loss of epidermis and dermis with sharply defined walls, crack in skin.	

Continued

Table 2-3 ***Characteristics of Secondary Skin Lesions—Cont'd***

SECONDARY LESION	DEFINITION	MORPHOLOGY
Scale	Thick stratum corneum that results from hyperproliferation or an increased cohesion of surface keratinocytes.	
Scar	A collection of new connective tissue (fibrosis); may be hypertrophic or atrophic (contracts with maturity); scar implies prior dermoepidermal damage.	
Ulcer	A full-thickness, focal loss of epidermis and dermis; heals with scarring.	

9. You did not mention an epidermal collarette; what is this lesion?

Epidermal collarettes are circular rings of scales; these are the "footprints" of a ruptured pustule or vesicle.

10. What is a follicular cast?

A follicular cast is an accumulation of keratin and sebaceous material adherent to a hair shaft extending above the surface of the follicular ostia. It is a primary lesion associated with vitamin A–responsive dermatoses, primary seborrhea, and sebaceous adenitis. Follicular casts are also seen as secondary lesions in dermatophytosis and demodecosis.

11. Are comedones primary or secondary lesions?

They can be either (Figure 2-1). A comedo is a dilated hair follicle filled with cornified cells, and sebaceous and sweat gland secretions. Comedones are primary lesions of feline acne, vitamin A–responsive dermatosis, Schnauzer comedo syndrome, and some idiopathic seborrheic disorders. Comedones are secondary lesions when associated with hyperadrenocorticism, topical applications of greasy medications, demodecosis, and dermatophytosis.

12. What is a maculopapular eruption?

It is a dermatitis composed of both macules and papules. Maculopapular eruptions are commonly seen with erythema multiforme.

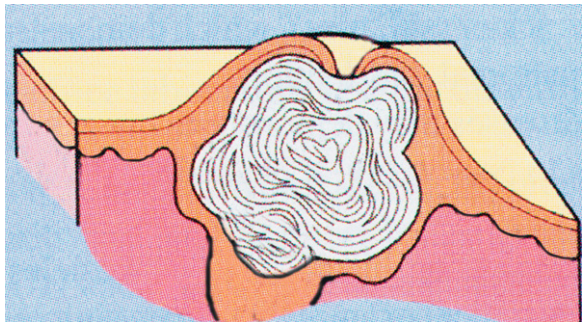


Figure 2-1 Schematic of comedo.

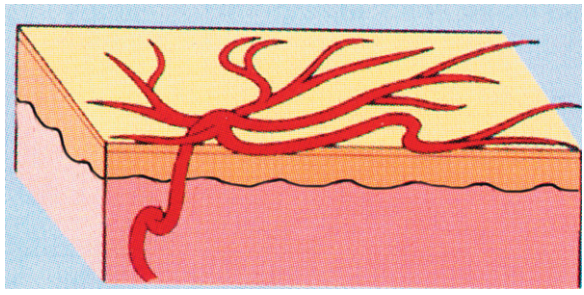


Figure 2-2 Schematic of telangiectasia.

13. What are telangiectasias?

Telangiectasias are small, dilated, superficial blood vessels (capillaries, arterioles, or venules) that blanch when pressure is applied (diascopy) (Figure 2-2). Telangiectasias occur in many cutaneous disorders. They are most commonly associated with hyperadrenocorticism, but can also be seen with dermatomyositis and cutaneous lupus erythematosus.

14. How can you differentiate between telangiectasia and petechiae? Purpura?

Telangiectasia blanches on pressure, while petechiae do not. Both petechiae and purpura are reddish lesions produced by extravasation of red blood cells (hemorrhage) into the dermis; petechiae are < 0.5 cm in diameter whereas lesions of purpura are larger.

15. What are target (iris) lesions?

Target lesions are centrally healing lesions produced when the skin heals behind an advancing disease process. The central zone is often hyperpigmented as a result of the previous inflammation. The surrounding zone may be pale and the outermost zone often appears as a rim of erythema. Target lesions are seen with bacterial folliculitis, dermatophytosis, demodicosis, and erythema multiforme.

16. What terms are used to refer to changes in pigmentation?

- Leukoderma—nonpigmented skin
- Leukotrichia (achromotrichia)—nonpigmented hair
- Aurotrichia—gold-colored hair

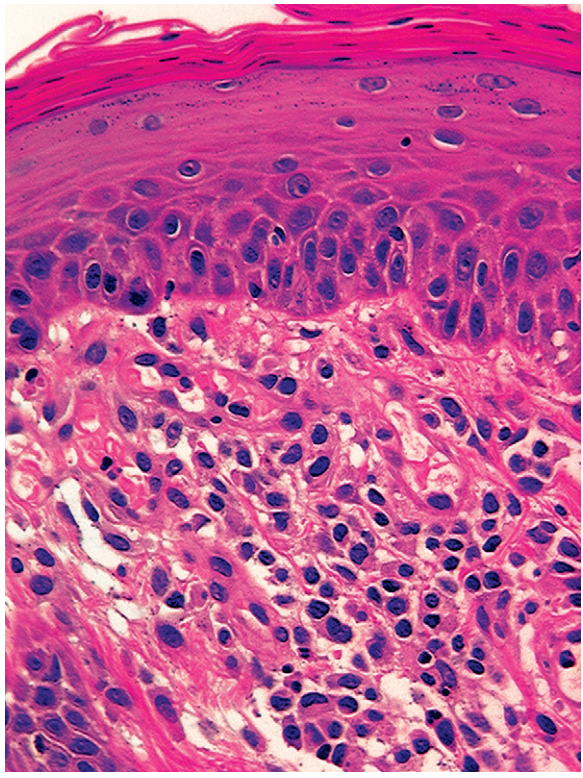


Figure 2-3 Chronic dermatitis with acanthosis. Note the rete ridge formation associated with hyperplasia of the stratum basale and stratum spinosum. Retention of nuclei (parakeratosis) is seen in the stratum corneum. Superficial dermal edema and a mononuclear perivascular infiltrate of lymphocytes and macrophages are also features of this chronic dermatitis.

- Hypopigmentation (hypomelanosis)—decreased amount of melanin, lighter than normal skin or hair color
- Hyperpigmentation (hypermelanosis, melanoderma)—darker than normal skin color, increased amount of melanin
- Melanotrichia—excess pigment in the hair

17. Differentiate between hyperkeratosis and lichenification.

Hyperkeratosis is an increase in the thickness of the stratum corneum. Lichenification refers to marked thickening of all layers of the epidermis; the lichenified areas may resemble tree bark with accentuation of skin lines. Lichenification is associated with chronic rubbing or scratching of the skin.

18. List and define the adjectives used in describing hyperkeratosis.

- Orthokeratotic—increase in anuclear cells in the stratum corneum
- Parakeratotic—retention of nuclei within cells of the stratum corneum, associated with zinc-responsive dermatosis, ectoparasitism, lethal acrodermatitis, some vitamin A–responsive dermatoses, *Malassezia* dermatitis, and other diseases (Figure 2-3)

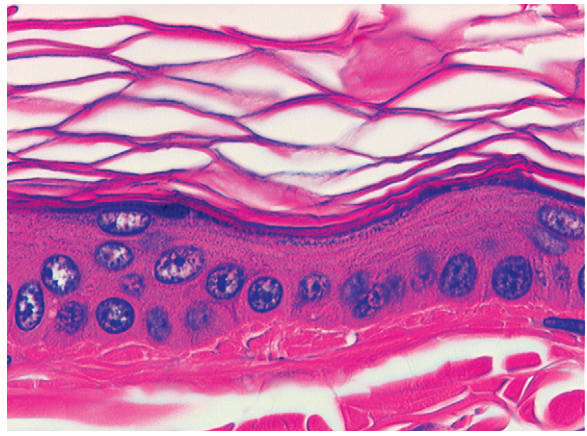


Figure 2-4 Normal canine epidermis showing basketweave keratin in the stratum corneum. Keratohyalin granules are visible in the single layer of the stratum granulosum.

- Basketweave—loosely woven cells in the stratum corneum (Figure 2-4)
- Compact—densely packed keratinocytes in the stratum corneum; associated with low-grade trauma to the skin
- Laminated—keratinocytes in the stratum corneum are layered; seen in ichthyosis

19. Differentiate between folliculitis, furunculosis, fistulas, and sinuses.

- Folliculitis—inflammation involving hair follicles. Mural folliculitis denotes targeting of the wall of the follicle. Perifolliculitis is an accumulation of inflammatory cells around the hair follicle without invasion of the follicular epithelium.
- Furunculosis—a perforating folliculitis with rupture of the hair follicle, may result in granulomatous inflammation.
- Fistulas—an abnormal passage between two organs or between a structure and a body surface; may develop from necrotizing furunculosis with a tract of purulent material leading from a ruptured hair follicle to the skin surface, or may lead from embedded foreign material to the surface of the skin.
- Sinus—a sinus is a tract leading from a suppurative cavity to the skin surface (a type of fistula).

20. What do the terms calcinosis and sclerosis refer to?

- Calcinosis is the deposition of mineral salts in the dermis. It is most commonly associated with hyperadrenocorticism (calcinosis cutis), but can also be dystrophic (dystrophic calcification), metabolic (metastatic calcification), or idiopathic (calcinosis circumscripta) in origin.
- Sclerosis is a general term indicating induration or hardening (fibrosis is a common cause).

21. What do the terms dyskeratosis and apoptosis refer to?

Dyskeratosis is a histopathologic term used to indicate abnormal keratinization of keratinocytes. Dyskeratotic cells are morphologically similar to apoptotic cells. Apoptosis refers to cells undergoing programmed cell death; this physiologic cell suicide may be triggered by the

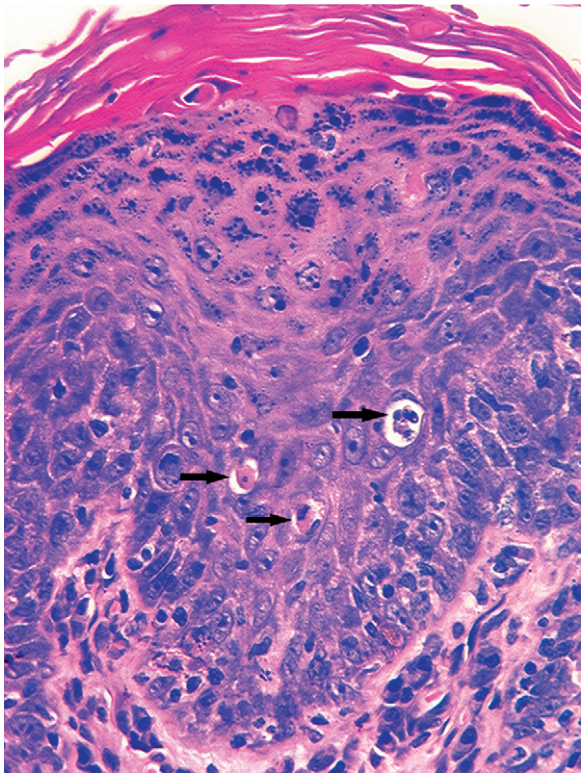


Figure 2-5 Epidermis showing apoptotic keratinocytes (*arrows*) in a dog with erythema multiforme.

immune system, cytokines, viruses, drugs, and many other mechanisms. Apoptosis is a feature of erythema multiforme, discoid lupus erythematosus, and many other diseases (Figure 2-5).

22. What are acantholytic keratinocytes?

Acantholytic keratinocytes are epidermal cells "floating free" within a vesicle or pustule. These are formed when there is a loss of cohesion between viable epidermal cells and are most often associated with the pemphigus complex of diseases but can also be seen with severe inflammation, viral diseases, bacterial, and fungal dermatoses (Figure 2-6).

23. Are acantholytic cells a sequela to acanthosis?

No. Acanthosis is hyperplasia of the stratum spinosum (increased number of keratinocytes in the spinous layer). Acantholytic cells are relatively intact keratinocytes loose in pustules; the cells were released because of damage to the desmosomes (intercellular bridges). As noted previously, the damage is usually immune mediated; however, enzymes released from neutrophils in inflammatory skin diseases can also form acantholytic cells.

24. What are Pautrier microabscesses?

Pautrier microabscesses are focal accumulations of neoplastic lymphoid cells within the epidermis and are characteristic of epitheliotropic lymphoma.

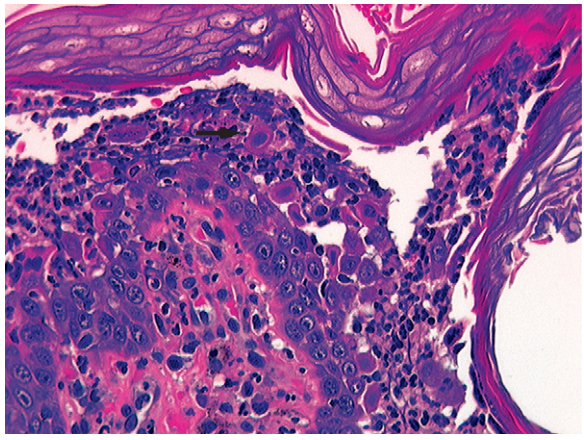


Figure 2-6 Subcorneal pustule filled with neutrophils and acantholytic keratinocytes in a dog with pemphigus foliaceus (*arrow* is pointing to an example of an acantholytic keratinocyte).

25. What is an interface dermatitis?

This is a histopathologic term used to denote an inflammatory pattern targeting and obscuring the dermoepidermal junction. There is usually hydropic degeneration of cells in the stratum basale. The inflammation may be minimal (as in SLE) or marked (as in DLE) with a lichenoid cellular infiltrate. Lichenoid cellular infiltrates are accumulations of inflammatory cells, most often lymphocytes and plasma cells, that "hug" the dermoepidermal junction in the superficial portion of the dermis and may infiltrate the stratum basale. Other common features include apoptotic keratinocytes, satellitosis (lymphocyte adjacent to an apoptotic keratinocyte), and pigmentary incontinence. Interface dermatitis is commonly seen in cutaneous adverse drug reactions, dermatomyositis, erythema multiforme, lupus erythematosus, toxic epidermal necrolysis, and may occur in other dermatoses.

26. Is it pyoderma or dermatitis?

Pyoderma is a clinical term for bacterial dermatitis. Dermatitis is a clinical and pathological term for inflammation of the skin. The prefix *pyo* in pyoderma indicates neutrophils are a major component of the inflammation; this is equivalent to suppurative dermatitis. In biopsy specimens obtained from bacterial pyoderma, neutrophils are often a component, but may not be the major leukocyte (Figure 2-7).

27. What is the difference between granulomatous and granulation?

Granulomatous refers to an inflammatory reaction in which macrophages are the predominant inflammatory cell. The reaction often includes multinucleated macrophages (giant cells) and sometimes the reaction is organized with fibrosis into nodules (granulomas). Granulation is the process of forming fibrous tissue to repair damaged tissue such as ulcerations, lacerations, and surgical incisions. New capillaries (neovascularization, angiogenesis) and reactive fibroblasts grow into fibrinous exudate in the area of tissue damage.

28. What is the difference between the subcutis, subcutaneous tissue, and panniculus?

The three terms are essentially synonymous terms for the fatty connective tissue layer deep to the dermis. This layer is composed of adipocytes, vessels, and connective tissue.

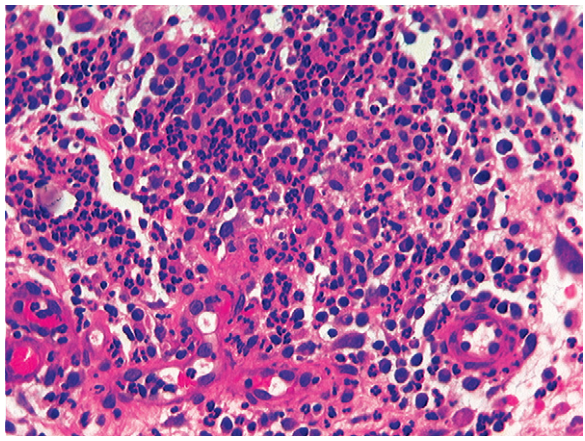


Figure 2-7 Suppurative dermatitis involving the deep dermis and panniculus of a dog. Neutrophils are the predominant inflammatory cell in suppurative dermatitis.

29. When is it panniculitis versus steatitis? Where does cellulitis fit?

Because the panniculus is adipose tissue, a panniculitis is also a steatitis (inflammation of fat). Internal systemic disease (pancreatitis or vitamin E and selenium deficiency) are differentials for causes of panniculitis, especially if there is saponification or lipofuscin. Cellulitis refers to purulent inflammation in the subcutis; the inflammation is usually extensive with copious exudate and effacement of the tissue.

30. What is the difference between special stains and immunohistochemistry (IHC) for biopsy tissues?

Special stains is a generic term for all stains applied to formalin fixed tissues other than the standard H&E (hematoxylin and eosin) protocol. Special stains include PAS or GMS for fungi, acid fast for mycobacteria, and Perl's iron for hemosiderin. IHC is a subset of special stains used to detect antigens of infectious agents (e.g. *Toxoplasma*) or of tumor markers (e.g., B versus T lymphocytes). In IHC, antibodies (immuno) for specific antigen(s) in tissue (histo) are bound and then detected by using a chromogenic substrate (chemistry) for an enzyme (usually peroxidase) that was attached as a label to the primary antibody, or more commonly, to a secondary antibody that is an antispecies antibody that detects bound primary antibody.

31. Why are so many biopsy results a "nonspecific" dermatitis?

The skin, like other tissue, has a limited repertoire of responses to injury. Although pattern analysis of histopathologic responses is quite useful, every disease does not have a specific pattern. Diseases causing perivascular dermatitis are especially numerous; other changes, clinical signs, and other assays are needed to arrive at the final diagnosis.

32. When is it hyperplasia? Neoplasia? Dysplasia?

Hyperplasia is a non-neoplastic increase in numbers of cells in a tissue; the reaction stops when the signal inducing the proliferation is removed. Neoplasia is an increase in cell numbers (increase in proliferation or decrease in natural death) of transformed cells no longer (or at least, incompletely) responsive to cell cycle control signals. Dysplasia, depending on the context, is atypical hyperplasia and potentially preneoplastic (e.g., in Bowen's disease) or is an abnormal tissue development (adnexal dysplasia) and is not preneoplastic.

33. Are hypertrophy and atrophy opposites?

Not completely. Hypertrophy is increased organ mass because of increased size of cells in the tissue, for example, reactive apocrine gland epithelium or reactive endothelial cells. If the cell numbers are also increased, a second process of hyperplasia is also present. In atrophy, organ mass is decreased because the tissue has a decrease in size of cells, loss of cells, or both.

Acknowledgment

Figures 2-1 and 2-2 and those used in questions 6 and 8 (Tables 2-2 and 2-3) were modified from Corvette DM: Morphology of primary and secondary skin lesions. In Fitzpatrick JE, Aeling JL (eds): *Dermatology secrets in color*, ed 2, Philadelphia, 2001, Hanley & Belfus, pp 8-14.

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3. DIAGNOSTIC TECHNIQUES IN DERMATOLOGY

Paul Bloom, DVM, DABVP, DACVD

1. Which diagnostic tests should a general practitioner perform when presented with a patient with a dermatologic problem?

Fortunately for veterinarians, dermatology is a low-cost, high-yield specialty. With a scalpel blade, mineral oil, microscope, hemostat, handheld magnifying lens, cytologic stain, biopsy kit, fungal culture plate, acetate tape, sterile toothbrush, cotton tip applicator sticks, and a flea comb, almost any dermatologic test may be performed. The most common tests performed include:

- Examination of the haircoat with a magnifying lens
- Flea combing
- Acetate tape prep
- Cytologies
- Trichogram
- Skin scrapings
- Wood's lamp examination
- Fungal culture for dermatophytes
- McKenzie toothbrush culture
- Bacterial culture and susceptibility testing
- Skin biopsies

2. What is a trichogram and how is it performed?

A trichogram is a microscopic examination of a plucked hair. A hemostat is used to gently pull the hair out. To get the bulb and not fracture the hair shaft, you should grasp the hair as close to the skin surface as possible. The hair is put on a microscope slide that has mineral oil on it and a cover slip applied. The hair is examined under 40X objective.

33. Are hypertrophy and atrophy opposites?

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3. What are you looking for in a trichogram and what diseases could it help you identify?

You want to examine the hair shaft and the hair bulb. A normal hair shaft should be uniform in diameter and come to a tapered end. Some of the abnormalities that may be seen are listed in Table 3-1. A trichogram is especially helpful in differentiating alopecia due to pruritus/self-trauma vs hairs that easily epilate (endocrinopathies, telogen defluxion, follicular arrest). In the former, the shafts are fractured, while in the later, the shafts are normal but all of the hairs are in telogen.

Table 3-1 ***Characteristic Trichogram Findings in Dermatologic Diseases***

DISEASE	HAIR SHAFT APPEARANCE	BULB APPEARANCE
Normal—anagen phase (active hair growth)	Uniform in diameter and has a tapered distal end (end opposite the bulb region). From outside in – the cuticle, cortex (may be pigmented depending on coat color) and medulla should be visible. Melanin, if present, is evenly distributed throughout the shaft.	Rounded, smooth, shiny, and the matrix (bulb) cells may be heavily pigmented. Melanin is evenly distributed in the matrix cells.
Normal—telogen phase (resting phase)	Uniform in diameter and has a tapered distal end (end opposite the bulb region). From outside in – the cuticle, cortex (may be pigmented depending on coat color) and medulla should be visible.	Club- or spear-shaped with a rough surface and is always nonpigmented (pigment is only produced in the bulb during anagen).
Pruritic diseases/ self-trauma	Fractured shaft. The rest of the hair shaft (proximal to fracture) is normal.	Normal – can be either an anagen or telogen bulb.
Dermatophytosis	Fractured shaft. The rest of the hair shaft (proximal to fracture) may be swollen, irregular and the cuticle, cortex and medulla are not clearly discernible. There may be arthroconidia (spores) on the surface or hyphae in the hair.	Normal – can be either an anagen or telogen bulb.
Demodex	Normal but MAY see mites associated with the hairs. A lack of mites does not rule out *Demodex* but this is a great way to screen dogs that you suspect have *Demodex*. If negative, you need to follow up with skin scrapings (see discussion on skin scrapings).	Normal – can be either an anagen or telogen bulb.

Table 3-1 ***Characteristic Trichogram Findings in Dermatologic Diseases—Cont'd***

DISEASE	HAIR SHAFT APPEARANCE	BULB APPEARANCE
Color dilution alopecia (CDA)	Breakage of hair with abnormal hairshafts. The remaining hairshafts will have irregular shaped clumps of melanin, distorted cuticle-cortical anatomy. Note that a normal-haired dog with color dilution will have hairs look the same as CDA except for the presence of abnormal hair shafts with CDA.	Melanin clumping.
Endocrinopathy (e.g., hyperadrenocorticism, hypothyroidism).	Normal for telogen but excessive (majority) of hairs in telogen.	Normal for telogen but excessive (majority) of hairs in telogen.

4. How are skin scrapings properly performed?

A scalpel blade coated with mineral oil is scraped along the skin. The exact technique depends on whether the mite you are looking for is superficial or deep dwelling. The material that is collected on the scalpel blade is then placed on a microscope slide and a cover slip is applied. Depending on the mite, the sample is then examined either with 40X (*Cheyletiella, Sarcoptes, Notoedres*) or 100X (*Demodex*) magnification.

5. How do you take a skin scraping to demonstrate the presence of superficial dwelling mites (e.g., *Cheyletiella, Demodex cati* [cats], *Sarcoptes, Notoedres*)?

Because these mites live on the surface or in the superficial layers of the skin, broad, superficial scrapings that collect scale and crusts should be performed.

6. How do you take a skin scraping to demonstrate the presence of deep dwelling mites (e.g., *Demodex canis* in dogs or *D. cati* in cats)?

Because these mites live deep in hair follicles, deep skin scrapings must be performed. The skin is squeezed to help extrude the mites from the hair follicles and then a scraping is performed with intermittent squeezing of the skin. The scrapings should be deep enough to create capillary oozing.

7. Are there other helpful hints in having success when performing skin scrapings?

Yes. Knowing which mite is suspected helps determine the sites and lesions that should be scraped (Table 3-2).

8. Are there differences in interpreting positive skin scrapings?

Yes. Because the superficial dwelling mites are not a commensal on the skin, finding even 1 egg, larva or adult *Cheyletiella, Sarcoptes,* or *Notoedres* is diagnostic of an infestation. It is important to remember that *Demodex* is a normal inhabitant of canine and feline skin so the rare adult mite may be found, especially if scraping around the animal's eyes or mouth. In cases of demodicosis, it is important to record the location from where the skin scraping was taken, the

Table 3-2 ***Skin Scraping Techniques for Common Mites of Cats and Dogs***

MITE	LOCATION(S) TO SCRAPE	LESION(S) TO SCRAPE
Demodex	Face (especially periorbital and by the commissures of the mouth), forelegs, trunk, feet (interdigital), and hind legs. Note – *Demodex* can also be in the ear canals – so an ear swab is also useful.	Papules, pustules, erythematous or hyperpigmented macules, comedones or hypotrichotic to alopecic lesions.
Sarcoptes	Edges of pinnae, elbows, hocks, and ventral chest,	Papules, papulocrusts or alopecic areas.
Notoedres	Edges of the pinnae, face, neck and feet.	Papules, papulocrusts or alopecic areas.
Cheyletiella	Dorsum (note: acetate tape impressions are more sensitive).	Scales, papules, papulocrusts or alopecic areas.

number of mites at each stage (egg, larva, nymph, and adult) found and the live/dead ratio. These results will be compared to future scrapings to help evaluate response to treatment.

9. Since *Cheyletiella* causes its symptoms due to a host hypersensitivity reaction, there may be very few mites on the dog or cat. This can make it difficult to find mites on skin scrapings (like looking for a needle in a haystack). What other techniques may be used to find the mites?

A useful technique is the acetate tape prep. Clear tape is applied and then removed from the coat and skin of the dog/cat. The tape is placed sticky side down on a microscope slide and examined under 40X. Flea combing large areas along the dorsum of the patient may be used to help recover *Cheyletiella*. The hair and scale collected are applied to a microscope slide with mineral oil placed on it. A cover slip is applied and the sample examined under 40X.

10. Wood's lamp examination, trichogram, and fungal cultures can all be useful in diagnosing dermatophytosis. We have already discussed trichograms; how does the Wood's lamp examination work?

The Wood's lamp uses ultraviolet light filtered through either nickel or cobalt. The wavelength of the light is 253.7 nm. Because the light's wavelength is temperature-dependent, the lamp should be turned on for 5 to 10 minutes before use.

The principle behind the Wood's lamp examination is that certain dermatophytes (*Microsporum canis, M. distortum* [strain of *M. canis*], *M. audouinni, Trichophyton schoenleinii*) may cause infected hairs (not scales, crusts) to fluoresce an apple-green color. In the case of *M. canis*, this occurs approximately 50% of the time. The exact metabolite of the dermatophyte that is responsible for the fluorescence has not been definitely identified but is suspected to be either pteridin or a metabolite of tryptophan.

11. What are the pros and cons of a Wood's lamp examination?

The advantage of the Wood's lamp is that it is a fast, inexpensive SCREENING tool for dermatophytosis. If hairs are found to fluoresce, those hairs should be plucked and submitted for a fungal culture. Remember, a negative examination result does not rule out dermatophytosis.

A disadvantage of the Wood's lamp is its poor sensitivity. Only 50% of the most common dermatophyte in dogs and cats, *M. canis*, fluoresces. In addition, depending on the operator, it can

have poor specificity. Bacteria (*Pseudomonas aeruginosa* and *Corynebacterium minutissimum*), scales, crusts, soap, and ointments may also cause fluorescence but are not apple-green in color.

12. What about fungal cultures. How do you perform these?

The hairs selected for culture should be hairs that fluoresce with a Wood's lamp (if possible), are broken, or are along the edge of an alopecic lesion. To decrease contaminants, the area should be first gently wiped with 70% alcohol. Hairs and scales are collected from the patient and inoculated into the medium. The McKenzie toothbrush collection technique is preferred in cases where there are poorly defined lesions, or if culturing an exposed but clinically unaffected animal. The toothbrush collection technique involves taking a sterile toothbrush and vigorously brushing the animal's haircoat to collect hair and scale. This material can then be removed from the toothbrush with a sterile hemostat and placed into the culture medium.

13. What are the common culture media used to diagnose dermatophytes?

Dermatophyte test medium (DTM) is the most common medium used in private practice. It contains Sabouraud's dextrose, phenol red (pH indicator), cycloheximide (inhibits growth of other fungi), gentamicin, and chlortetracycline (inhibits bacterial growth).

Rapid sporulation medium (RSM) has many of the same features as DTM but with different ingredients. It contains a pH indicator, bromothymol blue, which causes the medium to change from yellow to blue green; it contains antimicrobial agents, chloramphenicol and chlortetracycline, and an antimycotic agent, cycloheximide.

14. What are the advantages and disadvantage of each of these fungal culture media?

DTM is a useful medium for the rapid growth of dermatophytes and inhibits saprophytic bacteria and fungi. As the pH increases with the growth of dermatophytes, the medium will turn intensely red. This color change, when associated with a small amount of a white or buff colored, cottony, colony growth, is highly suggestive of dermatophytes (Table 3-3). Natural pigmentation on the underside of the colony (reverse color) is obscured because of the intense color change of the medium. The reverse color is a valuable diagnostic tool in identifying the various dermatophytes. DTM does not enhance the sporulation of dermatophytes, which is needed to speciate the dermatophyte present.

Table 3-3 ***Identification of Dermatophytes Based on Colony Morphology and Fluorescence***

ORGANISM	COLONY MORPHOLOGY AND APPEARANCE: TOP VIEW	UNDERSIDE VIEW OF COLONY (REVERSE COLOR)	WOOD'S LAMP RESULTS
M. canis	White cottony to wooly	Yellow	Positive approximately 50% of the time
M. gypseum	Buff-colored, flat and granular	Pale yellow to tan	Negative
Trichophyton mentagrophytes	White- to cream-colored powdery (zoophilic form) or white cottony (anthropophilic form)	Brown, tan, or dark red	Negative

RSM is useful for many of the same reasons that DTM is valuable: it allows rapid growth of dermatophytes; it has a pH indicator; and it has antimicrobial and antifungal agents to inhibit growth of saprophytic bacteria and fungi, respectively. In contrast to DTM, it enhances sporulation and allows visualization of the reverse colony color. These features allow proper identification of the dermatophyte. The major disadvantage of RSM is that the pH indicator does not create as intense a color change as DTM, thereby making one of the diagnostic clues (medium color change associated with a small amount of colony growth) more difficult to appreciate. In addition, some strains of dermatophytes grow better on DTM than on RSM.

The author uses a product that is the best of both worlds. Derm Duet, is a culture medium that contains DTM on one half and RSM on the other. Derm Duet is a flat plate that has a cover that opens like a book, allowing easy access to the colony growth. Most DTMs are small-mouthed jars, which hampers collection of colonies off the medium.

15. Any other tips regarding culturing for dermatophytes?

Regardless of which medium is used, the culture should be placed in the dark, with 30% humidity and a temperature of 30° C. In our practice, a child's pencil box that has a wet sponge in it is used. This is left on the counter in the laboratory as a reminder to examine the culture daily.

16. Because more than just dermatophytes may grow on the culture, what are some of the clues that the organism is a dermatophyte?

As the dermatophyte FIRST begins to grow, the color of the medium changes from yellow to red. This should occur within the first 14 days. The color change occurs because dermatophytes digest protein preferentially. When the protein is metabolized, the pH of the medium changes (increases) and causes the color change. It is important to examine the culture daily because, with time, all the protein in the medium is used and the dermatophytes begin to use carbohydrates. When this occurs, the medium will change back to yellow.

Saprophytes use carbohydrates first. Eventually the carbohydrate source will be exhausted and protein will be used. When protein is used the same color change occurs as previously described. The difference between dermatophytes and saprophytes is that with dermatophytes, there should be a small amount of growth associated with entire medium changing color, and with contaminants, there will be a large amount of growth and only localized (in the earlier stages) color change.

17. Any other clues?

Dermatophyte colonies should be white or buff and cottony in appearance, whereas bacteria look like slime and saprophytes are usually darker colored (see Table 3-3).

18. Veterinary dermatologists recommend microscopic examination of the colonies. How is this performed and what are you looking for?

Macroconidia are collected either by applying acetate tape to the surface of the culture medium or by using a 25-gauge needle to lift some of the growth off the medium. The collected material is placed on a microscope slide that has had 1 to 2 drops of lactophenol cotton blue placed on it. A cover slip is then applied and the sample is examined under 100X and 400X.

19. What is the benefit of this additional step?

The source of the infection may be determined by identifying the specific dermatophyte that is involved in the infection. Each dermatophyte has its own natural habitat. These habitats are: geophilic (soil), zoophilic (animal), or anthropophilic (human) (Table 3-4).

It is important to identify the specific dermatophyte involved in the infection because different dermatophytes have different reservoirs. By doing so, eliminating the source of the infection may be possible.

Table 3-4 ***Identification of Dermatophytes with Lactophenol Cotton Blue Examination Plus the Reservoir for Each Dermatophyte***

ORGANISM	MACROCONIDIA	MICROCONIDIA	RESERVOIR
M. canis	Spindle shaped with thick walls and knobs at the ends. Contains more than 6 cells (Fig. 3-1A).	Rarely found. Are club shaped but are nondiagnostic.	Zoophilic
M. gypseum	Spindle-shaped with thin walls with rounded ends. Contains less than six cells (Fig. 3-1B).	Frequently found, are club shaped but are nondiagnostic (same appearance as *M. canis*).	Geophilic
Trichophyton mentagrophytes	Only found occasionally. Are cigar shaped, thin walled with narrow attachment to the hyphae (Fig. 3-1C).	Usually present either singly along hyphae or in grapelike clusters.	Zoophilic

20. What are the indications for performing a skin biopsy?

The author will perform a skin biopsy for:

- Any skin disease that is not responding to appropriate therapy
- Any skin disease that may be potentially neoplastic
- Any skin disease that may be a cutaneous marker for a systemic disease (e.g., hyperkeratotic footpads associated with superficial necrolytic dermatitis)
- Any skin disease that may be autoimmune or immune-mediated
- Any nodular disease
- Any skin disease that appears unusual
- Any skin disease that requires expensive or potentially toxic drugs or therapy

21. Are there different methods used in collecting a skin biopsy? If so, what are the advantages and disadvantages of each method?

Two methods to biopsy the skin are the punch technique and the elliptical, incisional biopsy with a scalpel blade.

For punch biopsies, we usually will use a 6-mm punch biopsy instrument. Occasionally, a 4-mm punch may be used on the pinna. When using this instrument, DO NOT include normal tissue in the sample with a lesion. Because the sample is round, if you include normal tissue with the lesion, the sample could be sectioned in such a manner that lesions are missed (think of a doughnut in which you can cut with a knife and miss the hole). When using a punch instrument, press firmly and rotate the punch in one direction until the skin is completely penetrated. To avoid creating artifactual lesions, do not rotate the punch instrument back and forth.

We use elliptical, incisional biopsy with a scalpel blade for lesions that are ulcerated, erosive, or are suspected to involve the subcutaneous tissue (e.g., panniculitis). For subcutaneous lesions, a punch sample typically may not get all the subcutaneous tissue and therefore may miss important lesions. Excisional biopsy with a scalpel blade should be performed when you biopsy a pustule, vesicle, or bullae that exceeds the size of your punch.

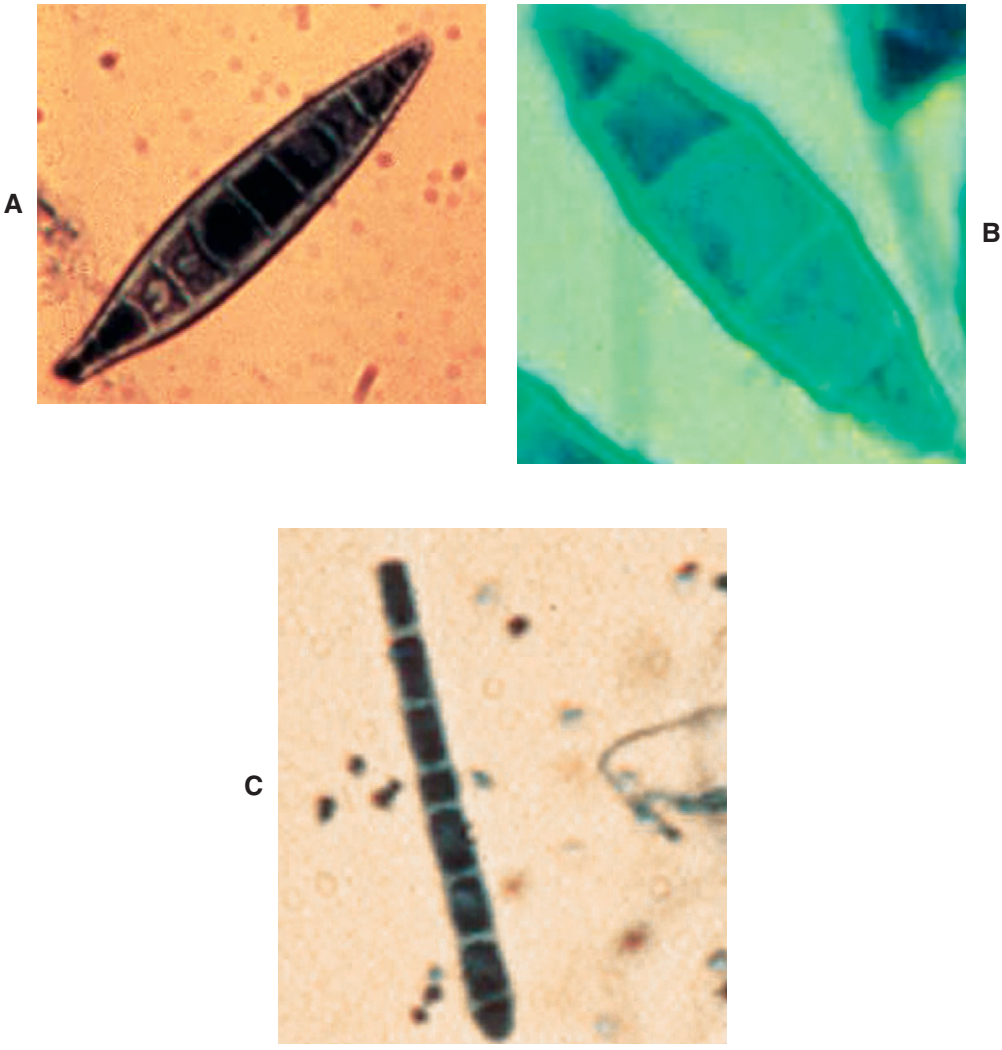

Figure 3-1 **A,** Macroconidia of *Microsporum canis*. **B,** Macroconidia of *Microsporum gypseum*. **C,** Macroconidia of *Trichophyton mentagrophytes*.

22. Are there any special techniques that you should use when you perform a biopsy of an area that is alopecic or hypotrichotic?

Yes. If a lesion is hypotrichotic or alopecic, then either a 8-mm punch is used or an elliptical incisional biopsy is performed. Either of these techniques will increase the number of hair follicles that can be examined (if present of course). Ideally, the sample should be trimmed so that the entire length of the hair follicles can be assessed. If the sample is elliptical, the piece is trimmed from tip to tip. However, with a punch (round sample) biopsy ideal orientation is difficult. To help properly trim a round sample to allow optimal orientation, a technique has been established using a Sharpie permanent marker. Before collection of the sample, a black line is

drawn in the direction that the hair should run with a Sharpie permanent marker. The sample is then collected along this line.

23. Can you explain in detail how you do your sampling if you have a lesion that is ulcerative, erosive, or alopecic? Are there tricks to getting the maximum information from your sample?

Yes. In those cases, an elliptical-shaped biopsy is the most valuable sampling technique. Using a scalpel blade, the incision begins in the center of the lesion and is curved into normal skin. The procedure is repeated making a second curved incision on the opposite side of the sample, thereby creating a football-shaped sample with one tip in the center of the lesion and the other in normal skin. This allows the pathologist to section the sample so that he or she can examine the skin as a continuum going from normal to abnormal. This frequently will help identify the pathogenesis of the disease because the sample allows the visualization of the step-by-step changes that caused the lesion.

24. Can you go through the step-by-step procedure of performing a skin biopsy?

Sure. Regardless of the method used to collect the biopsy, a local anesthetic containing 2% lidocaine is injected prior to collection. To prevent overdosing, don't exceed 1 cc of 2% lidocaine/10 pounds body weight of the animal. For small animals, or animals that will need biopsies of multiple sites, use a 1% lidocaine solution. This is made by mixing 2% lidocaine 50/50 with sterile water. By using this mixture, more sites can be anesthetized without concern about toxicity. Sites should NOT be clipped or scrubbed before collection because this may remove very valuable information. The hair may be clipped to visualize the lesion better, but to avoid traumatizing the skin, at least $\frac{1}{4}$-inch length of hair should remain. Skin biopsies are clean, not sterile, procedures except when the sample is being collected for a macerated tissue culture (see bacterial culture discussion for more details). The biopsy site is outlined with a Sharpie permanent marker. Most samples, except for nails, nasal planum, and pinnae, can be collected with only local anesthesia. In some cases, mild sedation can be helpful both to the patient and clinician (sedation of the patient, not the clinician!).

For biopsies of the nails, nasal planum, or pinnae, we use a combination of general and local anesthesia.

It is very important to avoid creating iatrogenic lesions during sample collection (e.g., crushing artifact secondary to grasping the tissue with forceps). These secondary lesions may be avoided by GENTLY grasping the sample deeply along the edge using fine thumb forceps.

After the sample is collected, close the site with one to two sutures placed in a simple interrupted pattern. The sample should be immediately placed into 10% buffered formalin and submitted to the laboratory for processing. Leaving the sample out of formalin, even for a brief period, may allow production of autolytic lesions.

If an infectious agent/cause is suspected, a sterile sample can be submitted at the same time for a macerated tissue sample (see bacterial culture discussion for more details.)

25. Any tips in getting the most out of a skin biopsy?

If you ask a dermatopathologist what is the number one item that can help with a diagnosis, other than the sample itself, the answer would be HISTORY, HISTORY, HISTORY (see Chapter 4). This includes the duration of the disease, clinical signs (e.g., pruritus, systemic signs), distribution of the lesions, whether owners are also affected, whether there is multiple animal involvement, all medications that are currently (or recently) being used and the response to any previous therapy. A list of rule-outs would also be helpful.

Other helpful tips include:

Send your sample to a veterinary dermatopathologist.

Submit multiple samples (usually three to four samples are ideal) of different lesions that represent various stages of the disease process. Perform a biopsy of only primary lesions

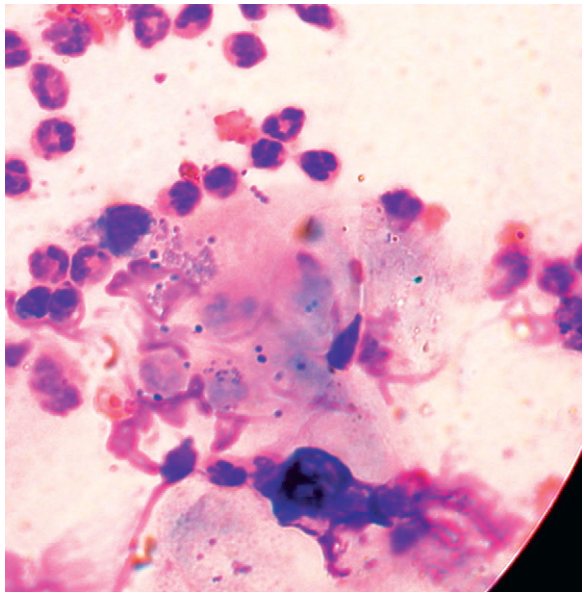

Figure 3-2 Intracellular and extracellular cocci found on skin cytology.

(macule, papule, pustule, vesicle, wheal, nodule, tumor, alopecia, scale, or crust). It is very important that samples selected represent the disease process (a variation on a theme) rather than one unique lesion that doesn't represent the disease process. In general, avoid old, ulcerative, or erosive lesions.

26. What is cytology?

Technically, cytology is the study of the internal structure and organization of cells. In dermatology, the term is used to describe the microscopic examination of fluid or tissue collected from nodules, tumors, cysts, pustules, vesicles, papules, bullae, or the surface of the skin.

27. What is the value of cytology?

Cytology can rapidly and inexpensively detect the presence of inflammation, infection (bacteria or fungi), autoimmune disease (presence of acantholytic keratinocytes in pemphigus), or neoplasia (Figures 3-2 through 3-4).

28. What are the different techniques used to collect samples for cytologic examination?

Fine needle aspirates, skin scrapings, impression smears, and roll smears.

29. Can you explain how each technique is performed and the indications for each?

Absolutely. When the skin is scaly, a superficial skin scraping can be useful. A very small amount of mineral oil is placed on a no. 15 scalpel blade to help keep the scale on the blade once it has been collected. The lesion is scraped a few times, and the material collected is placed on a microscope slide, stained (see below about staining samples), and examined microscopically at 400X and 1000X.

A fine needle aspirate is performed when a solid or fluid filled mass or lesion is present. A 22- to 25-gauge needle attached to a 12-cc syringe is placed into the lesion and suction is applied by pulling back the plunger of the syringe (one half to three fourths of the way). The syringe

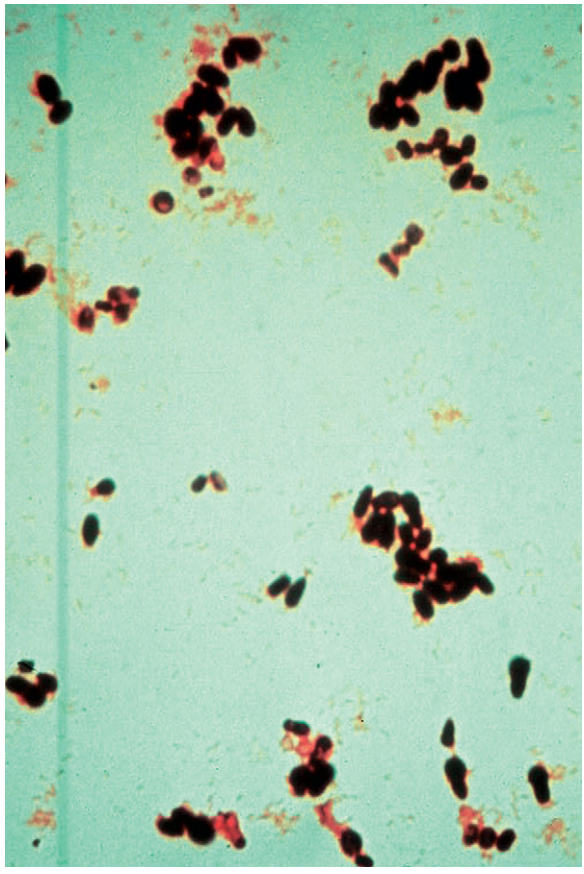

Figure 3-3 Numerous *Malassezia* found on skin cytology.

plunger is pulled back and released a few times if the lesion is a solid mass, while it is only pulled back once if fluid can be removed. The sample is placed on a microscope slide, stained, and examined as previously described for skin scrapings. Sometimes, a 22-gauge needle works well as a "core" biopsy instrument for solid masses. The needle is inserted into the lesion and gently rotated. The needle is then withdrawn and reinserted in a second spot. These steps are usually repeated three or four times. To extract the sample from the needle, the needle is attached to a syringe that already has been prefilled with air (do not draw back on the syringe plunger with the needle attached, it will suck the material further up the needle). Then push on the plunger while pointing the needle toward the slide; this expels the material in the needle onto the slide.

Impression (touch) smears are useful when there is an erosion, ulcer, crust, or moist or greasy lesion. If the lesion is fluid-filled (e.g., pustule) but is too small for a fine needle aspirate, "lance" the lesion with a 25-gauge needle and then do an impression smear. To perform an impression smear, a slide is firmly applied to a lesion and, in most cases, is then gently moved back and forth a few times to increase the yield. Some people will use slides that are "sticky" on one side (Durotak). These slides are reported to increase the yield of sample collected, but we find that a standard slide works quite well. Sticky slides will increase the number of organisms found even on normal dogs, so getting a "feel" for what is found on a normal dog with respect to

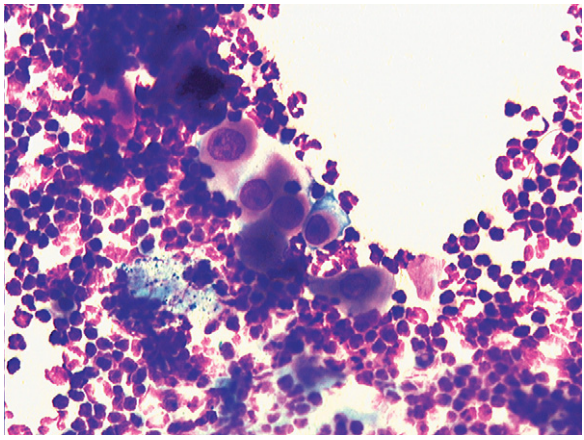

Figure 3-4 Acantholytic keratinocytes are suggestive of pemphigus.

number of organisms would be useful. The slide is then processed and examined as previously described for skin scrapings.

Roll smears (swabs) are used when it would be difficult to get a slide into the affected area. This could be a draining tract, the interdigital spaces on cats and small dogs, and the ear canals in all dogs and cats. A cotton-tipped applicator is gently rubbed back and forth across the lesion and then the material from the applicator stick is rolled back and forth on the slide. If the lesion is scaly, applying a small amount of mineral oil to the swab can help with collection. The sample is rolled onto a microscope slide, stained, and examined as previously described for skin scraping.

30. How do you process the sample for cytologic examination?

We heat fix the sample, using a cigarette lighter, and then wait a minute or so to allow it to cool. As a senior veterinary student learned, placing a warm slide into the fixative (containing 95% alcohol) will create quite a large flame! A modified Wright stain (DiffQuik) is used. There are three jars in this kit. The first jar is a fixative containing 95% alcohol, the second contains buffered xanthene dye, which stains the cells and organisms red, and the third contains buffered thiazine dye that stains the cells and organisms purple. The slide is placed into each jar for 3 to 5 seconds and then is placed into a bottle containing water. The slide is then dipped a number of times until the excess stain has been rinsed off. Since the stains are used many times before discarding (they are usually discarded monthly and the jars are thoroughly washed) there is a potential for debris to accumulate in the bottom of the jars. To decrease the potential for contaminating slides, allow the slides to rest in each jar for the allotted time rather than agitating them. Another tip is to use clothespins to hold the slides to avoid staining your fingers! Once the slides have been rinsed, they can either be air dried or blotted (NOT rubbed) with a paper towel. The sample is now ready to examine microscopically.

31. What specific diseases/conditions may be detected via cytology?

The presence (and/or type) of:

- Bacterial or fungal infections (*Malassezia*) (see Figures 3-2 and 3-3)
- Neoplasia
- Inflammation
- Autoimmune diseases (acantholytic keratinocytes associated with pemphigus) (see Figure 3-4)

32. What are acantholytic keratinocytes?

They are keratinocytes that have lost their intercellular "glue" due to an auto-immune or infectious (bacterial or dermatophytic) process. Once the keratinocytes have lost their anchors, they break away and will be free floating in a vesicle (pemphigus vulgaris) or pustule (pemphigus foliaceus). They are round cells with a purple cytoplasm and a dark purple nucleus, appearing singly or in clusters (see Figure 3-4).

33. When do you perform a bacterial culture and susceptibility test?

Bacterial cultures are not frequently performed in dogs with skin disease because *Staphylococcus intermedius* is the most common bacterial pathogen and has a predictable susceptibility profile. It would be uncommon to obtain culture specimens from cats with skin disease because they rarely get bacterial infections, except for cat bite abscesses. Indications for culture and susceptibility testing in the dog or cat would include the presence of:

- Nodules
- Deep draining tracts
- A bacterial infection of the skin (confirmed by identifying intracellular bacteria and degenerative neutrophils) that fails to respond to appropriate antibiotic therapy
- Otitis externa with chronic changes in the ear canals especially if a single population of rods is found on cytologic studies
- Suspicion of an uncommon bacterial infection (atypical mycobacteria, *Nocardia*, *Actinobacillus*)
- Suspicion of an anaerobic infection (gas pocket formation)
- Otitis media

34. What is the best way to collect a sample from a nodule for a bacterial culture?

Because the bacteria of interest are present in the deep tissue and not the surface, a macerated tissue culture should be performed on samples from nodules. To collect the sample for a macerated tissue culture, the site is sterilely prepped by clipping with a no. 40 blade and scrubbing with a chlorhexidine or tamed iodine-based shampoo. The area is then rinsed with alcohol. An incisional biopsy specimen, using sterile technique, is then obtained as previously described. The sample is then placed into a sterile container rather than a formalin container. At the laboratory, the surface is then scorched or the epidermis is sterilely removed. The remaining sample is ground up and placed into the culture medium.

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4. A GUIDE TO TAKING SKIN BIOPSIES: A PATHOLOGIST'S PERSPECTIVE

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1. Why a chapter on how to take a skin biopsy?

A skin biopsy is one of those procedures that appears so simple in execution that the subject may, at first glance, not appear to be a dermatology "secret." Although not technically difficult, ask any dermatopathologist and he or she will tell you the preference is to receive samples from dermatologists or those who have an interest in skin disease simply because the quality of the samples is so much better. Dermatologists know where to perform a biopsy. Biopsies can be further improved if clinicians (including dermatologists) use techniques that increase the ability of the pathologist to visualize the clinical picture through the microscope. The secrets in this chapter are a series of hints to improve the quality of a skin biopsy submission and to optimize the chances that a pathologist will give you a meaningful diagnosis.

2. When should I take a biopsy?

There are four occasions when a clinician will want to biopsy:

To Confirm a Diagnosis

There are many diseases in which the lesions are characteristic but the clinician will want to submit a biopsy sample to be absolutely certain the diagnosis is correct. Diseases of this type include superficial spreading pyoderma; forms of cutaneous neoplasia; and metabolic diseases, such as metabolic epidermal necrosis (superficial necrolytic dermatitis).

To Provide Direction without Always Receiving a Definitive Diagnosis

In many cases, therapy may not be effective or the clinician suspects more than one disease is occurring. In these situations, biopsy may be helpful not because it will give the clinician a definitive diagnosis but because it helps in identifying additional diagnostic tests or treatments that can help the patient. The most common example is that of an allergic skin disease. Only rarely will a skin biopsy define the type of allergy present but its histologic evaluation can confirm or deny the presence of other diseases (pyoderma, endocrinopathy, demodicosis, etc.) that may confound therapy.

Out of Curiosity

Sometimes a clinician will submit biopsies not because the lesions are debilitating or disfiguring to the patient but because they are unusual and he or she just wants to learn what a lesion represents histologically.

Out of Desperation

The patient is getting worse, no therapy seems to work, and the client is calling you three times a day. Biopsies in this situation are submitted primarily to obtain a diagnosis of therapeutic relevance but also as a means to share frustration with the pathologist.

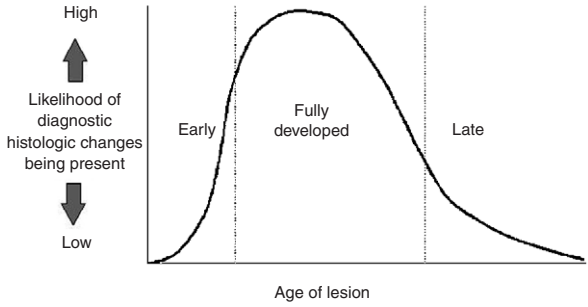

Figure 4-1 Diagram of the evolution of skin lesions. As depicted, fully developed lesions are the most diagnostic, and early lesions are more diagnostic than late lesions.

3. What should I biopsy?

Always Consider the Life of a Lesion

Lesions usually follow a progression from early to fully developed to late stages. As a rule, fully developed lesions are the most diagnostic. Early lesions usually appear as macules or patches. Fully developed lesions can also appear as macules and patches as well as papules, plaques, wheals, nodules, cysts, vesicles, pustules, comedones, and papillomas. Late or resolving lesions are usually less diagnostic than early lesions. Late lesions often appear as scales, crusts, erosions, ulcers, or fissures.

Selecting Lesions to Biopsy

Unless a lesion is extremely localized or all lesions are in the same stage of development, multiple skin biopsy specimens should always be submitted.

The ultimate objective of obtaining a skin biopsy sample is to allow the pathologist to see the evolution of the disease from early to fully developed to late lesions. Thus, the first biopsy should be of the lesions that are most representative of how the animal appears. Subsequent biopsies should be of early or fully developed lesions (Figure 4-1).

4. How do I prepare the site for a skin biopsy?

Note that preparation of a skin biopsy site i*s not a sterile procedure!* You should first trim hair with a scissors or clip with a no. 40 blade. Trim over (not through) areas where there is abundant scaling and crusting. There is seldom an advantage and, because of the chance of losing diagnostic lesions in the superficial epidermis, considerable disadvantages to washing the site of a skin biopsy, especially when a punch is being used. If you believe some cleaning is necessary, then the clipped site should be washed with plain water and patted dry. Crusts and scales should be left intact if possible—under the microscope, they often contain important diagnostic clues. For denoting the areas to be sampled, a dot does not do it! Instead of denoting the area with a circle or a dot, mark the area to be anesthetized by a line made with a fine-tipped indelible marker (Sharpie) parallel to the direction the hair lies. *This is extremely important because it helps the pathologist orient biopsy samples correctly when they are being trimmed for histologic examination* (Figures 4-2 and 4-3).

For local anesthesia, a bleb of no more than 1 cc of 2% lidocaine/site injected into the subcutaneous fat is standard but try to use less if multiple biopsy sites are to be obtained from a cat or a very small dog. To avoid pain and anxiety, use a general anesthetic if you are obtaining a biopsy specimen from sensitive tissues such as the nose leather or paw pad.

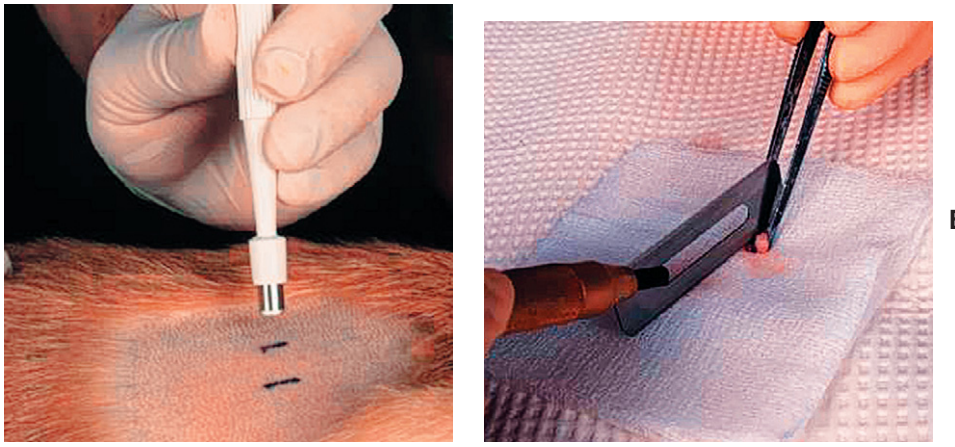

Figure 4-2 **A,** To allow the pathologist to better orient the skin biopsy sample, draw a line parallel to the direction the hair flows with an indelible marking pen. There are two lines on this dog indicating two biopsy specimens will be taken from this region. **B,** Note how the pathologist uses the black line to trim the punch biopsy.

5. How do I take a punch biopsy sample?

General Concepts

The standard punch biopsy size for veterinary medicine should be a 6- or 8-mm punch (Figure 4-4). Smaller diameter punches (4 or 3 mm) should only be used when a larger biopsy is technically difficult or could result in visible scarring (i.e., lesions near the mucocutaneous junctions or on the ear). **Please do not use a punch biopsy to delineate borders of lesions!** Such lines of demarcation are usually bleached with formalin fixation and are ignored because the punch is trimmed according to hair shaft orientation. If the borders of a lesion are important, use an excisional biopsy (see below). You should also avoid using a punch biopsy on large pustules or blisters (bullae) because rotation can shear the roof of these lesions. Instead, an excisional biopsy should be used when this situation arises. Finally, a punch biopsy should not be used to sample neoplastic or inflammatory diseases in the subcutaneous fat of dogs or cats or the deep dermis in large animals because biopsy punches often do not penetrate to a sufficient depth to obtain a representative sample.

Procedure

When taking the sample, position the punch over the center of a lesion or (preferably) at a site where only abnormal tissue is present. Once oriented, rotate the punch in one direction only, until it sinks into the subcutaneous fat (you know you are in the subcutaneous fat because the tissue "gives"). Gently support the plug of tissue (i.e., do not crush) and cut free with a small, iris-type scissors. Blot on a gauze pad to remove excess blood. Although older texts suggest placing the biopsy sample on a piece of tongue depressor or cardboard to minimize curling during fixation, this is optional for punch biopsy specimens that are too thick to curl but is mandatory for excisional biopsies (see below) that invariably twist and wrinkle during fixation. Do not dawdle! The time from removal of the biopsy sample to formalin immersion should be as short as possible (seconds not minutes).[1]

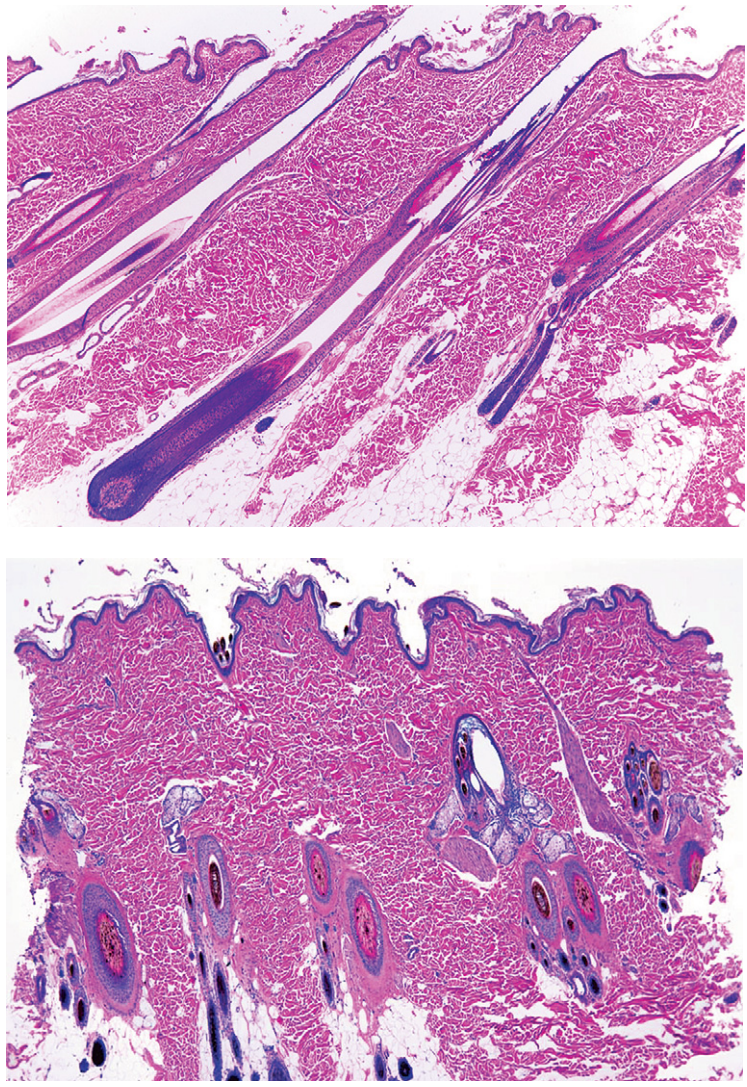

Figure 4-3 The appearance of a biopsy sample that was correctly sectioned **(A)** compared to a biopsy sample that was incorrectly sectioned **(B)**. Note that when a biopsy sample is correctly sectioned parallel to the flow of the hair, the entire structure of the hair follicle can be examined. When sectioned perpendicular or considerably tangential to the flow of the hair, the follicles look like "Swiss cheese."

Once the biopsy sample is removed, the site should be closed with 4-0 nonabsorbable monofilament using a cruciate suture or two simple interrupted sutures. Remember that black sutures can be lost in black-haired animals. Some clinicians will use "surgical superglue" (cyanoacrylate) as an alternative but we have found that using this method to effectively close a skin biopsy site takes practice and works better at sites or in breeds in which there is abundant loose skin.

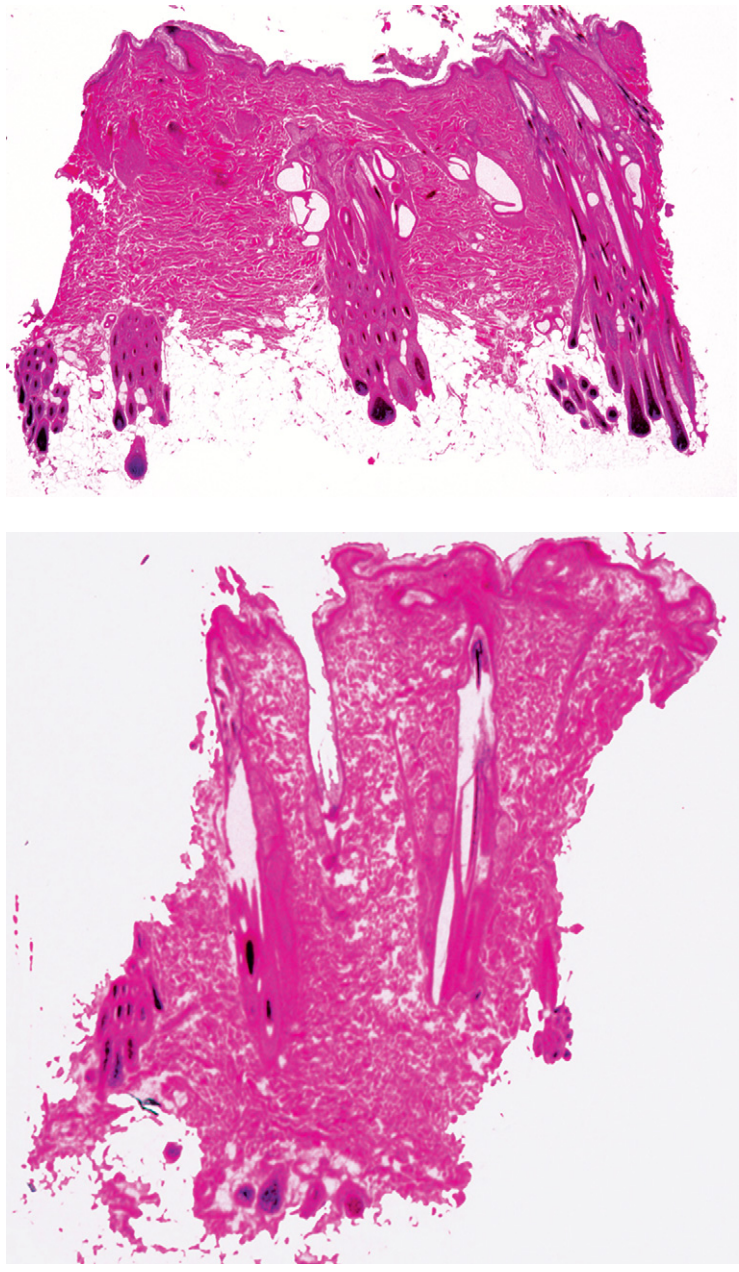

Figure 4-4 The difference in number of follicular units available for examination between a 6-mm **(A)** and a 3-mm **(B)** punch biopsy sample. From the pathologist's perspective, the 6-mm punch is always preferred.

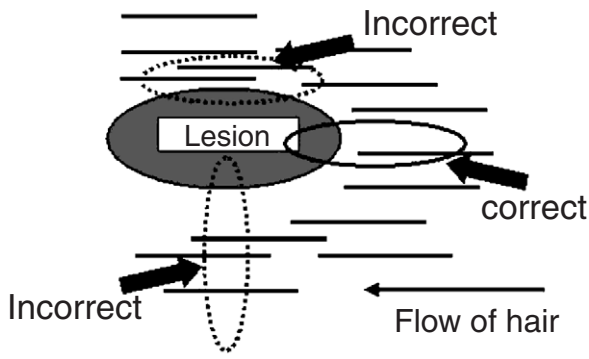

Figure 4-5 Diagram of how to orient an elliptical biopsy.

6. How do I take an elliptically oriented skin biopsy?

General Concepts

This technique is always preferred (or at least not contraindicated) by the pathologist because "more tissue often gives more information." An elliptical sample is especially helpful when it is oriented to cross the transition zone from normal to abnormal skin. If you are sampling such a site, the lesion should be at one point of the ellipse and normal skin at the other point. In addition, you should try to orient the ellipse along the "lay" of the hair so the entire follicle can be examined (the sample will be cut along its length during trimming for histologic evaluation) (Figure 4-5).

Technique

For small elliptically oriented biopsies, the site is prepared as for the punch biopsy—less is more. As with the punch biopsy procedure, the use of a local versus a general anesthetic will depend on the site of the lesion as well as the depth of the tissue to be sampled. Know that an elliptical biopsy does not have to be large, only representative. Thus a 1-cm ellipse provides plenty of tissue for the pathologist to examine. Use a no. 15 blade on the scalpel handle to incise an ellipse of tissue. Cut the base free with an iris scissors, then blot excess blood and place the biopsy "epidermis up" on cardboard or piece of tongue depressor. Turn the tongue depressor upside-down and immerse in formalin immediately. Close the site with simple interrupted sutures.

7. How do I take a wedge biopsy?

General Concepts

This is a variant of the elliptically oriented skin biopsy. Most commonly, wedge biopsies are taken to sample raised lesions, nodules, margins of the ear pinna, and footpad lesions.

Technique

The technique is similar to the ellipse except it extends in a third dimension to the center of a nodule or into the subcutaneous fat. For example: for footpad biopsies, cut down into fat pad, narrowing at the base so that the sample will have a shape like a canoe. Close with a far-far-near-near (inverted) suture pattern. (These can be slow to heal!) A wedge can also be obtained after a nodule has been excised, affording better fixation because the sample is thinner.

8. What about fixation?

Ten percent neutral buffered formalin remains the fixation of choice for histopathology. Being the "fixative" of choice, however, does not mean that formalin is optimal. Formalin is a

proven irritant, a proven sensitizer to delayed-type hypersensitivity responses, and a known carcinogen. It should be handled with caution. If your container leaks in the mail, the post office may send the sample back to you. Although alternative, formalin-free, safer fixatives are currently on the market, they are simply not as good when evaluated with standard histologic stains and cannot be recommended at this time.

For adequate fixation, there should be at least ten times the volume of formalin per volume of tissue. In addition, assume formalin can only penetrate dermal tissue a maximum of 0.5 cm from any direction. Thus, tissues larger than 1 cm square may not be fixed in their center. Know also that approximately 24 hours are needed for the biochemical changes to occur that result in adequate fixation. Once tissues are fixed, they can be placed in smaller volumes of formalin or even 70% alcohol for storage and shipping provided enough of the liquid is present so the tissues do not dry out.

For samples sent from the North and, to a lesser extent, samples sent to the North, freezing of tissues in transit is a major problem during the winter. Frozen tissues develop such extreme distortion of normal morphology that in most cases they cannot be interpreted histologically. If the biopsy sample might be exposed to freezing temperatures, you can avoid this artifact by adding one part 70% ethyl alcohol to nine parts formalin (isopropyl alcohol works just as well!) and use this as a fixative.

Finally, **Michele's media** was once used as a fixative to evaluate for the deposition of immunoglobulins in the skin. Now equivalent results can be obtained with formalin-fixed tissues and it is seldom used. If for whatever reason, you are advised to submit a biopsy sample in Michele's media, make certain the person who requests the samples sends you the media. Michele's media has a notoriously short half-life and you should not use expired media.

9. What can you expect from your pathologist?

The first concern of most practitioners is **turnaround time**. We recommend that you avoid services that offer results in less than 24 to 36 hours! For skin pathology, preparation of the tissue for optimal evaluation requires at least 12 hours in a machine known as a tissue processor. Anything less than 12 hours results in tissue sections that are inferior to those of laboratories with longer processing times because the tissues are more difficult to section with a microtome. This is a major consideration with a relatively tough organ such as the skin and may interfere with histologic interpretations. In all fairness, a shortened processing time will not affect the outcome in most cases, but it can occasionally obscure subtle changes that could change the diagnosis. For most samples it will take at least 3 to 4 working days minimum to get results from an efficient laboratory: a day for trimming and processing, a day for making the slides and initial review by the pathologist, a day for dictating the report, and a day for sending the proofed report out. If additional stains are needed to confirm a diagnosis, a longer time should be expected. To shorten the delay by mail, many pathologists will send an e-mail message with a preliminary diagnosis or final report, especially on critical cases. Do not be afraid to ask!

Another concern is to make sure your pathologist has expertise in dermatopathology. As a rule, individuals who are Diplomates of the American College of Veterinary Pathology, a member of the American Academy of Veterinary Dermatology ***and*** the International Society of Veterinary Dermatopathology have special interests in dermatology and dermatopathology.

10. What should your pathologist expect from you?

The pathologist wants as brief but complete a history as possible. This should include (1) location, pigmentation of biopsy sites and type of lesion present; (2) signalment of patient; (3) medication history; (4) what you hope to learn from the biopsy; (5) YOUR differential diagnosis list; and (6) what diseases would you like to exclude (i.e., are *Malassezia* yeasts present? etc.).

Your technical assistant can write the address and signalment on the form but the clinician needs to take time to fill out or dictate the clinical features of the disease, biopsy sites, medication history, differential diagnosis, etc. Do not photocopy and send the patient's medical file.

11. How do I provide submissions for a molecular age?

More and more laboratories are using sophisticated techniques to analyze skin diseases. Thus, knowledge of additional methods for sampling tissues is required. The following is a list of protocols to submit samples for less routine morphologic tests and most molecular-based assays.

12. How do I submit a sample for electron microscopy?

Occasionally a diagnosis may require ultrastructural evaluation of a sample. For example, the characteristic lesions in some collagen fragility diseases can only be confirmed under extremely high magnification. Although you should follow the advice given by the laboratory that will receive the sample, we have found that formalin fixation is an adequate fixative for defining most ultrastructural alterations. Other options include fixing in glutaraldehyde or a combination of glutaraldehyde and formalin (Karnovsky's solution). The problem we have had with these fixatives is that the sample needs to be cut extremely small and fixed for a relatively short period in these compounds before it is placed in a phosphate buffer. Failure to do this correctly can ruin the sample. In short, glutaraldehyde and Karnovsky's fixation offers pristine samples for electron microscopy but are easy to ruin; formalin fixation offers adequate samples but is impossible to ruin. The choice is yours.

13. How do I submit a sample to look for proteins via immunohistochemistry that cannot be identified after formalin fixation?

Although most immunohistochemical stains have been adapted to work on formalin-fixed samples, some do not. This includes a number of valuable markers for lymphocytes and macrophages. For example, separating T helper (CD-4+) from cytotoxic T cells (CD-8+) and defining Langerhans cells in histiocytic proliferative diseases all require immunostaining on frozen tissues. Submitting a biopsy sample for such analysis can be done in either of two ways:

Option 1: Express Mailing the Sample on Ice

This is the most commonly used technique. Simply take a 6-mm biopsy sample, wrap in a gauze 4×4 soaked in physiologic saline, place in a plastic bag, and send in a cold pack for next-day delivery. Note that most pathology laboratories do not open the mail during the weekend so it is best if the sample is sent early in the week and the laboratory is forewarned about its arrival.

Option 2: Flash-Freezing a Skin Sample in OCT

This will require assistance from the laboratory doing the analysis. Briefly you will need a specialized embedding compound (OCT by Tissue-Tex, Torrance, CA), a cryomold (made by the same company) and dry ice. A 6-mm skin biopsy specimen should be cut in half vertically (epidermis to subcutis) oriented for hair flow (see previous section). The halves should be laid cut side down in a small amount of OCT placed in the bottom of the tissue mold. The mold is then filled with OCT, covering the sample, and is placed on top of dry ice until the sample is totally frozen. The sample should be sent by overnight delivery to the laboratory on dry ice. There are a number of alternatives to this method (dry ice and acetone, freezing in liquid nitrogen) but we have had best results with the above method.

14. How do I submit a sample for nucleic acid storage/analysis?

More and more breeders are interested in having deoxyribonucleic acid (DNA) samples stored from their dogs. Unlike ribonucleic acid (RNA; see below) every cell has exactly the same DNA; thus any sample with nuclei can be used. In addition, DNA is extremely stable and degrades very slowly (we have isolated usable DNA from the proximal ends of dog hairs stored at room temperature for 3 years!). **Know that when working with any sample for nucleic acid isolation, gloves need to be worn at all times to prevent contamination.**

DNA from whole blood: Three to 5 m of whole blood in **a Vacutainer tube containing EDTA (lavender top**) should be sufficient. Send the sample cooled but not frozen.

DNA from a skin biopsy: DNA can be harvested from paraffin-embedded skin biopsies, so each skin biopsy sample that you submit can be viewed as a DNA sample.

DNA from the buccal/oral mucosa: Laboratories that have DNA-based assays already established will often request that submissions consist of brushed oral mucosa. If this is the case, the laboratory you are using will provide you with a brush and directions. The technique is simple and non-traumatic consisting of brushing the area between the cheek and gum and keeping the brush from further contamination. This method does not provide a lot of DNA but this is almost always adequate for established tests. The sample can be sent in the envelope in which the brush came without refrigeration.

Submitting a sample for RNA analysis: In some diseases, full molecular evaluation requires isolating RNA rather than DNA. When RNA analysis is preferred, the laboratory should send you a vial of a compound called RNA Later (Ambion, Austin, TX). A 6-mm skin biopsy sample can be placed in approximately 2 to 3 mL of this compound and sent without freezing by express mail to the laboratory. Work quickly when taking the sample and placing it in RNA Later. Unlike DNA, RNA is extremely labile and time is truly of the essence.

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Section II
Dermatologic Therapy

5. SYMPTOMATIC MANAGEMENT OF PRURITUS

Paul Bloom, DVM, DABVP, DACVP

1. What is pruritus?

Pruritus (itch) is the unpleasant sensation that triggers the desire to scratch, chew, rub, lick, or bite at the skin.

2. How is the sensation of pruritus transmitted?

No clearly defined end organ has been found at this time. There are nociceptors (nerves involved with itch or pain) just below the dermal-epidermal junction or sometimes in the deep layers of the epidermis that initiate the transmission of pruritus. The sensation can be generated by chemical, electrical, mechanical, or thermal stimulation. It is then transmitted via either free nerve endings or a specific mechanoreceptor to polymodal units that contain C unmyelinated axons. A small amount is transmitted via Aδ myelinated axons. These nerves transmit the signal to the spinal cord where it then travels up to the sensory cortex in last brain.

3. What is meant by the "threshold theory of pruritus"?

A certain pruritic threshold is tolerated by all individuals without resulting in clinical signs. Any increase above this threshold, even a small amount, will result in clinical signs. A good way to think of this is that each individual has a paper bag that can hold a certain weight of groceries. Once that amount is exceeded, the entire content of the bag is lost, not just the last item.

4. What does the phrase "summation of effect" mean in regards to pruritus?

The additive effects of different pruritogenic mediators can, together, raise an animal's "pruritus level" above its threshold, resulting in clinical signs of pruritus. Therefore, even though an individual stimulus may not be enough to cause clinical signs, together, multiple stimuli may be. An example would be a dog with environmental allergen–induced atopic dermatitis (atopy) that is not clinically affected until it also has fleas. The combination of atopy and fleas (summation of effect) will push this dog over its pruritic threshold. This dog will not only show clinical signs associated with fleas (typically pruritus of the posterior one third of the body) but will also show clinical signs of atopy, that is pruritus of the feet, face, flexors, friction areas, or fold areas of the body. Treating only the fleas will resolve ALL clinical signs in this dog.

5. Why are these two concepts, pruritic threshold and summation of effect, important in the symptomatic treatment of pruritus?

These concepts reinforce the importance of treating ALL the causes of pruritus—pyoderma, dry skin, *Malassezia*, fleas, and the self-perpetuating cycle of itch-scratch-itch (trauma to the skin causes release of inflammatory mediators).

6. How do animals manifest the symptoms of pruritus?

They will scratch, chew, rub, lick, or bite at the skin, resulting in alopecia, hypotrichosis, excoriation, lichenification, or crusts. In some cases, quite remarkably, there are no cutaneous lesions despite moderately severe pruritus.

7. How can pruritus be treated in cats and dogs?

The FIRST step before instituting treatment is to attempt to identify the cause of the pruritus. The next step, if possible, would be to treat it specifically. In addition, symptomatic therapy may be necessary. Therapy can be broken down into three categories:

Topical therapy
Barrier therapy
Systemic therapy

Frequently a combination of all three categories is necessary to control pruritus.

8. What are the advantages and disadvantages of topical antipruritic therapy?

The advantages of topical therapy include direct access to diseased tissue and the ability to reduce or eliminate the need for systemic therapy. With less systemic therapy there is a lower likelihood of systemic adverse reactions. The disadvantages of topical therapy are the additional time and effort involved in administering topical therapy as opposed to systemic therapy. Also, the cost of topical therapy can be substantial. In fact, some topical therapies are so costly that they can only be used on localized lesions. Lastly, even topical medications can be absorbed and create systemic effects (e.g., topical steroids, especially potent ones, that are applied over large areas of the body and/or under an occlusive bandage can cause iatrogenic hyperglucocorticoidism).

9. What formulations are used in topical therapy and how are they different?

For review, please see Table 5-1.

Table 5-1 ***Formulations of Different Topical Therapies***

FORMULATION	DEFINITION/PROPERTIES/INDICATIONS/CONTRAINDICATIONS
Shampoo	Shampoos may cleanse the skin of adherent scale or debris (including allergens) and may be used to deliver medication to the skin in the treatment of widespread dermatologic disease.
Powders	Pulverized solids that are applied in a thin film. Powders can be components of a rinse (added to water), a suspension (added to a liquid), or a paste (added to an ointment) Indications: Because they are hygroscopic (take in water) they dry the skin. Powders are cooling, promote drying, lubricate intertriginous areas.
Wet dressings	Wet dressings are drying, astringent (decrease exudation by precipitation of protein), antipruritic, acidifying, and mildly antiseptic. Indications: For the treatment of acute inflammatory states characterized by exudative lesions, such as lesions that occur with pyotraumatic dermatitis.
Solutions	Solutions are solvents in which active ingredients are dissolved to clarity. Molecules are freely movable in this form from vehicle to skin and are 100% available for absorption. This does not mean there is 100% absorption since the stratum corneum is still a factor.

Table 5-1 ***Formulations of Different Topical Therapies—Cont'd***

FORMULATION	DEFINITION/PROPERTIES/INDICATIONS/CONTRAINDICATIONS
Rinses	Rinses are made by mixing solutions or powders with water. They may be sponged or sprayed on to the animal. As the rinse dries, the residual layer of active ingredients is left on the pet's skin. Rinses, like shampoos, are ideal for treating diseases that involve large areas of the body.
Lotions	Lotions are liquid preparations in which inert or active medications are suspended or dissolved. As the liquid evaporates, there is drying and cooling of the skin, which are properties desirable in the treatment of exudative dermatoses. Also as the base evaporates it leaves active, freely moveable molecules that now act like a solution. Lotions are indicated for acute exudative lesions and are contraindicated in dry, scaly lesions.
Suspensions	Watery lotions to which powder is added. Generally zinc oxide, talcum, calamine, glycerol, alcohol, or water is used. Specific drugs and stabilizers may be added. This preparation dries and cools exudative skin. A drawback of this formulation is a tendency to have sedimentation in the bottle. It is important to shake the container before each use in order to obtain a homogeneous suspension. In addition, when the water has evaporated from the skin, the powder particles may clump together and become abrasive.
Gels	Gels are transparent, colloidal dispersions that liquefy on contact with skin. They are clear, colorless, greaseless, and water miscible. When applied to the skin, gels dry as a nonocclusive film and are preferable to creams or ointments because they penetrate through the haircoat without leaving residual film. While having the advantage of being water-washable, nongreasy, and cosmetically elegant, gels have the disadvantage of lacking any protective or emollient properties.
Creams	Creams are emulsions of oil in water. In a cream, the oil droplets are dispersed in a continuous phase of water or a polar liquid. Creams are used widely for their cooling, moisturizing and emollient effects. They form a protective covering that reduces contact with the environment. Certain occlusive types may reduce water loss, thereby softening and rehydrating the skin. They are contraindicated for exudative lesions.
Ointments	These spread easily to form a protective film on the skin and are more lubricating than creams. Due to their occlusive nature, ointments generally provide better topical penetration of incorporated drugs than do creams or lotions. They are insoluble in water and are difficult to wash off.
Pastes	Pastes are ointments into which 20 to 50% powder (e.g., zinc oxide, starch) is incorporated. The powders must be insoluble in the ointment base in order to exert an absorbent effect. Pastes are more drying, less greasy, and may be tolerated on slightly exudative skin (powder takes up water), whereas creams and ointments are contraindicated in these lesions.

10. What ingredients are useful for topical antipruritic therapy and what is their mechanism of action?

For review, please see Table 5-2.

Table 5-2 ***Topical Antipruritic Agents***

INGREDIENT	MECHANISM OF ACTION (IF KNOWN)
Sulfur	Unknown
Tars	Anesthetizes peripheral nerves
Pramoxine hydrochloride	A surface or local anesthetic to peripheral nerves. Its unique chemical structure is likely to minimize the danger of cross-sensitivity reactions in patients allergic to other local anesthetics.
Ketoconazole	By its anti-*Malassezia* properties and its ability to decrease leukotriene C4, a potent inflammatory cytokine.
Solutions of aluminum acetate, acetic acid, and calcium carbonate	Unknown
Aloe vera extracts	Salicylic acid and magnesium lactate are the two chemical compounds that produce the antipruritic effects. Salicylic acid inhibits the production of prostaglandin from arachidonic acid by inhibiting cyclo-oxygenase, whereas the magnesium lactate inhibits the conversion of histidine to histamine in mast cells via an enzyme called histidine carboxylase.
Menthol	Menthol activates cold-sensitive Aδ fibers, this substitutes a cooling sensation for pruritus.
Dimethyl sulfoxide (DMSO)	DMSO is anti-inflammatory (via free radical scavenging; decreases prostaglandin synthesis; stabilizes lysosomal membranes) and is analgesic by blocking C fibers.
Glucocorticoids (GCs)	See text for complete discussion. GCs decrease the synthesis of proinflammatory molecules and other mediators of inflammation. GCs also profoundly affect the replication and movement of cells. They induce lymphocytopenia, eosinopenia, and monocytopenia and have a greater effect on T cells than on B cells. Macrophage functions (phagocytosis, antigen-processing and cell killing) are also decreased.
Diphenhydramine	First-generation H1 antagonist, antipruritic properties may be derived from competitive antagonism with histamine for H1 receptor binding.
Tacrolimus	Aminophyllin binding macrolide that is related to cyclosporine. Tacrolimus inhibits T cell activation and cytokine production by blocking calcineurin. Calcineurin is a calcium and calmodulin (widespread calcium binding protein) dependent protein phosphatase that dephosphorylates (activates) the transcription factor NFAT (nuclear factor of activated T cells). Without the action of NFAT, cell activation is blocked.
Colloidal oatmeal	May inhibit prostaglandin synthesis. Also a humectant leading to moisturizing of the skin, thereby raising the pruritic threshold.

11. What is meant by the term "barrier therapy"?

These are items that physically prevent the dog or cat from scratching. This could include Elizabethan collars, T-shirts, onesies, bandages, etc.

12. How does barrier therapy help control pruritus?

When the skin is damaged from scratching, inflammatory cytokines are released from the damaged keratinocytes. More pruritus then occurs because of the inflammation, which causes more scratching, which causes more inflammation, leading to the vicious cycle of itch-scratch-itch. By preventing or minimizing the damage to the skin, the itch-scratch-itch cycle is interrupted. Also, one of the functions of the skin (specifically the dead stratum corneum) is to act as a barrier, keeping substances from penetrating into the living epidermis and deeper. When the barrier is physically disrupted, this function is impaired, allowing substances (e.g., antigens) to more easily penetrate the skin.

13. What are the advantages and disadvantages of barrier therapy?

The advantages of physical barriers are that they break the itch-scratch-itch cycle by decreasing damage to the skin without systemic side effects, are inexpensive, and are less labor-intensive than topical therapies.

The disadvantages are:

Some animals will tear the barrier off

Some animals may get clothing "paralysis" (won't walk or move around with clothing on)

The need to keep the barrier clean and dry

Clothing may need to be altered (holes for the tail and genitals)

The barrier may need to be removed before the pet is allowed to eliminate

14. Why are antibiotics sometimes effective in decreasing pruritus?

Antibiotics can have antipruritic activity by two methods. One is by eliminating bacteria that produce pruritogenic substances (e.g., proteases, lipopolysaccharides). Second, some of the appropriate "skin" antibiotics also have direct effects on inflammation. Examples of these are trimethoprim, which decreases leukocyte chemotaxis; fluoroquinolones, which decrease IL1, tumor necrosis factor-α and various leukotrienes; and macrolides, which decrease leukocyte chemotaxis, IL1, and lymphocyte blastogenesis.

15. How do antifungal agents help decrease pruritus?

Ketoconazole (KCZ) can decrease pruritus by a variety of mechanisms. The first is its direct antifungal activity against *Malassezia*. Like bacteria, *Malassezia* produces substances that are pruritogenic. These substances also may trigger type I hypersensitivity reactions. KCZ also affects pruritus by its ability to block the enzyme 5-lipoxygenase. This enzyme is involved in the formation of inflammatory cytokines such as leukotriene C4.

16. People seem to have strong opinions (both pro and con) about the administration of glucocorticoids (GCs) for the symptomatic treatment of pruritus. How do GCs work?

Glucocorticoids (GCs) are the most commonly used medications for the symptomatic treatment of pruritus. GCs passively diffuse through the cell membrane and bind to soluble receptor proteins in the cytoplasm. This hormone–receptor complex then moves to the nucleus and regulates the transcription of target genes; some of the most important of these actions appear to be their inhibitory effect on the transcription factors AP-1 and NF-κB. GCs decrease the synthesis of proinflammatory molecules, including cytokines, interleukins, and proteases, largely through their negative effects on these transcription factors. Other mediators of inflammation such as the inducible form of nitric oxide synthetase and cyclooxygenase-2 are also inhibited.

GCs may also have a positive effect on gene transcription. One of the more important gene functions is to increase the synthesis of lipocortin 1. One of lipocortin's actions is to inhibit

phospholipase A_2 (PLA_2) activity. PLA_2 is the enzyme responsible for the release of arachidonic acid (AA) from membrane phospholipids. Because AA is the parent compound for the formation of proinflammatory prostaglandins and leukotrienes by inhibiting its release, there is less precursor available to form these inflammatory mediators.

GCs profoundly affect the replication and movement of cells. They induce lymphocytopenia, eosinopenia, and monocytopenia.

GCs can cause mast cell depletion in the skin, possibly via decrease in stem cell factor, which is a necessary growth factor for mast cells.

17. How should GCs be used in small animal practice?

The following caveats must be followed for the safe and appropriate administration of glucocorticoids:

GCs should not be used in lieu of identifying the animal's underlying pruritic disease. For animals that have seasonal symptoms of environmental allergen–induced atopic dermatitis and must stay on GCs long term (>2 months out of the year), it is strongly recommended that intradermal allergy testing be performed and allergen specific immunotherapy (ASIT) be instituted. If the symptoms are nonseasonal then it is appropriate to investigate the possibility of cutaneous adverse food reaction causing the pruritus. The owner is instructed how to properly perform a food trial. A homemade diet is preferred. The second choice is a commercial "hypoallergenic" diet, which is a less sensitive test. Commercial foods for use in restrictive feeding trials are either a hydrolyzed diet or a novel protein diet. Regardless of which food is used, the trial should last a minimum of 60 days for dogs and 90 days for cats. If the animal fails to respond to ASIT, a properly performed food trial and an antihistamine trial, or if the owner refuses these options, then GCs should be administered long term rather than have the animal euthanized or left to suffer.

Only short-acting GCs (prednisone, prednisolone, methylprednisolone) should be administered to dogs. Long-acting GCs (methylprednisolone acetate) may be given to CATS as long as they are used only once or twice yearly.

Use the lowest possible dose of GCs that keeps the animal "humanely" pruritic. The goal is to balance the discomfort of the pruritus with the risk of GC administration. Owners should be educated to keep the animal "humanely" pruritic, NOT necessarily pruritus free.

In dogs, administer GCs every other morning. It is currently unknown whether cats should be medicated at night because they are nocturnal animals.

To minimize the amount of GCs needed long term, it is critical to break the itch-scratch-itch cycle. This means giving GCs at a high enough dose for a long enough period of time that the animal stops excessive scratching. It takes less medication to prevent the onset of pruritus once pruritus is RESOLVED than it does if you start at the same dose without resolving the pruritus. One of the most common reasons, other than unidentified *Malassezia* and pyoderma, that GCs are ineffective or minimally effective for pruritus is the failure to give an appropriate starting dose. The author uses prednisone or prednisolone at $\frac{1}{4}$ mg twice daily for 7 days, every day for 7 days, then every other day for 7 days in dogs. Cats require double the previously described dose for clinical effectiveness. Because of the differences in anti-inflammatory potencies, when using methylprednisolone, the previously described calculations should be performed and then substitute one 4-mg methylprednisolone pill for every 5 mg prednisolone/prednisone pill needed. Because methylprednisolone is slightly more expensive but causes less polyuria or polydipsia (pu/pd), it is used in animals that develop pu/pd from prednisolone/prednisone.

18. What tests or monitoring should be performed for animals on long-term GC therapy?

In cases when the animal is on GCs >6 months/year, a complete blood cell count and serum chemistry profile should be performed semiannually to establish "normal" values for that animal. At the same time, a urinalysis is performed to identify pyuria, hematuria, and proteinuria. A urine culture is performed to identify a "silent" urinary tract infection (asymptomatic bacteriuria without pyuria), associated with long-term GC administration.

19. What is the difference between prednisolone, prednisone, and methylprednisolone? How are these drugs used in the author's practice?

For prednisone to be active, it must be converted to prednisolone in the liver. In dogs, prednisolone, prednisone, and methylprednisolone work equally well. Because some cats have a limited amount of the enzyme system necessary to convert prednisone to prednisolone, the author will only use prednisolone in cats. There have been cats where prednisone was ineffective but when prednisolone was administered at the same dose, clinical response was noted. Rather than have both prednisone and prednisolone, only prednisolone is stocked in my practice. This avoids the possibility of inadvertently changing a cat from prednisolone to prednisone.

Prednisone and prednisolone are equally potent in their anti-inflammatory activity, while methylprednisolone is slightly more potent on a milligram per milligram basis. Because methylprednisolone comes in a 4 mg vs a 5 mg tablet like prednisolone and prednisone, tablets of any of these drugs are equivalent.

As stated previously, animals receiving methylprednisolone tend to have less pu/pd than those receiving prednisone or prednisolone.

20. Antihistamines, specifically H1 blockers, seem to have mixed reports of effectiveness. Why are there disparate reports?

Histamine is one of many inflammatory mediators, some that are preformed and others that are newly generated at the time of mast cell activation (Table 5-3). It is unclear at this time which of the mediators is most important in humans, dogs, and cats. Another unanswered question—Are there differences between species and between individuals of the same species? So blocking histamine in one individual or species may be effective because histamine is an important pruritogenic factor, while in others it will be ineffective because histamine is not as important of a mediator of pruritus.

Table 5-3 ***Human Mast Cell Inflammatory Mediators***

PREFORMED	NEWLY GENERATED
Histamine	Leukotrienes B_4-E_4
Tryptase	Prostaglandins D_2 and F_2
Chymases	Platelet activating factor
Carboxypeptidases	Thromboxane A_2
Acid hydrolases	Cytokines
Arylsulfatase	
Eosinophil chemotactic factor of anaphylaxis	
Neutrophil chemotactic factor	
Heparin	
Chondroitin sulfate	

21. How does histamine create inflammation?

Histamine causes vasodilatation and increased permeability of vessels that contributes to local edema formation. It also stimulates nerve endings, creating the sensation of pruritus.

22. What is the mechanism of action of antihistamines?

They work either by blocking the release of histamine or more commonly by competitive inhibition for H1 receptors on inflammatory cells. First generation antihistamines also block the muscarinic receptors (creating atropine-like side effects), serotonin receptors, and α-adrenergic receptors. Currently only H1 receptor blockade is considered important for the symptomatic treatment of pruritus.

23. What are the dangers and side effects of antihistamines?

Antihistamines in general are very safe but, because they are metabolized by the liver, should be used cautiously or avoided in animals with liver disease. Side effects include sedation; paradoxical restlessness/agitation; gastrointestinal (GI) disturbances (anorexia, vomiting, diarrhea); dry mouth, sometimes creating polydipsia +/- polyuria; and anticholinergic effects, such as tachycardia and urinary retention.

Because antihistamines have anticholinergic effects, they are contraindicated in patients with narrow angle glaucoma, chronic obstructive pulmonary disease, severe congestive heart failure, and conditions that create urinary retention (e.g., prostatic hypertrophy, bladder neck obstruction). Some reports have described the lowering of seizure thresholds and recommend avoiding their use in epileptics.* I have not seen an increase in seizures when antihistamines are used in epileptics. However, antihistamines stimulate the cytochrome P450 enzyme system in the liver, which can facilitate metabolism of anticonvulsants, and therefore they should be used cautiously in animals receiving anticonvulsant medication.

24. Which antihistamines do you use and at what doses?

It is better to begin with the upper dosage and frequency and lower it if the pet responds, because it can be difficult to convince clients to try an antihistamine a second time (Tables 5-4 and 5-5).

Table 5-4 ***Antihistamines for Dogs***

DRUG	DOSAGE	FORMULATIONS	ADDITIONAL COMMENTS
Hydroxyzine	0.5-1 mg/lb bid-tid Initial trial: 14 days	Liquid: 10 mg/mL Pills: 10, 25, 50 mg	Hydrochloride form has become very expensive ($0.70-0.90/50 mg pill); the pamoate form can be used.
Chlorpheniramine	0.2-0.25 mg/lb bid Initial trial: 14 days	Pills: 4 mg Capsule: 8, 12 mg	Bitter tasting DON'T exceed dosage listed. Sudden death has occurred with this medication at doses higher than 0.5 mg/lb/day Available as an over-the-counter medication.
Diphenhydramine	0.5-1.0 mg/lb bid –tid Initial trial: 14 days	Liquid Capsule: 25, 50 mg Caplet: 25 mg	Seems to be the most sedating of all the antihistamines. Available as an over-the-counter medication.
Clemastine	0.05-0.1 mg/kg bid Initial trial: 14 days	Tablets: 1.34, 2.68 mg	Available as an over-the-counter medication.

*Antihistamines in the phenothiazine class (which includes promethazine hydrochloride and trimeprazine tartrate [Temaril]) are the most likely to lower the seizure threshold and should be avoided in animals with a history of seizures.

Table 5-4 ***Antihistamines for Dogs—Cont'd***

DRUG	DOSAGE	FORMULATIONS	ADDITIONAL COMMENTS
Amitriptyline	0.5-1 mg/lb bid Because of the long $T_{1/2}$ the initial trial should be 21 days	Capsules: 10, 25, 50, 100 mg	Useful for obsessive-compulsive behavior that may complicate pruritus in dogs.
Cyproheptadine	0.5-1.0 mg/kg bid-tid Initial trial: 14 days	Pill: 4 mg	Because of the size of the pill and the dose required, large dogs will frequently need 5-8 pills tid. May cause polyphagia in cats. May cause agitation (hallucinations?) in cats. To avoid, start at the lower dose and give sid for 2 days, bid for 2 days and then **full** dose tid.
Doxepin	0.5-1 mg/lb bid Because of the long $T_{1/2}$ the initial trial should be 21 days	Capsules: 10, 25, 50, 75, 100 mg	Useful for obsessive/compulsive behavior that may complicate pruritus in dogs.

Table 5-5 ***Antihistamines for Cats***

DRUG	DOSAGE
Hydroxyzine	0.5-1 mg/lb bid-tid Initial trial: 14 days
Chlorpheniramine	0.2-0.25 mg/lb bid Initial trial: 14 days
Clemastine	0.05-0.1 mg/kg bid Initial trial: 14 days
Amitriptyline	5-10 mg/cat/day given either sid or divided bid. Because of the long $T_{1/2}$ the initial trial should be 21 days
Cyproheptadine	0.5-1.0 mg/kg bid-tid Initial trial: 14 days

25. All the antihistamines listed are first generation. Why not use second-generation antihistamines?

Second-generation antihistamines are used in humans because they are less likely to penetrate the blood-brain barrier. By less penetration into the brain, there are fewer CNS effects (e.g., sedation). In contrast to first-generation antihistamines, they also lack the antimuscarinic properties (anticholinergic). I do not use these agents because they have not been reported to be any more effective in dogs and cats and are very costly.

26. What benefit can be expected from antihistamines?

Unfortunately there are very few published blinded, placebo-controlled studies of the effectiveness of antihistamines in the treatment of pruritus in dogs with atopy. Using data from open studies, antihistamines were reported to adequately control pruritus associated with atopy in 0-60% of dogs. Antihistamines alone will adequately control pruritus in <10% of atopic dogs. However, this population of dogs is biased because I am in a referral practice and only see dogs and cats that are very pruritic.

Antihistamines may, instead of adequately controlling pruritus alone, act as steroid-sparing agents, allowing a lowering of the dosage of GCs necessary to control pruritus.

27. What are tricyclic antidepressants (TCAs) and how do they help pruritic dogs and cats?

These animals are not depressed! Tricyclic antidepressants have a variety of activities including inhibiting the reuptake of monoamine neurotransmitters (biogenic amines) such as norepinephrine (NE) and serotonin, which are in the nerve terminals within the CNS. Another action is their ability to block histamine (H1) receptors. Both these activities can help the pruritic dog or cat. The theory of obsessive-compulsive behavior is that low levels of these biogenic amines are responsible for the behavior. The author believes that some breeds of dogs are very focused on their licking behavior, well in excess of overall pruritus, leading to the opinion that some dogs have pruritus that is *partially* caused by obsessive-compulsive behavior. This is especially true in the Bichon Frise and Jack Russell Terriers. Doxepin's antihistamine activity is 779 times more potent than diphenhydramine.

It is currently unknown whether TCAs' antihistamine properties, their reuptake inhibition of the neurotransmitters (NE and serotonin), or some other unknown properties are responsible for the antipruritic activity.

28. What are the dangers and side effects of tricyclic antidepressants?

The side effects are mostly related to their blocking α-adrenergic receptors and muscarinic receptors (anticholinergic actions). These side effects include dry mouth (possibly leading to polydipsia +/- polyuria), sedation, tachycardia, tachyarrhythmias, urinary retention, and GI disturbances (constipation and anorexia). They should be avoided in patients with narrow angle glaucoma. Some authors recommend a pretreatment electrocardiogram (ECG) and serum chemistry profile (to evaluate the liver); however, this is not necessary unless there is something historical about the patient that makes them at risk for cardiac or hepatic complications. In humans they only worry if they are using high doses in patients with cardiac conduction problems. They will perform pretreatment ECG if the patient is older than 55 years old. They will then do a follow-up ECG in 30-60 days. It is rare to see any changes in the ECG in these patients.

Monoamine oxidase inhibitors (MAOIs) will increase the concentration of these monoamine neurotransmitters by inhibiting their metabolism. It is contraindicated to use TCAs and MAOIs in the same patient. Examples of MAOIs that are used in veterinary medicine include L-deprenyl and amitraz.

29. Because serotonin is also a monoamine neurotransmitter, what about using selective serotonin reuptake inhibitors for dogs with pruritus associated with atopic dermatitis?

There is insufficient evidence to recommend the administration of these drugs at this time.

30. What is cyclosporine (CSA)?

Cyclosporine is a very potent immunosuppressive macrolide lactone that lacks antimicrobial activity. It is produced by the fungus *Tolypocladium inflatum*.

31. What is the antipruritic mechanism of action of CSA?

It blocks T cell activation and cytokine production. By inhibiting cytokine production, it interferes with antigen presentation. It also decreases skin mast cell counts, survival, degranulation upon stimulation, and production of cytokines.

32. How does CSA interfere with T cell activation and antigen presentation?

CSA binds to calcineurin and blocks its activity. Calcineurin is a calcium and calmodulin (widespread calcium binding protein)–dependent protein phosphatase that is responsible for calcium dependent transmission of signal information from the cell membrane to the nucleus. Calcineurin achieves this transmission by dephosphorylating NF-AT (nuclear factor of activated T cells). NF-AT is a transcription factor that penetrates the nucleus. In the nucleus it induces cell activation. One of the essential processes in activation is the transcription of the genes controlling the synthesis of IL2. IL2 is a key T cell growth factor that, when inhibited, leads to impairment of T-helper and T-cytotoxic lymphocytes.

33. What dose of CSA has been used for atopy?

The best formulation of CSA is the microemulsified form (Neoral). Absorption of this formulation is the most consistent. The induction dose of microemulsified cyclosporine (mCSA) is 5 mg/kg once daily given 2 hours before or after a meal. It is given on an empty stomach to provide more consistent absorption. This was more of an issue with the older formulations of CSA than with the mCSA formulation. If the animal responds to this dose, which typically will occur within 4-6 weeks, the dose is decreased to 1-3 mg/kg once daily for 30 days and then every other day. In some cases, after 2-3 months of therapy, CSA can be discontinued and pruritus is still controlled.

34. Anything else that we should know about prescribing mCSA?

If you initiate therapy with 5 mg/kg once daily, at least 50% of the animals will have intense vomiting. To minimize this problem, I use the following mCSA protocol:

Give mCSA with a small amount of food

For the first 10 days of mCSA therapy, administer metoclopramide 30-60 minutes before mCSA treatment. Give the metoclopramide as follows:

<10 lbs body weight (BW)—2.5 mg

11-40 lbs BW—5 mg

>40 lb—10 mg

Slowly introduce mCSA. Start with 1 mg/kg once daily for 2 days, 2 mg/kg once daily for 2 days, 3 mg/kg once daily for 2 days, 4 mg/kg once daily for 2 days, and then 5 mg/kg once daily.

35. How effective is CSA in treating atopic dermatitis–induced pruritus in the dog?

To my knowledge, there have only been two studies evaluating the effectiveness of CSA for the treatment of pruritus in atopic dogs. The first was an open uncontrolled study in which there was a 100% decrease in pruritus within 14 days.

In the second study, 30 dogs were entered into a randomized controlled trial. They were treated for 6 weeks either with mCSA at 5 mg/kg once daily or prednisolone at 0.5 mg/kg once daily. At the end of the study, the percentage reduction in pruritus was not different between the two groups.

In my experience, in an unpublished study of 20 atopic dogs, only 10% responded enough to stop prednisolone administration and another 10% responded enough to lower the prednisolone dose by approximately 50%.

36. What are the disadvantages and side effects of CSA administration?

There are a number of disadvantages with CSA. The number one barrier is cost. It currently costs approximately $7.00-8.00/100 mg of mCSA. Because a 20-kg dog would require 100 mg mCSA/day, it would cost $200.00-300.00/month.

The second barrier to using this drug is the intense vomiting that occurs during the first few days of therapy. This can be overcome as previously described.

Additional side effects that have been reported in cats and dogs include hypertrichosis, papillomatosis, gingival hypertrophy, other GI disturbances (diarrhea, anorexia), and weight loss.

Another consideration in using CSA is the effects that other drugs have on the metabolism of CSA. CSA is metabolized by the cytochrome P450 (cP450) system in the liver. Drugs that inhibit cP450 will increase blood levels of CSA, possibly into the toxic range. Examples of commonly used inhibitors of cP450 in veterinary medicine include doxycycline, fluconazole, ketoconazole, itraconazole, prednisolone, methylprednisolone, and furosemide.

Other drug interactions that need to be considered are drugs that decrease CSA concentrations by stimulating cP450 enzymes. Phenobarbital is an example of a drug that stimulates these enzymes.

At this time increases in parasitic or bacterial infections associated with CSA administration have not been reported.

37. How can the dose of CSA be lowered to try to decrease these side effects?

Because ketoconazole (KCZ) interferes with CSA metabolism by blocking cP450 enzymes in the liver, some authors combine mCSA with ketoconazole to try to decrease the side effects and cost. It has been reported that 3-10 mg/kg KCZ will lower the required CSA dose by 50%. Because the absorption and metabolism of mCSA varies from animal to animal, the appropriate dose when using KCZ with mCSA has not been established at this time. Liver enzymes should be monitored when chronically administering KCZ because of the concern for hepatotoxicity. I do not recommend this combination at this time because:

There is little to no cost savings over full-dose mCSA exclusively when the total cost of both medications is calculated and added to the additional cost of monitoring liver enzymes;

Using KCZ adds additional potential side effects including GI disturbances (vomiting, anorexia) and hepatotoxicity.

38. What is cyclic adenosine monophosphate (cAMP) and what does it do?

cAMP is an intracellular "second" messenger that is synthesized from ATP. A second messenger amplifies the signal that is generated when a cell surface receptor is activated.

cAMP stabilizes mast cells, T cells, macrophages, and eosinophils, inhibiting cell activation and the release of inflammatory mediators.

39. What is phosphodiesterase (PDE)?

PDE is a family of enzymes that converts cAMP to 5-AMP. Because cAMP is an inhibitor messenger, by converting cAMP to its inactive form (5-AMP), there is less inhibition of mast cell degranulation.

Of the various PDE isoenzymes, PDE-4 appears to be the predominant type in mast cells, T cells, macrophages, and eosinophils.

40. What role does PDE play in the pathogenesis of pruritus associated with atopic dermatitis?

One of the theories of the pathogenesis of atopic dermatitis is that there is a blunted cAMP response due to an increased activity of PDE. Because of this overactivity, there is then less cAMP. With less (inhibitory) cAMP, the inflammatory cells are more active.

41. What pharmacologic therapies are being investigated to correct this defect?

There are a number of PDE inhibitors currently available, none being specific for PDE-4. Currently, only drugs in the methylxanthine family are used in veterinary medicine. Examples are aminophylline, theophylline and pentoxifylline. Pentoxifylline, in contrast to theophylline and aminophylline, does not have cardiac effects.

Pentoxifylline has been used for a variety of diseases, including atopic dermatitis in dogs. The reports of successful treatment of atopic dermatitis with pentoxifylline have been mixed. Currently, the author does a 30-day trial using 15 mg/kg thrice daily.

42. What therapeutic role does prostaglandin E_1 (PGE_1) play in the treatment of canine atopic dermatitis?

PGE_1 elevates cAMP and, as previously described, this elevation inhibits activation of many different inflammatory cells. Misoprostol, a PGE_1 analog, has been reported to be effective in some dogs with atopic dermatitis. The author has not seen any patients respond to this therapy.

43. There are two families of essential polyunsaturated fatty acids (PUFAs) in cats and dogs—omega 6 and omega 3. What are their roles in the normal animal?

Essential PUFA are important for epidermal barrier function, formation of cell membranes, and as precursors of inflammatory mediators.

44. Which PUFAs are involved in pruritus and how?

Arachidonic acid (AA), an omega 6 PUFA, is the major PUFA involved in inflammation. AA is bound in an inactive form to phosphatidylcholine in the cell membrane. When cell surface receptors are activated or the cell is damaged, phospholipase A_2 (PLA_2) is activated. PLA_2 breaks down phosphatidylcholine, releasing active AA. AA is then metabolized by cyclo-oxygenase (COX) and lipoxygenase enzymes into inflammatory mediators. These inflammatory mediators are the even-numbered series of leukotrienes (LT), thromboxanes (TXA), and prostaglandins (PG).

45. Omega 6 PUFAs have been touted as an effective therapy for pruritus. What is the theory behind this recommendation?

γ-Linolenic acid (GLA) and dihomo γ-linolenic acid (DGLA) are omega 6 PUFA that when metabolized by COX and lipoxygenase enzymes form anti-inflammatory (odd-numbered series of LT, PG and TXA) products. In addition to these anti-inflammatory products, GLA and DGLA are competitive inhibitors for the COX and lipoxygenase enzymes, thereby decreasing the amount of AA that is converted to inflammatory byproducts.

46. What other mechanisms can contribute to omega 6 PUFA's effectiveness in the treatment of pruritus?

It has been suggested that dogs with atopy have abnormal barrier function and excessive transepidermal water loss (TEWL).

Barrier function, the ability to prevent penetration of a variety of substances through the skin, is primarily controlled by lipids in the skin. The major lipid involved in this function is linoleic acid, a type of omega 6 fatty acid. When there is defective barrier function, environmental allergens can more effectively penetrate into the living epidermis, where they are able to trigger an inflammatory response.

In addition to its role in barrier function, linoleic acid (LA) is critically important in controlling TEWL. When there is excessive TEWL, the skin becomes excessively dry, and this may also contribute to pruritus.

By administering LA, TEWL can be decreased, which may improve the epidermal barrier function.

47. How are omega 3 fatty acids beneficial in the treatment of pruritus?

Omega 3 fatty acids (e.g., eicosapentaenoic acid [EPA]), a PUFA that, when metabolized by COX and lipoxygenase enzymes, produce anti-inflammatory series of PGs, LTs, and TXAs. In addition to anti-inflammatory end products, omega 3 fatty acids are competitive inhibitors of AA (compete for the COX and lipoxygenase enzymes). So, like some omega 6 fatty acids (GLA, DGLA), they are anti-inflammatory. But in contrast to omega 6 fatty acids, they are not converted to AA and therefore cannot be metabolized into inflammatory mediators.

Some authors report that the combination of omega 6 and 3 fatty acids work synergistically, while others report that omega 3 alone is more effective for the treatment of pruritus.

48. How do you use these PUFAs (omega 3 and 6)? How are they dosed?

Because these PUFAs may work synergistically with antihistamines, the author uses them simultaneously with antihistamines. As in treatment trials with antihistamines, treatment trials should be done with these PUFAs. If the combination omega 3+6 product is ineffective, then an exclusive omega 3 product should be tried.

To be effective, PUFAs must be incorporated into the phospholipids of the cell membrane. When the cell receptors activate PLA_2, the anti-inflammatory PUFAs are available to be released. Once they are released they are then acted upon by both COX and lipoxygenase. To be incorporated into cell membranes, trials with PUFAs should last 60-90 days.

Combination products (containing omega 3 and 6) are administered at double the label dose. For products with only omega 3, animals should receive approximately 18 mg EPA/lb body weight daily. As mentioned previously, these products are used for 60-90 days before deeming them a failure.

If the animal is seasonally pruritic, omega 3 and/or 6 PUFA should be started 60 days before the onset of the pruritic season.

49. What are the side effects or disadvantages associated with PUFAs?

The biggest disadvantage is the limited success that the author has experienced with their use. Another disadvantage is that these supplements are costly, especially for large dogs.

Side effects are very limited and may include GI disturbances (vomiting or diarrhea) and the pet having a fish smell to the breath. Additionally, if the owners puncture the capsules and squirt the contents into the food, they may also complain of the fish smell on their hands. Reports of prolonged bleeding time due to platelet dysfunction have not been a problem clinically.

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6. ANTIMICROBIAL THERAPY

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1. Why is knowledge about antimicrobial therapy important in dermatology?

Skin infections are common clinical problems in veterinary medicine. Skin infections may occur if the integrity of the skin is weakened by trauma, if there are changes in surface immunity, or if there are changes in microclimate and resident microflora. Skin infections are classified as primary or secondary depending on whether an underlying cause for the infection can be found. Secondary infections are by far the most common and may reflect abnormalities in the skin, immune system, or changes in metabolism. Skin infections may frequently complicate other conditions.

Bacterial infections, such as superficial staphylococcal pyoderma, are often secondary to underlying causes, such as hypersensitivity skin disease (atopy, food allergy, flea bite hypersensitivity), endocrinopathies (hypothyroidism, hyperadrenocorticism), parasitic skin disease (*Sarcoptes, Demodex*), immune-mediated disease, or keratinization disorders. The vast majority of bacterial skin infections in dogs involve *Staphylococcus intermedius*. Occasionally *Proteus* spp., *Pseudomonas* spp., and *Escherichia coli* are involved as secondary invaders. In cats, *Pasteurella multocida* and β-hemolytic streptococcus are involved. *Malassezia* dermatitis is also becoming a common diagnosis, most often secondary to other skin diseases, especially those involving any degree of greasy seborrhea (seborrhea oleosa).

The key to successful management of bacterial and yeast skin infections is early recognition followed by appropriate therapy. Skin cytology is the key to an appropriate diagnosis. The extent of therapy instituted will normally depend on the type of infection, severity of the disease condition, and the number of body sites affected.

2. What are the first steps in deciding how to treat a skin infection?

Many veterinarians make the mistake of not assessing the patient thoroughly enough before instituting therapy for a skin infection. This often leads to doubts about the effectiveness of the chosen therapy. Treatment success will be significantly improved if a logical approach to diagnosis and appropriate diagnostic testing is used. As mentioned previously, skin cytology from the affected areas is an important step in diagnosis. Bacterial culture and sensitivity may also be indicated although this is often not performed unless rods are noted on cytology. Elimination of a confirmed bacterial or yeast infection is a crucial part of the treatment plan for many allergic individuals. This is especially important because bacterial or yeast involvement may be contributing significantly to the degree of pruritus noted.

3. When would topical therapy be considered?

Topical therapy should be regarded as more than just a useful adjunctive therapy for dermatologic disease. It may be a way to significantly decrease the need for systemic antimicrobial therapy. The decision to use topical therapy is usually dictated by the extent of the infection and the severity of the problem. Topical therapy may be particularly useful when focal areas of the body are affected, such as the interdigital areas or skin folds. Antiseptic creams, gels, or lotions may be the only treatment required, especially if treatment is required on a chronic basis such as in a Bulldog with chronic facial fold pyoderma. Most dermatologists tend not to use ointment formulations, because ointments can be occlusive, slowing healing and drying of the affected areas, risking further spread of infection.

Infections limited to the skin surface can be effectively treated with topical therapy alone. Superficial or surface infections such as puppy impetigo, intertrigo (skin fold pyoderma), or acute moist dermatitis (pyotraumatic dermatitis, hot spots) may be treated with topical antimicrobial treatment alone. The horny layer of the skin, the stratum corneum, is relatively impermeable, impeding topical drug penetration. Because transdermal absorption may be limited, topical therapy may not be suitable for deeper infections except as an adjunctive therapy. Also, if the lesions are more widespread it may be more practical to consider systemic therapy.

In the vast majority of cases, a combination of topical and systemic therapy is the preferred and most appropriate way to resolve a skin infection. Topical therapy may reduce the need for systemic therapy by decreasing or eliminating the bacterial population in an area of infection as well as removing tissue debris.

4. What antibacterial agents are available for topical use?

The most commonly used antibacterial agents for topical use are mupirocin, fusidic acid, neomycin, gentamicin, bacitracin, polymyxin B, and thiostrepton. Because of potential systemic toxicity, mupirocin, fusidic acid, neomycin, thiostrepton, and polymyxin B are only available in topical formats. Mupirocin (Bactroderm; Pfizer Animal Health) and fusidic acid (Fucidin; Leo) are the most effective topical treatments for staphylococci. Mupirocin has poor activity against gram-negative organisms. Polymyxin B and bacitracin in combination have activity against some gram-negative as well as gram-positive organisms. Neomycin has been incriminated as a potential contact allergen. Polymyxin B and gentamicin may have good activity against *Pseudomonas* isolates in the treatment of ear disease. The surfactant TrisEDTA has been shown to potentiate the effects of the topical antibiotics, in particular the aminoglycosides, in the treatment of *Pseudomonas* ear infections.

Benzoyl peroxide gels are also available. Benzoyl peroxide is bactericidal, keratolytic, and also has a flushing effect on hair follicles. Benzoyl peroxide gels are available in a 5% concentration. Benzoyl peroxide gel has to be used with care, because it bleaches and may be irritating with repeated use.

5. Is shampoo therapy a useful way to control skin infections?

Shampoo therapy is a very effective way to decrease bacterial skin colonization. Even though topical therapy may not be appropriate for therapy by itself it can be very useful as an adjunctive therapy in many skin infections. Although veterinarians are often discouraged from recommending shampoo therapy because of compliance issues, it can be very useful especially in ensuring clients' involvement in the treatment process. Product selection depends on the owner's preference and clinician's recommendations. Choosing a milder or more client-pleasing shampoo (fragrance, consistency, lathering ability) will often increase owner compliance.

Owner compliance can be improved if clients are shown how to bathe their pet using either handouts, videotapes, or by demonstration. Adequate contact time is crucial for successful shampoo therapy. It takes 5-10 minutes to rehydrate the epidermis, and 10-15 minutes to allow penetration and a treatment effect. Frequency of bathing depends on the severity of the problem. Clients are normally advised to bathe their pet every 2-3 days during the induction phase, reducing to once a week or so for maintenance.

Heavy-coated dogs may need to be clipped to allow the product to reach the skin surface. A shorter coat will significantly decrease the amount of shampoo used. Clipping is essential when dealing with any deep infection or acute moist dermatitis. Clipping helps remove crusts and allows the medication to penetrate into the deeper tissues.

Although shampooing is beneficial, soaking lesions may be even more beneficial at the start of treatment. Hydrotherapy softens and removes crusts, decreasing bacterial colonization and promoting epithelialization. Warm water soaks may also dilate blood vessels, increasing the delivery of systemic antibiotics to the skin. Typically, hydrotherapy is performed for the first 3-7 days of a treatment protocol before switching over to a shampoo therapy regimen. It is important not to overdo the hydrotherapy as it may lead to maceration of the skin.

6. What shampoo ingredients have antimicrobial activity?

Many shampoo agents can be regarded as being at least mildly antimicrobial. Some agents are directly antimicrobial with activity against bacteria, *Malassezia*, or both, whereas others both kill organisms and produce an environment that is hostile to pathogens, restoring the microclimate to normal. Many agents are antimicrobial by virtue of their keratolytic and degreasing activity (particularly keratolytic agents such as sulfur, salicylic acid, or tar). Shampoo products are used most frequently for generalized or more widespread infections, although local treatment may be indicated for fold pyodermas or pododermatitis.

Benzoyl peroxide shampoos have been shown to be very effective antimicrobial agents by virtue of their bactericidal activity and follicular flushing ability. Residual activity for 48 hours after application has been noted. Superior activity has been noted for benzoyl peroxide compared to chlorhexidine, povidone-iodine, and triclosan. Concentrations greater than 5% have been shown to be irritating. Owners should also be warned that benzoyl peroxide products may bleach fabric. Once- or twice-weekly application is recommended. Because benzoyl peroxide is keratolytic and degreasing, following the shampoo with a moisturizing rinse is recommended. In my practice, I frequently combine benzoyl peroxide shampoo with a 2% chlorhexidine leave-on conditioner (Resichlor; Virbac) to maximize the residual antimicrobial benefit.

Chlorhexidine has been shown to be an effective antimicrobial agent with broad-spectrum activity against bacteria and yeasts, as well as dermatophytes. Chlorhexidine is available in either solution or shampoo formulations. Solutions are normally used at 0.5% concentrations. Shampoo and leave-on conditioning formulations are available at 2%. Residual activity has been noted with all formulations. Moisturizing agents are included in the shampoo and the rinse formulations to allow long-term use. Chlorhexidine may be less irritating than benzoyl peroxide in individuals with sensitive skin.

Imidazoles, such as ketoconazole and miconazole, may be effective in therapy for *Malassezi*a and other fungal organisms. They act by interfering with ergosterol synthesis within the organism, increasing cellular permeability, suppressing metabolic function, and inhibiting growth. Ketoconazole also decreases keratinocyte growth in culture, suggesting a possible keratoplastic effect. A once- or twice-weekly degreasing bath using a sulfur/salicylic acid or coal tar/sulfur/salicylic acid shampoo followed by a 2% ketoconazole or miconazole shampoo is recommended for severe *Malassezia* dermatitis cases. The 2% ketoconazole shampoo may be used on a regular basis for focal treatment of interdigital or lip-fold *Malassezia* problems. Unfortunately, there is currently no miconazole veterinary product available in Canada.

Enilconazole (Imaverol; Janssen) is an effective topical rinse for *Malassezia* dermatitis and dermatophytosis. A 1:50 solution is recommended. Acetic acid also has good activity against *Malassezia*. An acetic acid–boric acid shampoo product recommended as a cleansing shampoo is available (Malacetic; Dermapet). The use of povidone iodine products has decreased in popularity because of the development of more efficient products, the risk of irritation, and their tendency to stain the hair coat. A full list of antimicrobial shampoo agents is included in Table 6-1.

Table 6-1 ***Antimicrobial Agents in Shampoo Formulation***

INGREDIENT	ATTRIBUTES	PRODUCTS
Benzoyl peroxide	Antibacterial	Benzoyl Plus (EVSCO, 2.5%)
	Antifungal	Pyoben (Allerdem, Virbac, 2.5%)
	Follicular flushing	SulfOxydex (DVM, 2.5% with 2% sulfur))
	May be drying/irritating	
	May bleach fabric	ChlorhexiDerm (DVM, 2% or 4%)
Chlorhexidine	Antibacterial	Hexadene (Virbac, 2%)
	Antifungal	Ketochlor (Virbac, 2% with 1% ketoconazole)

Continued

Table 6-1 *Antimicrobial Agents in Shampoo Formulation—Cont'd*

INGREDIENT	ATTRIBUTES	PRODUCTS
	May be drying Available as a rinse	Malaseb (DVM, 2% with 2% miconazole) Resichlor (Virbac, 2%) SebaHex (EVSCO, 2% with 2% sulfur, 2% salicylic acid)
Povidone-iodine	May be drying/irritating May stain coat	2% povidone-iodine
Triclosan	Antibacterial	SeboRx (DVM, 0.5% with 2% sulfur, 3% salicylic acid)
Benzalkonium chloride	Antibacterial	Canadian Medicated Shampoo (Vet Solutions, 0.1%) Renew C (Bimeda-MTC, 0.1%)
Ethyl lactace	Antibacterial Follicle flushing	Etiderm (Virbac)
Acetic acid	Antifungal	MalAcetic (DermaPet)
Enilconazole	Antifungal	Imaverol (Janssen)
Ketoconazole	Antifungal Keratoplastic? May be irritating	Nizoral (Janssen, 2%) Ketochlor (Virbac, 1% with chlorhexidine)
Miconazole	Antifungal	Dermazole (Virbac, 2% with 0.5% chlorhexidine) Miconazole shampoo (EVSCO, 2%) Malaseb (DVM, 2% with 2% chlorhexidine) ResiZole (Virbac, 2%)

7. How do you decide what is the most appropriate antibiotic for systemic use?

Bactericidal antibiotics are recommended for skin infections; however, bacteriostatic drugs may be effective if the patient is not immunocompromised. Ideally the drug chosen should have a narrow spectrum to limit the effects on the normal flora of both the skin and gastrointestinal tract.

The most important factors in determining the choice of antibiotic are the susceptibility of the organism and ensuring that the antibiotic builds up effective levels within the skin. Because only 4% of cardiac output reaches the skin, this is critically important—there may be a dramatic difference in the epidermal levels of antibiotic compared to serum levels. For instance, cephalexin levels in canine epidermis are only 20-40% of the peak plasma concentrations.

Most antibiotic use in dermatology is empirical, based on *Staphylococcus intermedius* as the causal agent of pyoderma in dogs. The vast majority of *S. intermedius* isolates show > 95% sensitivity to fluoroquinolone antibiotics, clavulanic acid–potentiated amoxicillin, oxacillin, and cephalosporins. Although the individual fluoroquinolones and cephalosporins each have their own unique attributes as far as *S. intermedius* is concerned, if one drug shows sensitivity, the others in the class should be effective as well. The macrolides such as erythromycin, lincomycin, and clindamycin generally show very good sensitivity against *S. intermedius* for first-time cases when resistance should not be an issue. Potentiated sulfonamide antibiotics have been shown to show excellent susceptibility in some studies while others showed only 50% of isolates were sensitive. The use of potentiated sulfonamide antibiotics has decreased dramatically because of an increased risk of significant side effects, including immune-mediated drug reactions, keratoconjunctivitis sicca, and thyroid suppression if used for longer than 3-4 weeks.

Most dermatologists use cephalexin as their first choice drug because it has been shown to be a very effective drug against *S. intermedius* with minimal change in resistance pattern over the years. Fluoroquinolone use for pyodermas is controversial. I personally do not believe that they perform as well as cephalexin, and the development of class-specific resistance by gram-negative organisms is of major concern. Generally, fluoroquinolone use is best reserved for situations when it is indicated based on the results of bacterial culture and susceptibility testing. A full list of antibacterial agents and recommended doses is included in Table 6-2.

Table 6-2 ***Antibiotic Therapy in Veterinary Dermatology***

DRUG	DOSE (ORAL UNLESS OTHERWISE NOTED)	COMMENTS
Narrow Spectrum		
Lincomycin	20-30 mg/kg q 12h	First time empirical therapy only
Clindamycin	5-10 mg/kg q 12h	GI upset common
Erythromycin	15 mg/kg q 8h	First time empirical therapy only
Tylosin	10-20 mg/kg q 12h	
Broad Spectrum		
Cephalexin/cefadroxil	20—30 mg/kg q 8-12h	Most commonly used antibiotic in canine therapy 4-12 weeks of therapy
Clavulanic acid potentiated amoxicillin	12.5-25 mg/kg q 12h	Most commonly used antibiotic in feline therapy Second choice for canine therapy
Cloxacillin	20-40 mg/kg q 8h	
Oxacillin	22 mg/kg q 8h	Should be dosed three times daily
Chloramphenicol	50 mg/kg q 8h (D) 50 mg/kg q 12h (C)	Risk of human blood dyscrasias
Ciprofloxacin	5-15 mg/kg q 12h	Potential activity against *Pseudomonas* Not in immature animals
Difloxacin	5-10 mg/kg q 12h	Not in immature animals.
Enrofloxacin	5-20 mg/kg q 12h	Potential activity against *Pseudomonas* Not in immature animals Maximum dose 5 mg/kg q 24h in cats
Marbofloxacin	2.75-5.5 mg/kg q 24h	Potential activity against *Pseudomonas* Not in immature animals
Orbifloxacin	2.5-7.5 mg/kg q 24h	Not in immature animals
Trimethoprim-sulfadiazine	15-30 mg/kg q 12h	KCS, drug reactions, hypothyroidism (high doses)
Trimethoprim-sulfamethoxazole	15-30 mg/kg q 12h	KCS, drug reactions, hypothyroidism (high doses)
Ormetoprim-sulfadiazine	55 mg/kg q 24h (day 1) then 27.5 mg/kg	KCS, drug reactions, hypothyroidism (high doses)
Mupirocin 2% cream/ointment	Topical q 12h	Localized lesions

8. How long a course of systemic antibiotics is required to eliminate a pyoderma?

Because of the difficulty in achieving effective drug concentrations within the epidermis, a minimum 3- to 4-week treatment course is recommended and at least 1-2 weeks after clinical cure. Longer courses are recommended for deep infections. At the Ontario Veterinary College, a 4-week course may be inadequate to completely eliminate superficial pyoderma. Recurrent pyoderma cases are routinely treated for 12 weeks while an attempt is made to look for predisposing causes for the infection.

9. Why are bacterial culture and susceptibility testing not performed more regularly in veterinary dermatology?

Unlike the human staphylococcal bacteria, *S. aureus*, the sensitivity pattern of *S. intermedius* has not changed dramatically over the years. For this reason, culture and susceptibility testing (C&S) is not normally used unless there has been a failure to respond to rational antibiotic therapy. As always, the results of the C&S should be interpreted in the light of skin cytology results. It is also important to note that multiple strains of *S. intermedius* may be found on the same dog, each with its own virulence and resistance pattern. Susceptibility testing of individual isolates is therefore of doubtful value.

Culture and susceptibility testing is usually reserved for cases where a less than adequate response to appropriate therapy has been noted or the patient has experienced an allergic reaction or displayed drug intolerance. In my experience, it is much more common that a dog fails to respond because the chosen drug was not appropriate, the dose was not high enough, or the course not long enough. Under these circumstances, especially if a drug like cephalexin has been used, then the question that has to be raised is, Does this dog really have a pyoderma?

10. Give four reasons why a chosen antibiotic would not be effective.

- Resistance: the organism is not sensitive to the antibiotic. Because *S. intermedius* organisms produce β-lactamase, antibiotics that are resistant to this enzyme are usually preferred.
- Dosage: the dosage is insufficient to maintain an inhibitory concentration within the skin.
- Duration: the duration of the antibiotic course was not long enough. A minimum 4-week course is recommended. Four to 12 weeks may be required to resolve deep infections.
- The organism is surviving within macrophages, necrotic tissue, or has been walled off by host reaction.

11. Why is it that most veterinary dermatologists seem to use cephalexin almost exclusively for superficial pyoderma?

Most antibiotic use in veterinary dermatology is empirical. Culture and susceptibility is not normally used unless there has been a failure to respond to rational antibiotic therapy. Most dermatologists use cephalexin as their first choice drug because it has been shown to be very effective against *S. intermedius*, with minimal change in resistance pattern over the years.

12. What other treatment options are available to treat superficial pyoderma?

Topical therapy can be an important adjunctive treatment for superficial pyoderma. Antimicrobial shampoo therapy, twice weekly for the first 2 weeks then once weekly, is often recommended. If a benzoyl peroxide shampoo is used, a conditioning rinse is often recommended because benzoyl peroxide may be drying.

Corticosteroids should be avoided during antibiotic therapy because they decrease inflammation and may suppress the host's immune response to the infection. The use of corticosteroids may interfere with the ability to determine if the antibiotic therapy is successful.

13. How do I cope with recurrent pyodermas in dogs?

Relapse is common in dogs that are treated with short courses or sub-therapeutic doses of antibiotics. The first step in evaluating such cases is to be sure that an appropriate antibiotic has

been used, at the appropriate dose for the appropriate length of time. Once you are sure that appropriate therapy has been used, it is then important to look for underlying conditions such as allergies or endocrinopathies that may be impeding resolution of the pyoderma.

In rare cases no underlying cause for the recurrent pyoderma will be found. Some of these individuals may have a confirmed immunodeficiency, although it is not unusual for dogs to appear normal because of the currently limited testing options available to diagnose immunodeficiencies. In these circumstances, the options available are either to try immunoadjuvant therapy or maintain the dog on long-term antibiotics.

14. How do immunoadjuvants work?

The goal of immunoadjuvant therapy is to normalize the immune response. The immunomodulatory agent is normally administered at the same time as antibiotic therapy for a period of weeks (normally 4-6 weeks) before the antibiotic therapy is withdrawn and the dog maintained on the immunoadjuvant therapy alone. If the therapy is successful, the dog will not relapse. Many different immunoadjuvant therapies have been recommended, although most are only supported by anecdotal reports of their effectiveness.

The most investigated immunoadjuvants available are Staphage Lysate (SPL, Delmont Laboratories), an immunostimulant prepared from *Staphylococcus aureus* bacteria using a bacteriophage, and Immunoregulin (ImmunoVet), a *Propionibacterium acnes* bacterin. The exact mechanism of their action is unknown but is believed to be associated with enhanced cell-mediated immunity, as well as a nonspecific effect on humoral immunity. Both have been shown to be beneficial in placebo-controlled clinical trials.

SPL is normally administered twice weekly at 0.5 mL subcutaneously at the same time as a 6-week antibiotic course. Cases should be re-evaluated for progress at the end of the first 10 weeks of therapy (end of the first 10 mL treatment vial). The frequency of injections is gradually reduced to once weekly and then every other week after 20 weeks if the pyoderma remains under control.

15. Is long-term antibiotic therapy an option for recurrent pyoderma?

Dogs with recurrent pyoderma may be maintained on long-term antibiotic therapy as an alternative to the use of immunoadjuvants. Two forms of therapy are generally used: low-dose continuous therapy and pulse therapy. The use of low-dose or pulse therapy is controversial because of an increased risk of resistance development. Cephalexin is the only antibiotic recommended for this type of therapy because of a documented lack of resistance development over time. In low dose continuous therapy, the dose is reduced by half once monthly until the lowest dose that keeps pyoderma at bay is determined. In intermittent pulse dosing, a full therapeutic dose is administered for 7-14 days once monthly. The number of days it takes for the patient to relapse is used to determine which method of administration would be most appropriate. If the patient relapses within a few days, daily therapy is likely to be necessary. If relapses take 2-4 weeks, pulse therapy may be successful. Because individuals on chronic therapy may be more at risk for drug-related side effects, close monitoring and regular re-evaluations are recommended.

16. What would be the most appropriate antimicrobial therapy for *Malassezia*?

Malassezia dermatitis is an increasingly common diagnosis, most often secondary to other diseases, especially those involving any degree of greasy seborrhea (seborrhea oleosa). Diagnostic and treatment strategies include the elimination of the *Malassezia,* plus evaluation for underlying etiologies such as allergy (may form part of hypersensitivity complex) or keratinization disorders.

Malassezia dermatitis may often be successfully treated with topical antimicrobial therapy. Mild cases may benefit from a once or twice weekly degreasing shampoo (coal tar/sulfur/salicylic acid) followed by a 2% ketoconazole shampoo (Nizoral, Janssen).

More severe cases are best treated with systemic antifungal agents such as ketoconazole (Nizoral; Janssen) at 5-10 mg/kg orally every 12-24 hours or itraconazole (Sporanox; Janssen)

at 5 mg/kg orally every 12-24 hours. These drugs should always be given with food to enhance absorption.

Adverse effects include elevated liver enzymes (dog and cat), anorexia, and gastrointestinal upset. Itraconazole appears to be better tolerated with a decreased incidence of side effects. Treatment should be discontinued if side effects are noted. The significance of any *Malassezia* involvement is often determined by the degree of improvement with appropriate systemic therapy.

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7. PARASITICIDES IN DERMATOLOGY

Robert Kennis, DVM, DACVD

1. **Briefly describe the flea life cycle.**

The flea life cycle consists of the egg, larva, pupa (pre-emergent adult), and adult. Adult female fleas are capable of laying up to 30 eggs per day. The eggs are not sticky so they fall onto the ground where the pet spends its time. Eggs hatch in 7-14 days into a larval form. Larvae are motile and active feeders consuming pet dander and flea feces. They are attracted to darkness and by gravity so they seek refuge deep within the carpet or within the surface layers of the outside environment. In 7-14 days, they spin a cocoon where they undergo metamorphosis, changing into a pre-emergent adult. Pre-emergent adults may remain dormant for several months, and are impervious to virtually all insecticides. Direct pressure and vibration signal the pre-emergent adult to hatch and jump onto its host. Fleas are obligate parasites and will remain on their hosts for the remainder of their lives. Adult fleas may survive for several months, depending on environmental conditions.

2. **What active ingredients are licensed and approved for the treatment of fleas on dogs and cats?**

Adulticidal agents include pyrethrin and permethrins, imidacloprid, fipronil, selemectin, nitenpyram, carbamates, and organophosphates (phosmet). Ovicidal/larvacidal agents include methoprene, pyriproxifen, and lufenuron. It is interesting that broad-spectrum antiparasitic agents, such as amitraz, ivermectin, and lime sulfur dip, are not effective against fleas. Pennyroyal oil, D-limonene, and tea tree oil are considered "natural" flea treatments. However, the side effects, toxicities, and lack of scientifically proven efficacy preclude their usage.

3. **List the mechanism of action and spectrum of activity of fipronil, imidacloprid, selemectin, and pyrethrin.**
   - Fipronil: The mechanism of action is inhibition of GABA-regulated chloride flux into the nerve cell. Its spectrum of activity includes adult fleas and ticks.
   - Imidacloprid: The mechanism of action is prevention of postsynaptic binding of acetylcholine, leading to respiratory paralysis. Its spectrum of activity is limited to adult fleas.

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- Selemectin: This drug is a semisynthetic avermectin. Its mechanism of action is not completely defined. It probably involves an increase in permeability to chloride ions through interaction with GABA binding sites, similar to other avermectins. Its spectrum of activity includes fleas, scabies, *Dermacentor* spp., heartworms, and *Otodectes cynotis* in the dog. For the cat, the spectrum also includes heartworms, fleas and *Otodectes cynotis*, along with hookworms and roundworms. Recent evidence supports efficacy against *Cheyletiella* spp. No mention on the package indicates efficacy against ticks or *Notoedres* spp. in cats.
- Pyrethrin: The mechanism of action involves disruption of neurologic function by prolonging Na^+ conduction. Pyrethrins are among the most broad-spectrum antiparasitic agents available. They have efficacy against fleas, ticks, lice, *Cheyletiella* spp., *Otodectes cynotis*, and *Lynxacara radovsky*.

4. What are the differences between pyrethrins and permethrins?

Pyrethrins are natural chemicals derived from chrysanthemum flowers. Permethrins are synthetic pyrethrin-like compounds sometimes referred to as pyrethroids. Pyrethrins are generally used in concentrations of approximately 0.1-0.5%, are short-acting because they are broken down by ultraviolet light, have a quick kill, and are considered safer than other products. Permethrins can range in concentration from 0.1-65%. At concentrations above 2%, they are toxic to cats. Permethrins are more ultraviolet stable but have a slower knock-down than pyrethrins. They also have very good repellent effects. Both products are sometimes combined to provide a quick kill with longer residual and increased repellent effects.

5. Pyrethrin-based products are available in a variety of formulations. Give some examples along with the advantages and disadvantages of each.

- Powders: safe and relatively inert, but messy and must be applied frequently.
- Sprays: ease of application but may be irritating in an alcohol base; care in avoiding hypothermia due to evaporation in puppies and kittens; cats hate to be sprayed.
- Shampoos: effective as adulticides, remove flea feces; when combined with an oatmeal product provide antipruritic relief. Shampoos are short-lasting, as most of the active ingredient goes down the drain; for large animals the procedure is labor-intensive; care should be taken with young animals to prevent hypothermia.
- Dips: very cost effective, providing thorough application, very messy for indoor usage, toxicity may occur if bottle instructions are not followed correctly.
- Foams: easy to apply (even to cats) but not very cost effective as a formulation.
- Spot-on formulations: usually consist of permethrins to improve efficacy, many over-the-counter products are available in concentrations that are toxic to cats if used incorrectly.

6. What is an insect growth regulator (IGR)? Give two examples of flea IGRs.

An insect growth regulator is a compound that mimics juvenile hormone. As the larva matures, its level of juvenile hormone decreases until a critical threshold is reached, signaling it to form a cocoon. IGRs artificially maintain high levels of juvenile hormone and prevent maturation to the next life stage. These products directly disrupt the egg and prevent it from hatching. Methoprene (Precor) and Pyriproxyfen (Nylar) are commercially available in a variety of products. The overall effect of these products is environmental control of fleas. They do not kill adult fleas; they only prevent them from reproducing by preventing metamorphosis.

7. How is lufenuron different from other IGRs?

Lufenuron is classified as an insect development inhibitor (IDI). Lufenuron's mechanism of action is interference with chitin synthesis, polymerization, and deposition. It is administered orally with food or may be injected into cats. Lufenuron is taken up by the female flea as she consumes a blood meal. The lufenuron disrupts the ability of the larva to emerge from the egg, thereby halting reproduction. Lufenuron is excreted unchanged in the flea feces. If a larva

consumes the feces with lufenuron, it prevents a normal pupa from developing. Ultimately, the net effect is environmental control. Lufenuron must be given orally monthly or injected every 6 months in cats to be effective. Also, the flea must feed for lufenuron to work. Other IGRs can be applied to the pet or to the environment and will work without the flea feeding first.

8. Describe how nitenpyram might be used in a clinical setting.

This oral tablet kills literally all adult fleas starting within 6 hours but is rapidly eliminated and is not effective after about one day. Because it does not prevent newly emerged fleas from jumping onto the pet, additional tablets must be given to kill those fleas. This product has limited use in the hands of the client when used as the sole method of flea control. However, it can be an excellent drug for the practitioner. Nitenpyram can be given to all pets that require hospitalization to avoid clinic infestation. It can also be given to a pet before it leaves the hospital. This will avoid any complaints of "my pet got fleas from your hospital." This product is also highly effective in humane shelters and pet shop settings to avoid sending fleas home on the pet. It might be possible that flea eggs that are on the pet at the time of adoption may ultimately infest the new home; however, using nitenpyram greatly diminishes this possibility.

9. Define "integrated pest management" as it pertains to fleas.

Integrated pest management involves using a combination of products that kill both the adult and juvenile stages of fleas. There are several products that are adulticides but adults only make up about 5% of the flea population. Combining an adulticide with an IGR or lufenuron will soon reduce the population of fleas within an environment to zero. This is especially important for flea-allergic pets. Although the argument can be made that many adulticides reach 100% efficacy, there is no doubt that over time resistance will develop if a single product is relied upon for flea control. Using integrated pest management with a combination of products is cost effective and very safe. There is really no reason not to use an IGR or lufenuron in all flea households along with an adulticide.

10. Diatomaceous earth and sodium polyborate are sometimes used for environmental flea control. What are the advantages and disadvantages of these products?

These products are sometimes placed into carpeted surfaces in large amounts. The larval stages of the flea will consume these products, causing them to die. The advantages are that they may be highly effective in providing environmental control within the household. The disadvantages are several. First, they are very messy when first applied. Secondly, unless an adulticide is added to the powder, additional products must be used on (in) the pets. Lastly, there have been anecdotal reports about similarities in particle size to asbestos. Lung lesions have developed in some borate workers similar to those who had inhaled asbestos. With the plethora of excellent commercial products available, diatomaceous earth and sodium polyborate should be considered to be on the bottom of the list for flea control (my opinion).

11. Which active ingredients are licensed and approved for the treatment of ticks on dogs and for cats?

Fipronil and pyrethrin are the only licensed products effective for ticks for both dogs and cats. Permethrin products are available for dogs that are in concentrations that are toxic to cats. Amitraz is licensed in a collar form for dogs only. Amitraz dip is efficacious against ticks but it is not labeled for this use. Selemectin is licensed for the treatment of one tick species on dogs only. It may have unproved efficacy in cats. Organophosphate dips (phosmet) are licensed for dogs but toxicities are a major concern when using these potent cholinesterase inhibitors.

12. Amitraz is available in a collar for the treatment of ticks on dogs. Define the mechanism of action, age restriction, potential side effects, and antidote for toxicity.

Amitraz is a monoamine oxidase inhibitor (MAO) drug. When incorporated into a collar it

causes feeding ticks to drop off and quickly die. In a recent report it was shown that the quick kill prevented the tick from spreading *Borrelia* spp. to research dogs and may thus protect dogs from getting Lyme disease. This collar is only licensed for dogs and they must be older than 16 weeks of age. The concentration of amitraz in the collar is significantly lower than the amount applied as a dip for the treatment for *Demodex*. However, if the dog ingests the collar, then signs of amitraz toxicity including bradycardia and lethargy or coma may occur. If there is historical evidence that the collar may be responsible for the clinical symptoms, then yohimbine may be given as an α-2 adrenergic receptor antagonist, which reverses the signs of amitraz toxicity. Yohimbine should be given before attempting other procedures to prevent further absorption of the amitraz from the collar. Because yohimbine is short acting, it may need to be given several times. It is important to keep good records regarding the sale of amitraz collars. Having this information readily available may save a dog's life because the list of potentially toxic drugs that may induce similar clinical symptoms is staggering.

13. What active ingredients are safe to use in treating cats with ticks?

There are few drugs that are licensed and approved for treating cats with ticks. Pyrethrin-based products and those containing fipronil are reasonable options. Selemectin has labeled efficacy for canine ticks but not feline, but may be helpful for some cats. Carbaryl-based products are increasingly hard to come by and regardless should not be used on cats. Organophosphates are highly toxic to cats and should be avoided.

14. List the active ingredients in licensed and approved products for the treatment of canine scabies.

Lime sulfur dip, organophosphate dip (phosmet), and selemectin are licensed for the treatment of scabies. Lime sulfur dip should be used weekly for 6 weeks. This product is among the safest products for young puppies. Selemectin is excellent and may be used on dogs as young as 6 weeks. I prefer to use this product every 14 days for three treatments instead of the monthly treatments as recommended on the package. Phosmet dip clinically appears to be ineffective in many cases and is not recommended for routine treatment of canine scabies. Amitraz dip at 250 ppm is highly efficacious but not licensed for the treatment of canine scabies. The use of 1% ivermectin at 200 μg/kg every 14 days for three treatments is also highly effective, but it is not licensed nor approved for this purpose and is toxic in some breeds of dogs (e.g., Collies and other herding breeds).

15. What should be considered before using off-label 1% ivermectin for the treatment of canine scabies?

Age and breed must be considered before using ivermectin. It is generally agreed upon that ivermectin should not be given to dogs younger than 12 weeks of age. In shelter situations and some clinical settings, this precaution is sometimes ignored. There are certain breeds that are at risk of adverse reaction to ivermectin, but any dog can be affected. The "at risk" breeds include: Collie, Shetland Sheepdog, Border Collie, Australian Shepherd, and Old English Sheepdog. There is a little rhyme "white feet, don't treat" that many clinicians follow. In general, with highly effective commercially available products for the treatment of scabies, there is no reason to continue to use off-label ivermectin.

16. What treatment options are available for the treatment of *Notoedres cati* infestations in cats?

The only licensed product for the treatment of feline scabies is lime sulfur dip. Off-label ivermectin has been used with good effects. However, dosing errors are sometimes encountered, especially when treating small kittens. Also, idiosyncratic reactions may occur. The author uses off-label selemectin every 2 weeks for three treatments if the kitten is old enough (> 6 weeks) and greater than the 2-lb minimum body weight listed on the package.

17. How are organophosphates different from carbamates?

The mechanism of action of organophosphates is to bind irreversibly to acetylcholinesterase, leading to the accumulation of acetylcholine at the postsynaptic junction. The end result is paralysis. Treatment for toxicity includes atropine and 2-PAM. These products are very toxic, especially to cats, and are not recommended for routine use. In contrast, carbamates (carbaryl) bind reversibly to acetylcholinesterase. Treatment for toxicity includes atropine but not 2-PAM. Because these products are considered "safer" than organophosphates, there are still carbaryl-containing products on the market approved for use on cats, but these are decreasing in availability and much safer products are available.

18. What are the licensed and approved active ingredients available for the treatment of *Otodectes cynotis* (ear mites)?

The licensed products include pyrethrin, thiabendazole, milbemycin, ivermectin otic drops, and topically applied selemectin. With the plethora of excellent products available, there is no reason to use oral or injectable cattle ivermectin off-label. Pyrethrin or thiabendazole drops should be applied for three consecutive days each week for 3 weeks. All contact animals should be treated. It is strongly recommended to use a pyrethrin spray or shampoo weekly, especially on the head and face and rear feet, to kill all aberrantly located mites. Newly licensed otic medications containing milbemycin or ivermectin are highly efficacious. A second treatment is recommended 14 days after the first application. Selemectin is also an excellent option. Although effective against ear mites when used monthly, I routinely recommend a second treatment 14 days after the first.

19. Describe the possible side effects that should be discussed with an owner before prescribing topical application of amitraz for the treatment of generalized demodicosis.

The most common and expected side effect of an amitraz dip is lethargy. Additional side effects include pruritus, bradycardia, hypothermia, and hypotension. Uncommonly, hyperexcitability may occur. If adverse side effects are seen, yohimbine will quickly reverse the problems. Because the side effects of amitraz may be prolonged, several treatments with yohimbine may be needed. Yohimbine may be used before the application of amitraz for those dogs with a history of adverse reaction. Large animal formulations of amitraz should *never* be used in the treatment of demodicosis because off-label use of these products is a serious Environmental Protection Agency (EPA) violation.

20. What is Goodwinol ointment?

This is a product that is licensed for the treatment of localized demodicosis in dogs. The active ingredient is rotenone. Side effects are uncommon. Because many cases of localized demodicosis are self-limiting, it is difficult to determine the true efficacy of this product. Nonetheless, it is a reasonable treatment option that beats a "wait and see" attitude.

21. Which products may be useful for repelling biting flies and mosquitoes?

Pyrethrin and permethrin products have the advantage of repellent properties. Preparations in a gel formulation are preferred due to their ease of application to ear tips and nose. Flea sprays containing pyrethrins or permethrins are also effective. However, these products are usually needed for spot treatments instead of total body application. Shampoos containing these active ingredients have an inadequate residual activity to be effective. Spot-on formulations containing selemectin, fipronil, or imidacloprid do not have repellent properties. A new formulation of the combination of imidacloprid and permethrin has been developed.

22. List the active ingredients that may be useful for the treatment of infestation of *Cheyletiella* spp.

Pyrethrin and permethrin products are the preferred treatment for *Cheyletiella*. Because these mites are surface feeders, avermectin drugs may be inconsistently effective. Lime sulfur

dips are also safe and effective. Organophosphates are effective but not recommended. Imidacloprid and fipronil are ineffective against *Cheyletiella*. Selemectin has been shown to be effective against *Cheyletiella* on cats. Remember that *Cheyletiella* spp. may live off of the host longer than other ectoparasites. Therefore environmental treatment, along with the treatment of all contact animals, is recommended.

23. What are some of the precautions and side effects associated with lime sulfur dip?

Lime sulfur dip tends to be safe and effective. Hypothermia due to evaporation, especially in young animals, must be avoided. Dogs tend to tolerate this product much more than the typical owner. The offensive odor and staining make these products among the least favored of our clients. Lime sulfur dip may also tarnish jewelry. There are indeed precautions to follow when using lime sulfur dips on cats. It is best to apply an Elizabethan collar to prevent cats from licking the dip while it is still wet. Lime sulfur dip can cause vomiting, lethargy, and inappetence. The treatment for side effects is purely supportive because there is no reversing agent.

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8. IMMUNOADJUVANT THERAPY

Karen L. *Campbell*, DVM, MS, DACVIM, DACVD

1. What is the goal of immunoadjuvant therapy?

The goal of immunoadjuvant therapy is to strengthen the immune defense mechanisms of an animal. It is also called nonspecific immunotherapy, immunostimulation, immunologic enhancement, immunomodulation, immunoaugmentation, and immunopotentiation. Agents used for immunoadjuvant therapy are often referred to as biologic response modifiers.

2. What are the indications for using immunoadjuvant therapy?

- A need for improving the immune potential of an old or very young animal.

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2. What are the indications for using immunoadjuvant therapy?

- A need for improving the immune potential of an old or very young animal.

- When the immune system is suppressed by an infection (e.g., retroviral infections, bacterial or fungal sepsis).
- To counter physiologic, pathologic, or environmentally induced suppression of immune function.
- To potentiate immune responses to eliminate a tumor.

3. What is the mechanism of action of levamisole as an immunoadjuvant?

The functions of levamisole as an immunoadjuvant are similar to those of the thymic hormone thymopoietin. Levamisole stimulates T-cell differentiation and T-cell responses to antigens. It also stimulates phagocytosis and intracellular killing by macrophages and neutrophils. The effects of levamisole are greatest in animals with depressed T-cell function and it has little or no effect on the immune system of healthy animals. Adverse side effects include gastrointestinal and hepatic dysfunction, neurotoxicity, agranulocytosis, erythema multiforme, and toxic epidermal necrolysis. Levamisole at a dose of 2.2 mg/kg orally every 8 hours has been reported to benefit approximately 10% of dogs with recurrent pyoderma.

4. What is the protocol for using *Propionibacterium acnes* as an immunoadjuvant?

Propionibacterium acnes is available commercially as a killed suspension in 12.5% ethanol in saline. *P. acnes* stimulates macrophage activity. The manufacturer recommends using it in dogs as an adjuvant to antibiotic therapy in the treatment of chronic recurring canine pyoderma. It is dosed based on body weight (a 45-lb dog receives 1.0 mL intravenously) and is given twice weekly for 2 weeks, then once weekly until symptoms abate or stabilize, and then once per month for maintenance. Anaphylactic reactions can occur, more common side effects include fever, chills, anorexia, and depression, lasting several hours after the injections. It can cause a necrotizing dermatitis if given subcutaneously or intramuscularly.

5. What is in Staphage Lysate? How does this product work?

Staphage Lysate (SPL) contains 120-180 million colony-forming units of *Staphylococcus aureus* and 100 million staphylococcus bacteriophage plaque-forming units in each milliliter. SPL is indicated for the treatment of canine pyoderma. SPL has been shown to stimulate both T and B cells *in vitro* and enhances the capability of macrophages to kill staphylococci. The recommended protocol is to administer 0.5 mL subcutaneously twice weekly for 10-12 weeks and then 0.5-1.0 mL every 1 to 2 weeks for maintenance. Concomitant antibiotics are recommended for the initial 4-6 weeks of treatment. Side effects can include localized reactions with erythema, pain, and pruritus or systemic reactions with fever, malaise, and inappetence, and in severe cases anaphylaxis. Anecdotally, SPL appears to be effective in increasing the lesion-free intervals in approximately 25% of dogs with chronic recurrent staphylococcal pyoderma.

6. Is it true that cimetidine works as an immunoadjuvant?

Histamine receptors are found on the cell surface of many cells including H_2-receptors on T-suppressor cells. Through its function as an H_2-antagonist, cimetidine can block histamine-induced immunosuppression. For use as an immunoadjuvant, cimetidine is given to dogs at a dosage of 6-10 mg/kg every 8 hours. While side effects are rare, the efficacy as an immunoadjuvant in the treatment of chronic recurrent staphylococcal pyoderma is also low.

7. What are the effects of vitamin E in immunostimulation?

Vitamin E is an antioxidant that stabilizes lysosomes, reduces prostaglandin E_2 synthesis, and increases IL-2 production. Vitamin E has been shown to promote B cell proliferation and increases antibody production when administered with vaccines in cattle. A deficiency of vitamin E results in T-cell dysfunction. While more research is needed to delineate the roles of vitamin E in enhancing immunity, supplementation of diets with vitamin E may increase resistance to disease. Dosages of 400-800 IU every 12 hours are currently recommended for dogs.

8. What are the immunoadjunctive actions of interferons?

Interferons (INF) are regulatory proteins that can act on a variety of different cell types. Interferon-α is normally produced by monocytes and macrophages. It has nonspecific antiviral activity affecting RNA and protein synthesis and induces extracellular antiviral proteins. It also enhances natural killer cell activity and has antiproliferative effects on both normal and neoplastic cells. Interferon-β is produced by fibroblasts and shares a similar structure and similar actions to INF-α. Interferon-γ is produced by activated T_H cells and natural killer (NK) cells. It serves as an important macrophage-activating factor, upregulates type-I and type-II MHC antigens, increases antimicrobial activity, increases antitumor activity, increases tumor necrosis factor-α synthesis, and inhibits macrophage migration. It also increases IL-2 synthesis, enhances cytotoxic T-cell and NK cell activity. INF-γ also induces antibody-dependent cytotoxicity, stimulates B-cell activity, inhibits the growth of normal and neoplastic cells, and has nonspecific antiviral activity. High doses of INFs, especially of INF-γ, are toxic, causing severe fever, malaise, anorexia, thrombocytopenia, granulocytopenia, and in some cases liver, kidney, or neural toxicity.

9. What conditions have been reported to respond to interferon therapy?

Anecdotal reports have indicated INF-α2a (Roferon-A) may be of benefit in treating dogs with multiple papillomas, epitheliotropic lymphoma, and recurrent bacterial pyoderma. Possible indications for the use of INF-α in cats include herpesvirus, idiopathic facial dermatosis, and indolent ulcers. The oral dosage for cats is 30-120 IU/cat/day. In dogs, we have used 1000-2000 IU orally every 12-24 hours in treating oral papillomatosis and 1000 IU orally every 24 hours in treating recurrent bacterial pyoderma. Much higher doses have been recommended for use in treating epitheliotropic lymphosarcoma; i.e., 3 million IU given by subcutaneous injection every Monday, Wednesday, and Friday.

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9. PRINCIPLES OF TOPICAL THERAPY

Randall C. Thomas, DVM, DACVD

1. When is topical therapy indicated?

Topical therapy is an integral part of dermatologic therapy in the dog. Depending on the active ingredient, topical therapy can be used to moisten or dry the skin; treat bacterial, fungal, or parasitic infections; alter the maturation of the epidermis; or ease pain and pruritus. Cats are less appreciative of bathing and dipping than their canine counterparts. However, topical treatments are critical in some feline skin disorders, and these instances will be noted throughout the chapter.

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2. Why use topical therapy?

Topical therapy is important because it allows application of the active ingredient directly onto the skin. It may be used alone, or as an adjunct therapy to reduce the need for systemic medications. With few exceptions, topical therapies are very safe for use in both the dog and cat. Lastly, many owners want to be actively involved in the treatment of their pet.

3. What types of topical therapy are useful in the dog and cat?

Topical therapy comes in many forms, including shampoos, rinses/dips, lotions, powders, sprays, and ointments. Shampoos and rinses are ideal for generalized use, and powders, lotions, and ointments are more useful for local application. Because there are literally hundreds of products available, it is beneficial to be familiar with active ingredients, as well as the manner in which they may be delivered.

4. What are the disadvantages of using topical therapy?

Not every topical treatment is free of potential adverse effects. Because of the grooming habits of our veterinary patients, it should be assumed that topical agents that are not rinsed off are subject to ingestion. Side effects can range from gastrointestinal upset to toxicosis (rare). When using topical products that have toxic potential, application of an Elizabethan collar may be considered to avoid ingestion. Occasional patients may have contact allergic or irritant reactions to certain products. Topical therapy is also labor intensive and relatively expensive. Client and patient compliance issues must be considered when deciding whether to prescribe topical therapy. Lastly, shampoos have traditionally had little residual effect once rinsed off the animal.

5. Are there shampoo products that provide residual effects?

Microvesicle technology has allowed some shampoo and conditioner products to have residual effects. Novasomes (EVSCO) are microvesicles with five to seven lipid bilayers around a central holding area with moisturizers. The Novasomes remain attached to the haircoat after rinsing. Over several days, the lipid bilayers break down, releasing the inner contents. The moisturizers in Novasomes may counteract the drying effects of some active ingredients in medicated shampoos. Spherulites (Allerderm/Virbac) are microvesicles with 10 to 1000 layers. Various active ingredients can be incorporated into the many layers of these microvesicles. A positive charge allows them to bind to the skin and haircoat. As they break down, the active ingredients are slowly released. Spherulites also incorporate chitosanide, which has moisturizing effects.

6. What are the beneficial effects of water (hydrotherapy)?

Water (hydrotherapy) can act as a therapeutic agent in many ways. Cool water is soothing to the skin and helps decrease pruritus. Rinsing the patient with cool water can provide relief from itching. In addition, whirlpool baths are an effective way of using hydrotherapy to treat the entire body. These baths gently rinse away crusts and other organic debris, inflammatory mediators, and infectious organisms. Hydrotherapy is ideal for the treatment of canine deep pyoderma.

7. Educate the owner about topical therapy!

For pets to benefit from topical therapy, it must be done correctly. Figure 9-1 describes important points that should be discussed with the owner regarding topical therapy (Box 9-1).

8. Why can't owners use human or over-the-counter (OTC) products in their pets?

The character and pH of human skin is different from that of canine and feline skin. For that reason, products that are highly effective for human conditions may not be useful for our veterinary patients. Some human products can be drying, exacerbating pruritus. Use of a baby shampoo or dish soap may occasionally be indicated in dogs that are overly soiled or greasy before use of a prescription veterinary shampoo.

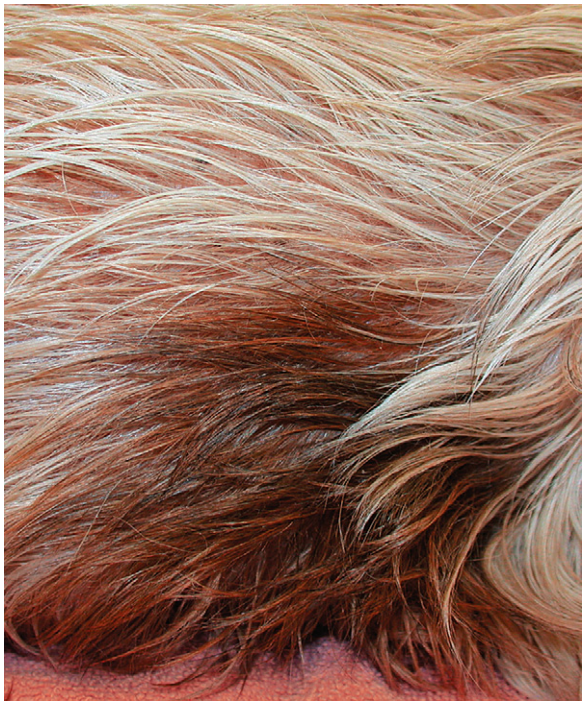

Figure 9-1 Atopic dog with superficial pyoderma and seborrhea oleosa. Benzoyl peroxide may be useful topical therapy in this case to treat pyoderma and degrease the skin and haircoat.

Box 9-1 ***Important Points for Owners to Know About Topical Therapy in the Dog and Cat***

Frequency of use: Be specific about how often the product should be used. For most skin conditions, topical therapy should be done one to two times weekly. As the pet improves, less frequent use may be possible. Give the owner guidelines on what to look for as the treatment progresses.

Application of the product: This seems obvious, but owners don't always know how to shampoo their dog or cat. The entire animal should be wetted down with cool water. Then the shampoo product should be applied to the entire body. Some medicated products don't lather well, and owners should be warned of this. Using excessive quantities of the product to generate a good lather is wasteful, and makes it hard to effectively rinse the product.

Contact time: 10-15 minutes contact time is required for the active ingredient in most shampoos to work. Contact time starts when shampoo has been applied to the entire animal. Owners must be educated on the proper use of conditioners, as well, to maximize their residual effects.

Rinsing: In general, it should take about twice as long to rinse the pet as it did to apply the product. This ensures that the product is effectively rinsed from the skin and haircoat. Unless the product is intended to be left on the animal, it may cause irritation if not rinsed properly.

Drying: After rinsing, pets should be dried well to prevent chilling and maceration of the skin. Thorough towel drying is often effective for larger dogs. Warm-air drying should be done carefully in smaller dogs and cats. Only experienced personnel should use cage-dryers due to the risk of hyperthermia and thermal burns.

Numerous "medicated" shampoos are available OTC for animals. In my experience, owners tend to believe that these shampoos are effective against all skin conditions. While these products are less expensive than prescription items, they are often misused, making them ineffective. Quality control and stability may also be a problem for generic or OTC products.

9. When is topical antibacterial therapy indicated?

Superficial bacterial pyoderma is one of the most common disorders in the dog. Deep pyoderma is also relatively common in the dog. Treatment of pyoderma in the dog typically involves the use of both topical and systemic antibacterial therapies. The practitioner should choose an active ingredient with good activity against *Staphylococcus intermedius*, the most common cause of canine pyoderma. In the cat, bacterial pyoderma is less common. Deep bacterial infections, such as bite-wound abscesses and opportunistic (atypical) mycobacterium infections, are not responsive to topical antibacterials, so wound management and/or systemic treatment is the mainstay for these disorders.

10. What are the common antibacterial agents available as shampoo products?

- Benzoyl peroxide
- Ethyl lactate
- Chlorhexidine
- Povidone-iodine

11. What's the difference between these active ingredients?

Figure 9-2 shows the advantages, disadvantages, and indications of the common antibacterial agents (Table 9-1).

Table 9-1 ***Active Ingredients in Antibacterial Shampoos***

ACTIVE INGREDIENT	ADVANTAGES	DISADVANTAGES	INDICATIONS
Benzoyl peroxide 2.5-3%	• Excellent activity against *S. intermedius* • Good degreaser • Follicular flushing • Keratolytic properties • Some residual activity	• Drying • Bleaches colored fabrics • Doesn't lather well • Occasionally irritating	• Superficial pyoderma • Deep pyoderma • Localized bacterial infection
Chlorhexidine 0.5-4%	• Good activity against *S. intermedius* • Activity against *Malassezia* when 1% or greater • Less drying than benzoyl peroxide • Not inactivated by organic debris	• Rarely causes contact irritation	• Superficial pyoderma • Mixed (bacterial and *Malassezia*) infections
Ethyl lactate 10%	• Good activity against *S. intermedius* • Penetrates hair follicles and sebaceous glands • Good for sensitive skin • Breakdown products may acidify skin	• May not be as effective as benzoyl peroxide	• Superficial pyoderma • Impetigo
Povidone-iodine	• Good activity against *S. intermedius*	• Stains light-colored pets and fabric • Inactivated by organic debris	• Superficial pyoderma

12. Why would I choose benzoyl peroxide over the other antibacterial agents?

I use a benzoyl peroxide product in most cases of superficial pyoderma. Because this active ingredient can be drying, using a product that contains a moisturizer (MicroPearls Benzoyl Plus, EVSCO) or following the shampoo with a moisturizing rinse may be indicated. Benzoyl peroxide is also useful when pyoderma presents as greasy seborrhea (Figure 9-1). In dogs that already have dry skin and haircoat, use of a milder product, such as chlorhexidine or ethyl lactate, may be indicated. Benzoyl peroxide is the topical antibacterial agent of choice in dogs with deep pyoderma.

13. How do I decide which strength chlorhexidine product to use?

Chlorhexidine shampoos come in a variety of concentrations from 0.5 to 4%. One study indicates that chlorhexidine is effective against *S. intermedius* at each of these concentrations.[1] The higher concentration chlorhexidine products may provide better efficacy; however, this has not been proven. I recommend using a product that is at least 2% chlorhexidine to provide good efficacy against both *S. intermedius* and *Malassezia pachydermatis*, the two common cutaneous pathogens in the dog.

14. If benzoyl peroxide is a better antibacterial, why would I use chlorhexidine?

Chlorhexidine is a good antibacterial, and can be used with confidence against superficial pyoderma in the dog. Because chlorhexidine is milder than benzoyl peroxide, it may be more appropriate in dogs with sensitive skin, or when seborrhea sicca (dry skin) is already present. Chlorhexidine is also indicated in dogs with mixed (bacterial and yeast) infections.

15. What about ethyl lactate and povidone-iodine?

Ethyl lactate has good to excellent activity against *S. intermedius*. It is hydrolyzed to lactic acid and ethanol on the skin, so it has acidifying properties that may contribute to its antibacterial properties. It is a milder agent than benzoyl peroxide, and adverse effects are rare. I use an ethyl lactate shampoo (Etiderm, Allerderm/Virbac) for puppies with impetigo or dogs with sensitive skin.

Although there are several povidone-iodine products available, I think that benzoyl peroxide, chlorhexidine, and ethyl lactate are superior products with less potential to be irritating or sensitizing.

16. Is modulation of skin pH an effective way to treat pyoderma?

Recent studies have shown that the growth of *S. intermedius* is suppressed at a pH of 6.0 and below.[9] A novel product (Advanced pHormula Spray, EVSCO) is available that reduces the pH of canine skin to below 6.0 for longer than 48 hours. No clinical trials have been published to show that *in vivo* use of this product reduces the incidence of canine pyoderma. However, I have found this product useful in reducing the relapse of infection in some dogs with recurrent superficial pyoderma. For best results, clearance of an active infection with traditional means (antibiotics and antibacterial topical therapy) must be accomplished before use of this product.

17. Are there products available for localized bacterial infections?

Mupirocin (Bactoderm, Pfizer) is very effective against *S. intermedius*, but has limited activity against gram-negative organisms. Mupirocin penetrates the skin well, and has a low incidence of topical irritation. It is effective against methicillin-resistant *S. intermedius*. Mupirocin is indicated for localized infections due *to S. intermedius* such as intertrigo, chin pyoderma, callous pyoderma, or mild impetigo.

For localized use, 5% benzoyl peroxide lotions/gels (Oxydex gel, DVM Pharmaceuticals; Pyoben gel, Allerderm/Virbac) are also available. These products are well tolerated by most pets, but are more likely to cause irritation than mupirocin. Neomycin-based products are often effective against *S. intermedius*, but resistance can develop with repeated use, and neomycin is associated with an increased number of allergic contact reactions. Combination products with both an anti-

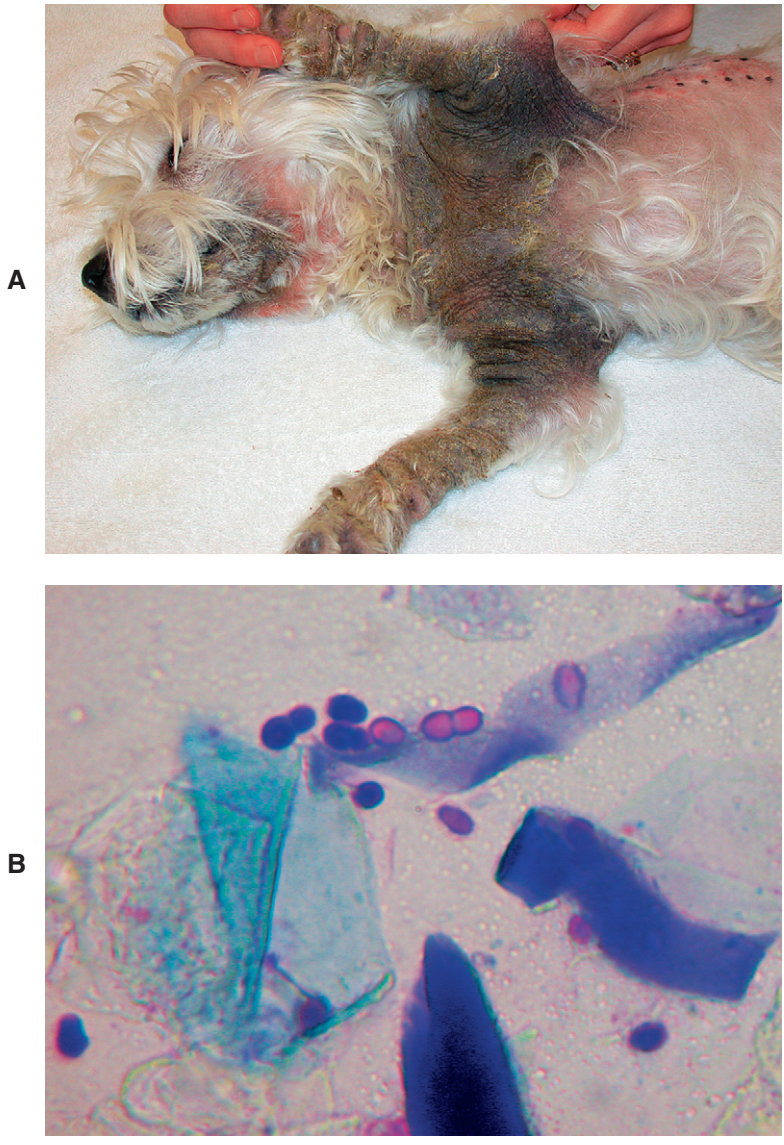

Figure 9-2 **A,** *Malassezia* dermatitis in an atopic West Highland White Terrier. **B,** Acetate tape preparation cytology of *Malassezia* dermatitis.

biotic and a potent corticosteroid should be used with caution outside the ear canal (see discussion of topical steroids below).

18. When is topical therapy for *Malassezia* dermatitis indicated?

Once *Malassezia* dermatitis has been diagnosed, topical therapy is almost always indicated in the dog or cat (Figure 9-2). Initially, I prefer to treat most cases of *Malassezia* with topical therapy. With severe infections, use of both systemic and topical therapy may be indicated from

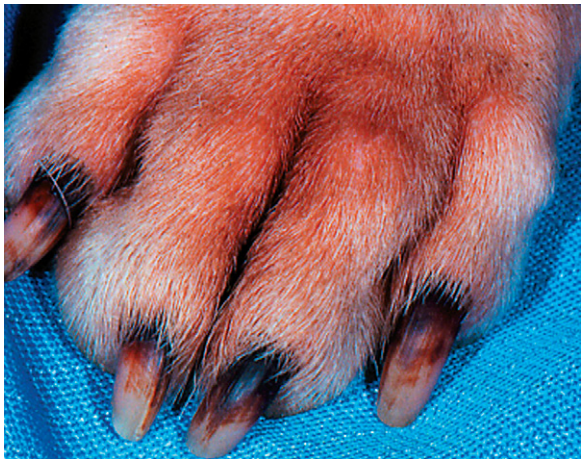

Figure 9-3 *Malassezia* pododermatitis and paronychia in a dog. Topical therapy alone may be ineffective in eliminating yeast from the clawfold region.

the start. In addition, when yeast is present within the clawfolds, or other "hard to reach" places, topical therapy alone may not be effective (Figure 9-3).

19. What antifungal products are available to treat *Malassezia*?

Chlorhexidine (1-4%)
Hexadene (Virbac/Allerderm)
Chlorhexiderm (DVM)
Chlorhexiderm Maximum (DVM)
Sebahex (EVSCO)

Ketoconazole (1-2%)
Nizoral (Janssen)

Ketoconazole/chlorhexidine
KetoChlor (Virbac/Allerderm)

Selenium sulfide (1%)
Selsun Blue (Chattem)
Head & Shoulders Intensive Treatment (Procter & Gamble)*

Miconazole
MicroPearls Miconazole (EVSCO)
Dermazole (Virbac/Allerderm)

Miconazole/chlorhexidine
Malaseb (DVM)

Benzoyl peroxide/sulfur
Sulfoxydex (DVM)

This box includes common products, but is not intended to be all-inclusive.
*Head & Shoulders standard formula contains pyrithione zinc, which is contraindicated in the dog and cat (may cause ocular damage).

20. Are there products that provide residual activity against *Malassezia*?

Enilconazole rinse (0.2%) is effective against *Malassezia*, and may provide some residual activity after application. This product is available in many countries outside the United States. A leave-on, miconazole-based conditioner (ResiZOLE, Virbac/Allerderm) is available within the United States that provides residual activity. One study indicated that use of this product two to three times weekly resulted in a significantly decreased *Malassezia* population versus placebo treatment.[8] There are also anecdotal reports of successful management of *Malassezia* dermatitis

using dilute (2.5%) acetic acid (white vinegar and water) rinses, but the acidifying effect of acetic acid on the skin is short-lived.

21. Are over-the-counter antifungal creams effective against *Malassezia*?

OTC products containing miconazole and clotrimazole are effective against *Malassezia*. Use of these products may be indicated for localized and interdigital *Malassezia* infections. Terbinafine 1% cream (Lamisil) is also available OTC. This product is effective against dermatophytes, but is ineffective against *Malassezia*, and should not be recommended.

22. Are these products useful for treatment of skin fold infections (intertrigo)?

Intertrigo is dermatitis resulting from friction between two apposed skin surfaces (Figure 9-4). Cutaneous cytology is critical in determining whether this infection is caused by bacteria, yeasts, or both. I found that mupirocin (see previous section) is very useful in cases of intertrigo caused by *S. intermedius*. Clotrimazole or miconazole creams are effective when *Malassezia* is the predominant organism. Mixed (yeast and bacteria) infections are common in these areas, so use of multiple products is common. Long-term management of these skin folds is usually necessary if the owner is unwilling to have them surgically excised.

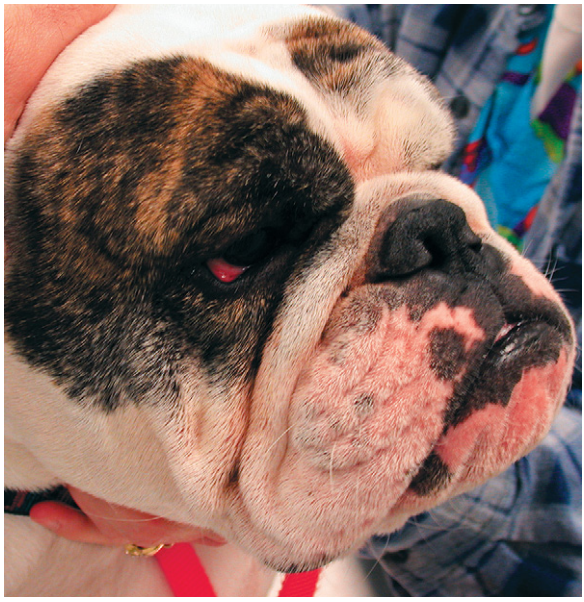

Figure 9-4 Intertrigo. Facial and nasal fold dermatitis in an English Bulldog may require long-term management.

23. What kind of long-term management of intertrigo is helpful?

Skin folds, regardless of location, need to be kept as clean and dry as possible. Because inflammation is often marked in these areas, short-term use of a corticosteroid-containing product (Otomax, Schering-Plough, or similar product) may be helpful. Once the inflammation is diminished (usually 3-4 days), I change to one of the products that does not contain a steroid. Once infection is resolved, using pledgets or swipes that contain acetic and boric acids (MalAcetic Wipes, DermaPet) or miconazole/chlorhexidine (Malaseb pledgets, DVM) makes it easier for owners to

regularly clean these areas (one to three times weekly). I have also used Advanced pHormula Skin pH Modulator (EVSCO) on a cotton ball for chronic management of intertrigo.

24. Is topical therapy effective against dermatophytosis in the dog and cat?

The recommendations for topical therapy versus dermatophytosis have changed in recent years. It has been shown that clipping hairs and bathing may cause initial worsening of symptoms by traumatizing the skin and spreading fungal arthrospores throughout the haircoat.[10] In spite of this, clipping and topical therapy are still indicated to diminish the number of infective hairs being shed into the environment.

Use of 2% lime sulfur or 0.2% Enilconazole dips is the most effective procedure against dermatophytes because they provide residual activity following application. Azole-containing shampoos (ketoconazole, miconazole) may spread arthrospores throughout the haircoat, and provide no residual activity. In a study of topical antifungal agents, chlorhexidine was determined to have poor efficacy against dermatophytes.[4]

25. Is localized treatment of dermatophytes with antifungal creams useful?

Localized treatment for dermatophytosis is usually ineffective. In the cat, dermatophytosis is often more widespread than clinically evident, so localized treatment may offer a false sense of security to the owner. In addition, there is no evidence that these creams are able to penetrate infected hair shafts to effectively inactivate the fungal spores. Most cases where antifungal creams have been successfully used to treat dermatophytosis probably represent self-resolution of the infection rather than true efficacy of the product (see Chapter 20).

26. When is topical therapy indicated as the sole treatment of dermatophytosis?

In dogs and shorthaired cats with localized lesions topical therapy may be the initial treatment of choice. Hairs should be gently clipped from the area immediately surrounding the lesions. Lime sulfur or Enilconazole dips can then be applied to the entire animal and allowed to dry. Animals (especially cats) should be prevented from ingesting the dip while it is wet by applying an Elizabethan collar until dry. Both of these products have been shown to be efficacious against dermatophytes and safe for use in both dogs and cats. Dips should be applied weekly until clinical lesions are resolved and two to three weekly dermatophyte cultures are negative. For best results, dogs and shorthaired cats with generalized lesions and *all* longhaired cats with dermatophytosis should be treated with both topical and systemic antifungal medications (see Chapter 20).

27. Should I bother with treating longhaired cats with topical therapy?

Yes! Use of systemic therapy is almost always indicated in longhaired cats with dermatophytosis. However, topical therapy can be helpful in clearing the infection and decreasing environmental contamination with infected hairs. These cats should have their entire trunk gently shaved to approximately 1/4 inch. Care should be taken to ensure that infective hairs are not disseminated throughout the clinic or grooming facility. Dipping with lime sulfur or Enilconazole solution once weekly is then initiated. The end-point of therapy is similar to that for cases of localized dermatophytosis above.

28. What if my clients complain about the smell of lime sulfur dips?

Not too many people appreciate the smell of lime sulfur. Warning owners about the foul odor of lime sulfur before use may result in fewer complaints. Additionally, make sure that owners understand the benefits of lime sulfur. This product is very safe, effective, and inexpensive. Once the dip has dried on the animal, the smell of the product is markedly decreased. Owners should be informed that lime sulfur tarnishes jewelry and stains porcelain tubs. I encourage owners to dip their pets outdoors when weather allows. For cats and small dogs, a plastic dish tub can be used for the process. For larger dogs, owners can buy a plastic children's pool in which to apply the dips. In-clinic dips can also alleviate client compliance problems with this product.

29. What is seborrhea?

Seborrhea is a term used to describe excessive scale formation on the skin surface and within the haircoat. Primary seborrhea is an inherited disorder of keratinization in which there is hyperproliferation of the basal cell layers. Secondary seborrhea is a reaction pattern of the skin to any number of conditions, and is much more common (Table 9-2). Seborrhea can present as excessive dry scale (seborrhea sicca) or greasy scale and haircoat (seborrhea oleosa). Seborrheic dermatitis applies to focal, pruritic areas of dermatitis, secondarily infected with *Malassezia* and/or *S. intermedius.*

Table 9-2 ***Causes of Secondary Seborrhea***

Allergic Diseases	**Parasitic Diseases**
Flea allergy dermatitis	Demodicosis
Atopy	Scabies
Food allergy	Cheyletiellosis
	Heavy intestinal parasitism
Infectious Diseases	**Nutritional**
Superficial pyoderma	Poor diet
Dermatophytosis	Malabsorption / maldigestion
Malassezia dermatitis	
Autoimmune	**Systemic Disease and Neoplasia**
Pemphigus foliaceus	Hepatic disease
	Epitheliotropic lymphoma
Environmental and Physical	
Low environmental humidity	
Inappropriate use of topical therapy	

30. Can seborrhea be cured?

Primary seborrhea is a congenital disorder that cannot be cured. Control of symptoms using both systemic and topical therapy can often be accomplished, however. Secondary seborrhea can be managed by controlling symptoms and identification and control of the inciting cause. Cases of secondary seborrhea that result from curable or easily controllable diseases (parasitic infestation, hypothyroidism) can be cured. Secondary seborrhea that results from chronic diseases such as atopy may require long-term management of both the primary and secondary disease.

31. What role does topical therapy play in control of seborrhea?

There are numerous topical products that are helpful in the management of seborrhea. The product of choice depends on the type and severity of the symptoms. Numerous moisturizer and emollient products are available as shampoos and rinses. For mild, dry seborrhea, these products help by increasing the moisture content within the stratum corneum. In mild cases of seborrhea that result from low environmental humidity or excessive bathing, moisturizers are extremely effective and may be all that is necessary. In moderate cases of seborrhea, sulfur and salicylic acid products may be necessary to control symptoms. Lastly, for severe cases use of a tar-based shampoo may be indicated. Tar products can be extremely drying to the skin and haircoat, so they should be used judiciously. The author rarely finds the use of tar-based shampoos necessary.

32. What does keratolytic mean and what role does this property play in treatment of seborrhea?

Keratolytic products are those that decrease the cohesion between the keratinocytes of the stratum corneum. This facilitates the desquamation of these surface cells, resulting in a decrease in visible scale. Because seborrhea results from an excessive rate of epidermal cell proliferation, desquamation of excess surface cells is helpful in management of the condition. Benzoyl peroxide, sulfur, selenium sulfide, and tar products all have keratolytic properties.

33. What does keratoplastic mean, and what role does this property play in treatment of seborrhea?

Keratoplastic agents help to normalize the excessive rate of keratinization that is present in seborrhea. In one study of Cocker Spaniels with primary seborrhea, the calculated epidermal cell renewal time was approximately 8 days, versus 21 days in normal Cocker Spaniels.[6,7] Because the epidermis of these dogs proliferates at a rate almost three times faster than that in normal dogs, excessive surface scale can result. Keratoplastic agents are thought to slow the maturation of epidermal cells, possibly by acting on the DNA of basal cells. Salicylic acid, sulfur, selenium sulfide, and tar products have keratoplastic properties.

34. Why are sulfur and salicylic acid often used in conjunction?

As mentioned previously, sulfur has both keratoplastic and keratolytic properties, while salicylic acid has keratoplastic properties. These agents are thought to be synergistic when used together. Sulfur and salicylic acid products are often found in combinations of about 2% each, and are typically well tolerated in the dog and cat.

35. Are products containing higher concentrations of salicylic acid useful in veterinary dermatology?

To the author's knowledge, there is only one veterinary product that utilizes a 6.6% salicylic acid concentration (Kerasolv, DVM Pharmaceuticals). Higher concentration products are available in human medicine, but are typically unnecessary in the dog and cat. Use of the 6.6% salicylic acid product is indicated for localized areas of hyperkeratosis, such as nasal hyperkeratosis, pressure point callus formation, and idiopathic hyperkeratosis of the footpads.

36. When are tar products indicated in the treatment of seborrhea?

Tar shampoos have keratolytic, keratoplastic, and degreasing properties. The tar products are the harshest of the antiseborrheic products, and their use should be confined to the most severe cases of seborrhea. When milder products will work, there is no need to use a tar shampoo. Tar shampoos can be extremely drying and often have an unpleasant odor. In most cases, a moisturizing conditioner should be used after a tar shampoo to decrease the drying effect. Tar shampoos are indicated in moderate to severe cases of seborrhea and some cases of seborrhea oleosa. The author recommends using a tar shampoo just long enough to resolve the worst symptoms and then changing back to a milder antiseborrheic. Cats are very sensitive to the irritating effects of tars and may be poisoned by phenolic compounds in tars, thus tar-containing products should not be used in feline dermatology.

37. If benzoyl peroxide is considered drying, why would it be useful in cases of seborrhea?

Superficial pyoderma is one of the most common causes of seborrhea in the dog (Figure 9-5). For that reason, use of a benzoyl peroxide product, in conjunction with systemic antibiotics, may be an effective antiseborrheic. As stated earlier, use of a moisturizing product in conjunction with benzoyl peroxide will help prevent overdrying of the skin. In addition, benzoyl peroxide (alone or with sulfur) may be an effective degreasing product in cases of seborrhea oleosa. All products that are effective degreasers should be used judiciously. Once the intended effect is accomplished, the animal should be changed to a milder product or bathed less frequently.

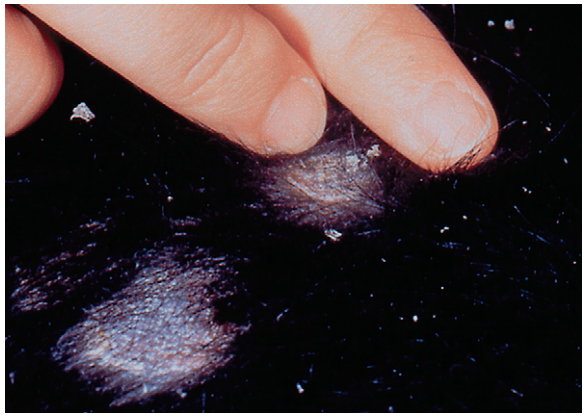

Figure 9-5 Chronic pyoderma in a dog, causing secondary seborrhea.

38. What are the indications for selenium sulfide?

Selenium sulfide is keratolytic, keratoplastic, antifungal, and degreasing. I think 1% selenium sulfide is useful in cases of seborrhea oleosa caused by *Malassezia* dermatitis. As stated previously, veterinary products with selenium sulfide are no longer available. A human product (Selsun Blue) is available over the counter. Selenium sulfide may be irritating to the cat and is contraindicated in this species.

39. What topical antipruritic products are available for use in the dog and cat?

A wide number of steroid and nonsteroidal products are available on the veterinary market. Numerous shampoo products are marketed as having antipruritic effects. These products have a place in treatment of pruritic patients, but they have limited residual effects after rinsing. A number of conditioners and rinses are also available for control of pruritus, and some of these products have residual activity. A number of steroid-containing ointments, pastes, and sprays are also available. Because of their nature, these products are more useful in treating localized areas of pruritus, rather than generalized symptoms.

40. Is colloidal oatmeal an effective antipruritic?

Colloidal oatmeal is a safe and relatively effective antipruritic. The exact mechanism of its antipruritic effect is poorly understood. A colloidal oatmeal-based shampoo and conditioner is available (EpiSoothe, Allerderm/Virbac). In addition, oatmeal rinses are available for use in the dog and cat (EpiSoothe bath treatment, Allerderm/Virbac). Oatmeal-based products are extremely safe, but tend to provide short-term relief (24-48 hours) of mild pruritus only. Oatmeal has no antibacterial or antifungal properties. If secondary infection is present in conjunction with pruritus, utilize an antimicrobial product first. Oatmeal-based products are most useful versus pruritus that is uncomplicated by infection. Many oatmeal-based products are available with additional ingredients in attempts to potentiate the antipruritic effect.

41. Are topical antihistamines effective antipruritics in the dog and cat?

Topical diphenhydramine products are available OTC. In addition, some veterinary products have combined colloidal oatmeal with diphenhydramine (HistaCalm, ResiHIST; Allerderm/Virbac). Again, these products may provide temporary relief of mild pruritus. ResiHist is formulated as a "leave-on" conditioner to provide residual, antipruritic effects. There are no clinical studies to support the claim of added efficacy. It is unclear whether topical antihistamines work directly on the skin, or via absorption into the systemic circulation.

42. Are topical anesthetics an effective way to control pruritus?

Numerous topical anesthetics are available, and they do have temporary antipruritic effects. Pramoxine has been the topical anesthetic of choice in veterinary medicine. Other products, such as lidocaine and benzocaine, may cause cutaneous sensitivity or toxic effects (methemoglobinemia). Pramoxine is usually combined in shampoo or rinses with colloidal oatmeal (Relief, DVM Pharmaceuticals; Dermal Soothe, EVSCO). It is also available as a spray (Relief spray, DVM Pharmaceuticals) and as a leave-on conditioner (ResiPROX, Allerderm/Virbac). Like colloidal oatmeal and topical antihistamines, pramoxine's effects are temporary and most effective versus mild pruritus, uncomplicated by secondary infections.

43. Is lime sulfur a useful antipruritic?

Lime sulfur is a very effective, nonsteroidal antipruritic. Because it is applied as a rinse and allowed to dry on the animal, it provides residual effect. Lime sulfur is safe for use in both dogs and cats. The author commonly recommends the use of lime sulfur dips while animals are being withdrawn from antihistamines and corticosteroids for allergy testing.

44. Are there other nonsteroidal, antipruritic products for use in dogs and cats?

A recently introduced product may be an effective antipruritic by combining novel ingredients. Allermyl (Allerderm/Virbac) contains linoleic acid and a monosaccharide, L-rhamnose, in a microemulsion. Topical application of linoleic acid has previously been shown to improve cutaneous barrier function in the dog.[3] Barrier function is a protective mechanism of the skin, and may be defective in dogs with atopic dermatitis. *In vitro*, L-rhamnose has been shown to decrease inflammatory mediators that may be involved in the pathogenesis of atopic dermatitis. To the author's knowledge, no clinical trials have been performed to critically evaluate the effectiveness of this product *in vivo*.

45. Are there topical corticosteroids that are useful in management of pruritus in the dog?

Topical corticosteroids are very effective antipruritic drugs, and are commonly used in treatment of pruritus in humans. Until recently, most veterinary topical steroid products came as ointments, creams, or powders for localized use. Generalized use of these products in our veterinary patients has been limited by the haircoat and concern over ingestion of the product. In recent years, products that lend themselves to generalized use have become available. Genesis Topical Spray (Allerderm/Virbac) contains 0.015% triamcinolone acetonide and is effective in short-term management of pruritus. Triamcinolone is a potent corticosteroid and should not be used long-term.

46. Are shampoos containing topical corticosteroids safe and effective?

A few corticosteroid containing shampoo products are available (Cortisoothe, Allerderm/Virbac; Capex Shampoo, Galderma Lab). Cortisoothe is a 1% hydrocortisone containing shampoo with a colloidal oatmeal base. Capex shampoo (formerly known as F/S Shampoo) contains 0.01% fluocinolone acetonide, a fluorinated corticosteroid. While topical application of fluorinated corticosteroids can be associated with systemic absorption, use of this product twice weekly did not result in systemic evidence of absorption or adrenal suppression.[2] While corticosteroid-containing shampoos appear to be safe, they do not result in significant residual activity.

47. Are there corticosteroid-containing products that provide residual antipruritic effect?

A 1% hydrocortisone-containing, leave-on conditioner (ResiCort, Allerderm/Virbac) is available. This product may be applied to the entire body and allowed to dry. The base of the product is non-irritating, and thus does not need to be rinsed off. When this product was applied to normal and atopic dogs twice weekly for 6 weeks, mean values for hematologic, biochemical, and adrenal response to exogenous ACTH remained within normal limits.[11] In one dog with inflamed skin, a lack of response to exogenous ACTH was detected at the end of the study,

suggesting that absorption of the product was increased through inflamed skin. For that reason, even 1% hydrocortisone should be used cautiously in small dogs with generalized erythema and pruritus. Genesis Topical Spray contains 0.015% triamcinolone acetonide. This spray is indicated for short-term use in managing a pruritic crisis; it is too potent to use on a long-term basis.

48. Is it safe to apply more potent corticosteroids to the dog or cat?

Numerous corticosteroid-containing products are available as ointments, creams, and sprays. While these products are effective antipruritics, they are intended for short-term use only. Numerous studies have demonstrated that application of fluorinated corticosteroids to the skin, ears, and eyes can result in systemic absorption and suppression of the adrenal axis. In addition to systemic effects, localized effects on the skin can occur. These include cutaneous atrophy, alopecia, comedone formation, and localized pyoderma (Figure 9-6). Subepidermal bullous dermatosis has also been associated with topical application of some fluorinated corticosteroids.

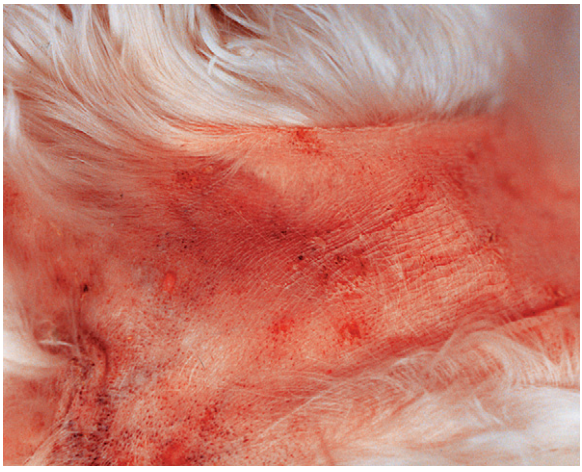

Figure 9-6 Cutaneous atrophy caused by overuse of a triamcinolone-containing ointment (Panolog). Note thin skin, pustules, and comedone formation.

49. What is the safest way to utilize topical corticosteroids?

When used, fluorinated corticosteroids should initially be applied once daily to decrease inflammation, and then rapidly tapered to the least frequent interval needed to maintain improvement. A less potent corticosteroid, such as 1% hydrocortisone, should be substituted as soon as possible to avoid possible adverse effects. A recent study indicated that use of a 0.015% triamcinolone solution (Genesis, Allerderm/Virbac) was effective for management of pruritus in the dog.[5] In that study, hematological and biochemical results of treated dogs did not change significantly over the 28 days of treatment. This product is intended for generalized use over short periods of time (28 days or less) as a safer alternative to oral or injectable corticosteroids. Chronic, excessive use of this product could certainly result in cutaneous atrophy, calcinosis cutis, or other symptoms of iatrogenic Cushing's disease.

50. Are topical corticosteroids safe for treatment of pruritus in cats?

Use of topical ointments and creams is limited in cats due to their propensity to overgroom areas that have substances applied. Cats are also much more tolerant of the systemic side effects of corticosteroids. To my knowledge, systemic effects of topical steroids have not been reported in the cat. Localized adverse effects such as cutaneous atrophy and alopecia can be seen in cats with overuse of potent topical corticosteroids.

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10. LASERS IN DERMATOLOGY

Mona Boord, DVM, DACVD

1. What does the term *laser* stand for?

LASER is an acronym for **l**ight **a**mplification by **s**timulated **e**mission of **r**adiation. Stimulated emission involves a photon of light entering an atom with an excited electron, the electron falls to a lower orbit and two identical photons leave the system. These two photons then enter two new atoms with excited electrons, starting a chain reaction and rapid multiplication of photon generation. The photons emit light that is reflected between two mirrors in a system that absorbs any light that is not perfectly parallel.

2. What are the special features of laser light?

Laser light has three important features:

1. Coherence. The laser light waves are aligned as the light leaves the laser, i.e., the peaks and valleys are aligned, producing a uniform wave front that can be focused to a very small area.
2. Monochromaticity. The laser light waves all have the same wavelength.
3. Collimation. All of the light exiting the laser is parallel and will not diffuse over distances.

3. Can a laser help my practice?

The laser is a tool that will augment your diagnostic and therapeutic options. There are many procedures that can be performed more easily, as well as procedures that cannot be done or

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3. Can a laser help my practice?

The laser is a tool that will augment your diagnostic and therapeutic options. There are many procedures that can be performed more easily, as well as procedures that cannot be done or

wouldn't normally be attempted with traditional surgery. The laser will also enhance the public image of the practice. The public is well educated and desires less painful alternatives to traditional surgery. Improved healing and increased comfort are non-economic factors that may lead to increased numbers of procedures and referrals.

4. How do lasers interact with tissue?

The energy from the laser light is transferred to tissue. Depending on the wavelength of the laser light, the optical properties of the irradiated tissue, and the technique of the surgeon, the laser energy may be reflected, absorbed, scattered, or transmitted when aimed at tissue.

There are different types of lasers available, which produce different wavelengths of light. This depends on the lasing medium. The lasing medium is usually the product the laser is named after. For example, in a CO_2 laser, the lasing media is CO_2, which produces a wavelength of 10,600 nm.

Tissues have different energy absorption coefficients based on their water, hemoglobin, melanin, and protein contents. Water better absorbs longer wavelengths of energy and hemoglobin absorbs shorter wavelengths preferentially. Therefore, the best laser for a procedure depends upon what type of tissue is being lased.

Photothermal, photochemical, or photodisruptive interactions occur between the laser energy and tissue. The first two are used in dermatology. A photothermal interaction occurs when the energy absorbed heats the tissue. The hyperthermia denatures proteins, coagulates blood and vaporizes tissues. With proper surgical technique there is minimal peripheral tissue damage. With improper technique, continued lasing of the tissue creates conduction of heat to surrounding tissues, producing collateral tissue damage. A photochemical interaction occurs when the energy from the laser breaks chemical bonds. This has been used in medicine with the development of photosensitizers that bind to cancer tissue and are activated by laser light to damage the cancer cells. This therapy is called photodynamic therapy. Photodisruptive interaction occurs when very rapid, short, high-power pulses of energy are in contact with target tissue. This disrupts the structure of the tissue and is important in lithotripsy.

5. Which laser is best for which type of tissue?

CO_2 has a very long wavelength of 10,600 nm. It is highly absorbed by water, creating a photothermal interaction. This results in vaporization of the tissue with high water content. The characteristics of this wavelength also result in minimal scatter, shallow penetration, and minimal peripheral tissue injury. These features make the CO_2 laser very useful for most cutaneous procedures. The shallow penetration of tissue is due to the long wavelength of the CO_2 laser. The long wavelength can only be delivered by hollow waveguides and articulated arms; therefore, it cannot be used for endoscopic procedures. Argon and potassium titanyl phosphate (KTP) lasers have short wavelengths of 524 and 532 nm, respectively. For tissues high in hemoglobin, argon lasers and KTP lasers are preferentially absorbed. The problem with these lasers is that their short wavelength allows them to transmit through tissue that does not have high hemoglobin content. This can result in peripheral thermal tissue injury. To minimize damage the amount of energy delivered to the target tissue should be closely monitored. Between these two lasers are diode lasers and neodymium: yttrium aluminum garnet (Nd:YAG) lasers with wavelengths of 635-740 nm, and 1064 nm, respectively. Water and hemoglobin will absorb these wavelengths but not as well as CO_2 is absorbed by water and argon is absorbed by hemoglobin. Therefore the depth of thermal injury to surrounding tissue may be greater if the amount of energy being delivered to the tissue is not closely monitored. Dye lasers have variable wavelengths of 400-1000 nm depending on the dye. They have been used together with photosensitizers for photodynamic therapy. Overall, for most daily procedures in the veterinary dermatology practice, the CO_2 laser is the laser of choice.

Thermal relaxation is the time it takes for tissue to cool. This knowledge has been used to produce lasers that deliver energy pulses versus continuous waves of energy. This allows improved surgical precision and decreases unwanted collateral tissue damage. When purchasing a laser, this upgrade is a little more expensive but worth the investment.

6. What are the risks or safety issues when using lasers in veterinary practice?

With proper training and conscientious adherence to safety protocols the risks are very manageable. Most of the lasers being used in veterinary clinics produce heat and vaporization of the tissue. This creates a plume of smoke. The plume may contain viable organisms (bacterial or viral) as well as cells and can be irritating when inhaled. There are laser-safe surgical masks available and the plume must be removed with a smoke evacuator. The evacuator has a filter that should be changed based on hours of use. The surgical technician is responsible for logging the amount of time the evacuator is in use.

As mentioned previously, heat is generated by the laser; therefore, surgical preparation should not include flammable products such as alcohol. Accidental fire can occur with use of flammable liquids, oxygen, paper drapes, or methane gases. It is imperative to prevent endotracheal tube fires. There are laser-safe endotracheal tubes available or the practitioner can protect standard tubes with saline or sterile water–soaked gauze when using lasers well absorbed by water. If surgery is being performed around the anal area, water-soaked gauze should be placed in the anus.

If proper technique is not used the surgeon, staff, or patient may receive accidental skin burns. Remember the laser is a light energy much like a laser pointer used in lecturing. If the laser pointer is aimed at a hole in the lecture screen the light continues to the wall behind it. When using the laser for cutting tissue, once through the tissue the energy continues until it comes in contact with whatever is beyond it. It is also common to cut through one area of tissue more quickly than another. If the laser is passed over an area already incised, it continues on and burns the tissue beyond. This may be the surgeon's finger or another tissue on the patient. Burns can be minimized by directing the beam at the surgical site, accurately using the foot pedal to activate the laser beam, and using sterile water–soaked gauze or tongue depressors as a backstop. The surgical technician should put the laser in standby mode when not in use.

The light from the laser can also be reflected and if reflected into the eye can cause damage. Care should be taken not to aim the light at surgical instruments. There are laser instruments available with ebonized or burnished finishes which decrease reflected light. Personnel in the operating room must all wear protective eyewear. The type of eyewear needed varies with the type of laser. Regular glasses or safety lenses are sufficient for the CO_2 laser. The patient's eyes should also be protected. Again sterile water–soaked gauze may be placed over the eyes or there are special eye-cups and masks available. The American National Standards Institute publishes a book of safety standards and regulations called *Safe Use of Lasers in Health Care Facilities.*

7. What are the advantages of using laser over traditional surgery?

One of the big advantages with most photothermal lasers is the sealing of small blood vessels. Using the laser provides a very dry surgical field even in highly vascular areas. A feline rhinectomy to remove squamous cell carcinoma may have taken 30-45 minutes with traditional surgery to control the hemorrhage, and with the CO_2 laser the procedure takes approximately 15 minutes.

Another very important benefit is decreased postoperative pain. The laser energy is painful at the time of surgery and general or local anesthesia must be used. However, postoperatively, patients seem to have less pain and return to normal behavior more quickly. This can best be seen following a feline onychectomy or rhinectomy. Following a feline rhinectomy our patients are grooming and eating within hours of recovery.

Another benefit is decreased swelling. If used properly, the laser energy does not crush or tear tissue; it vaporizes it. It also seals lymphatics, thereby decreasing swelling. However, if there is significant peripheral tissue damage due to thermal damage, additional swelling occurs.

8. How do you vary the "strength" of the laser beam?

- Varying the diameter of the laser tip
- Changing the power density (watts/cm^2)
- Changing the mode of gating: continuous wave, pulsed, or superpulsed
- Varying the distance from the laser tip to the tissue.

9. For what applications is the CO_2 laser used most frequently in dermatology?

The CO_2 laser has been very helpful in patients who have multiple epidermal lesions to be removed. Depending on size, these surgical sites once removed can heal by second intention as quickly as lesions closed with primary closure. Examples of more common lesions would include multiple sebaceous adenomas, hemangiomas, keratoacanthomas, and feline ceruminous cystomatosis. There are multiple breeds in which multiple sebaceous adenomas can affect the quality of life due to pruritus and secondary infections. The removal of these lesions can significantly decrease the requirement for medical therapy.

Highly vascular areas are more easily handled using the laser. One of the more common procedures it has been recommended for in dermatology is feline rhinectomy and/or pinnectomy to remove squamous cell carcinoma. In the hands of an experienced laser surgeon, this procedure takes about 15 minutes, with more hemorrhage occurring from the sutures than the tissue removal (Figure 10-1). Masses may be removed or biopsied from the oral cavity. Remember, care must be taken when oxygen is being administered. It has also been used to remove lesions on the penile sheath with less pain and hemorrhage, allowing this area to heal by second intention.

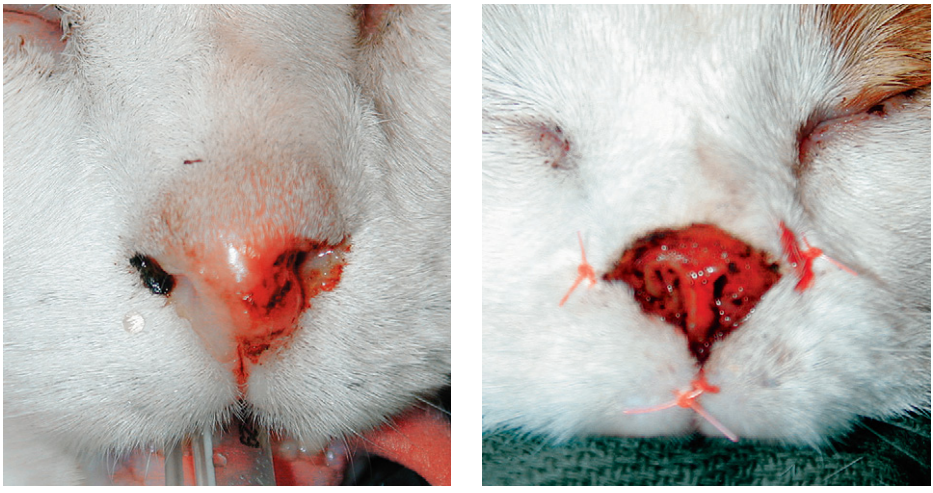

Figure 10-1 **A,** The squamous cell carcinoma involving the nose of this cat was debulked using a CO_2 laser. **B,** Photograph of the nose immediately after laser surgery.

The laser is also very helpful in removing epidermal lesions difficult to close with primary closure, and in some cases laser is the only therapy with good success. Feline ceruminous cystomatosis is an example. This is an entity in which multiple fluid-filled ceruminous cysts form initially on the tragal folds of the pinna. If left untreated, the cysts extend down into the canal, occlude the canal, and secondary otitis externa and/or media develop. The cystic tissue is very thin and adjacent to the pinnal cartilage. This makes removal of the entire cyst difficult with traditional surgery; without the removal of the entire cyst, recurrence is likely. Another example is cutaneous angiomatosis. In veterinary patients, due to the progressive proliferative nature of this condition, previous recommendations included wide surgical excision or amputation. If the lesions occurred in a location where this was not possible (such as the face) the pets were euthanised. Although multiple treatments may be required, laser therapy has been reported to be a successful alternative in these cases.[3]

Infected tissue can be vaporized or removed using the laser. Surgical technique is very important so that the healthy tissue to remaining is not contaminated with infected cells. The

types of infection where this is important include papilloma virus, herpes dermatitis, and sarcoids. The use of the laser with proper surgical technique has resulted in decreased recurrence rates after therapy.

Another type of infected tissue includes chronic proliferative infected tissue. This is most commonly seen in cases of chronic otitis in certain breeds such as the American Cocker Spaniel. If the proliferative tissue is identified and removed before calcifying, the duration of medical therapy may be shortened or total ear canal ablation may be avoided. Once the deep folded cauliflower-like tissue is removed, medical therapy is much more effective (Figures 10-2 and 10-3).

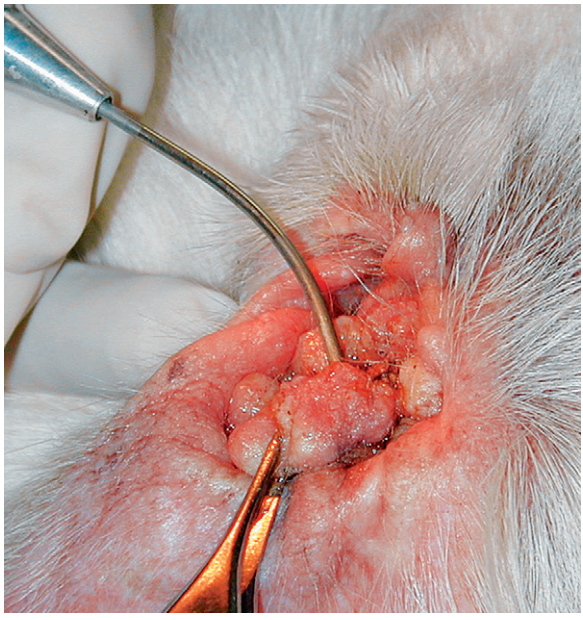

Figure 10-2 CO_2 laser being used to removal proliferative tissue associated with chronic otitis externa.

10. Discuss the advantages versus disadvantages of laser therapy.

The use of the laser in veterinary practice is not a panacea for every case needing surgery. It is a wonderful new tool available to us. Some of the major advantages using photothermal energy for surgery are that the energy-tissue interaction provides a dry surgical field and sterilizes the surgical area. It also provides less swelling and pain. There are some procedures that can be performed with much less aggressive tissue removal compared to traditional surgery. Lasers can be used for photodynamic therapy and better identify tumor margins. The disadvantages include the initial cost of the equipment and maintenance contracts. A location within the clinic for laser surgery should be provided so the beam is contained to a specified area. The staff must be trained to assist the surgeon and maintain logs for the equipment. It is imperative that the surgeon be trained in the use of the laser. Only by understanding the physics of the laser and how the energy is interacting with tissue can its use benefit the patient.

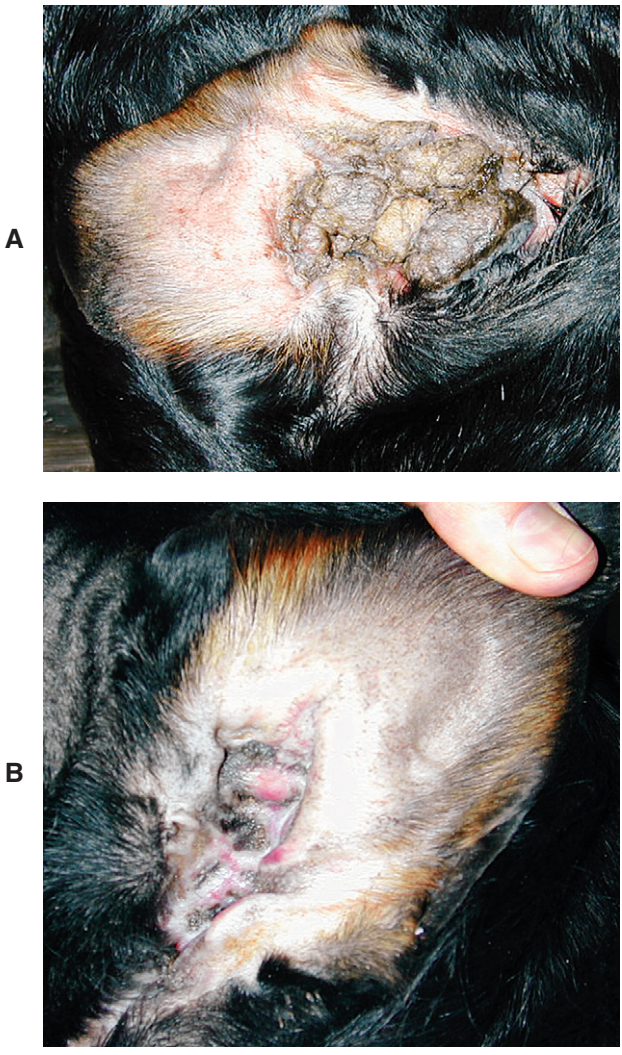

Figure 10-3 **A,** Proliferative otitis externa before removal with a CO_2 laser. **B,** Same dog 3 weeks after CO_2 laser therapy.

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Section III
Inherited Disorders

11. DISORDERS OF KERATINIZATION

Karen A. *Kuhl*, DVM, DACVD

1. What is a keratinization disorder?

A keratinization disorder is caused by a disorganization of the normal orderly progression of the epidermal cells maturing from the basal cell layer to the point of loss of the dead stratum corneum cells.

2. Why are keratinization disorders important?

Keratinization disorders are quite important because they interfere with the normal function of the skin as a barrier to water loss. Any one of the disorders described in this chapter may cause increased water loss and/or decreased hydration of the skin.

3. Describe how a keratinization disorder might appear.

A keratinization disorder can have many appearances. One appearance might be increased scaling. The scaling may be many loose white scales or the scales may appear to be adherent to the skin. Keratinization disorders may also result in frond-like projections along the margins of footpads, ear margins, or planum nasale.

4. Name some diseases classified as keratinization disorders.

- Primary seborrhea
- Familial footpad hyperkeratosis
- Ichthyosis
- Sebaceous adenitis
- Epidermal dysplasia in West Highland White Terriers
- Schnauzer comedo syndrome
- Dermatomyositis
- Idiopathic ulcerative dermatosis in Shetland Sheepdogs and Collies (vesicular cutaneous lupus erythematosus)
- Hereditary lupoid dermatosis of German Shorthaired Pointer (exfoliative cutaneous lupus erythematosus)

5. What is primary seborrhea?

This is an inherited keratinization disorder. The term seborrhea literally means excess sebum production, but is also associated with excessive scaling.

6. Are certain breeds more predisposed?

Primary seborrhea has been noted in several breeds. The most notorious breeds include the American Cocker Spaniel, English Springer Spaniel, West Highland White Terrier, and Basset Hound, although many other breeds may also be affected.

7. What are the clinical signs of primary seborrhea?

Generally, the signs begin at a young age and are progressive. The clinical signs may include ceruminous, hyperplastic otitis externa, a dull flaky haircoat, greasy flaky haircoat, scaly or crusty patches on the body, hyperkeratosis of footpads, and/or brittle claws. Many of these dogs actually present due to an offensive strong odor associated with the skin disease. The clinical signs may be present anywhere, but are often most severe in frictional areas. Pruritus may or may not be present. Pruritus often depends upon the severity of the disease. Many of these dogs are also prone to secondary *Malassezia* or staphylococcal infections.

8. Can seborrhea present differently in different breeds?

In a word, yes. Many Irish Setters and Doberman Pinschers will have dry flaky skin as the only sign (Figure 11-1). Cocker Spaniels, Springer Spaniels, West Highland White Terriers, and Basset Hounds may have very greasy accumulation of exudate and scales that may be generalized, but is often worse on the ventral aspects of the body, especially the ventral neck, axillary and inguinal regions. These are just generalities and the pattern seen in individual animals may be different.

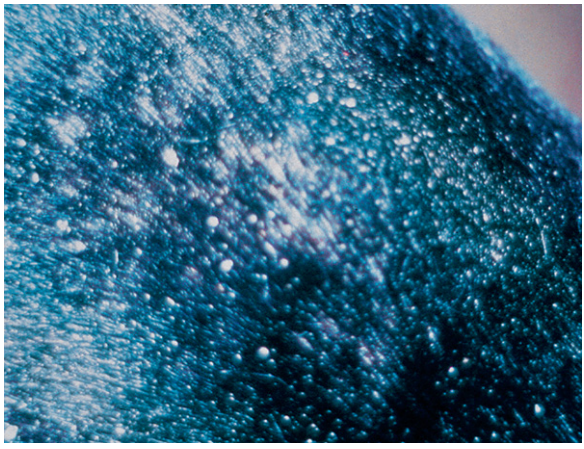

Figure 11-1 Note small white scales on dorsal trunk of a Doberman Pinscher, which are typical of seborrhea in this breed.

9. How is primary seborrhea diagnosed?

This is literally a diagnosis made by ruling out secondary causes of keratinization disorders. Primary and secondary seborrhea can look very similar. You should do a good basic dermatologic workup. Skin scrapings should be done to rule out ectoparasites (see Section IV), Tzanck preparations should be done to detect any secondary infection that must be treated (see Section V). Dermatophyte cultures may be necessary to rule out a dermatophyte infection (see Chapter 20). Depending on the animal's age, a complete blood cell count/chemistry screen and appropriate endocrine testing may be necessary (see Section VII). Some allergic dogs will have signs of seborrhea, thus necessitating an appropriate workup for hypersensitivity related diseases (see Section VI). Finally, biopsies will sometimes help differentiate primary seborrhea from secondary keratinization disorders.

10. What is the treatment for a dry, flaky case of seborrhea?

The key to remember in all cases of primary seborrhea and in most secondary keratinization disorders is that the goal is management, not cure. Secondary infections must be controlled with

appropriate therapies. Shampoos, rinses, and oral fatty acids can be quite helpful. When shampooing frequently, it often is beneficial to keep the haircoat clipped quite short. Often bathing is done two to three times per week initially and then backed off to a maintenance regimen (every 1-2 weeks). For mild cases of seborrhea sicca, bathing can be done with a moisturizing hypoallergenic shampoo or emollient oatmeal shampoos. For moderate-to-severe flaking, a sulfur and salicylic acid shampoo is best. Some dogs also benefit from an emollient rinse afterward. Omega 3 and omega 6 fatty acid supplements may be beneficial as well.

11. Then, what could I use for a greasy seborrhea?

This type of seborrhea tends to be more difficult to manage. As mentioned, shampoos are extremely useful in management. Shampoos recommended for use in seborrhea oleosa include benzoyl peroxide and tar shampoos. Tar shampoos, of course, should not be used in cats. Occasionally, these shampoos can be so drying that an after-bath rinse is recommended. This should be done on an individual basis because rinses can leave the haircoat oily again. For more information on advantages and disadvantages of individual shampoos, see Chapter 9.

12. Can the ceruminous otitis externa be managed?

Sometimes. These can be some of the most exasperating cases seen in small animal practice, especially in Cocker Spaniels. Otitis externa should be treated aggressively with appropriate medications (see Chapter 49). If the ears have frequent recurrent infections or if the canals become calcified or stenotic, a total ear canal ablation and/or bulla osteotomy may be necessary.

13. Are there any oral medications that can be used?

Retinoids have been used with varying results. Cost is often a deterrent. The synthetic retinoids include isotretinoin and acitretin. Vitamin A has also been used. Side effects may include keratoconjunctivitis sicca, altered liver metabolism, teratogenicity, and possible changes in serum triglycerides or cholesterol levels. Corticosteroids are not generally recommended because they may suppress the immune system in dogs or cats that are already predisposed to secondary infections.

14. What are the clinical signs of digital (footpad) hyperkeratosis?

Footpad hyperkeratosis has been reported uncommonly, but has been noted in several breeds including Irish Terriers, Dogue de Bordeaux, Kerry Blue Terriers, Labrador Retrievers, Golden Retrievers and mixed breeds. Affected dogs may develop a severe hyperkeratosis by 6 months of age. The footpads have marked feathery keratin projections and can become secondarily infected.

15. How is primary digital hyperkeratosis diagnosed?

The best means of diagnosis is via biopsy and histopathology of the affected areas. The disease is thought to be autosomal recessive in Irish Terriers. Differential diagnoses resulting in secondary forms of digital hyperkeratosis include canine distemper, generic dog food dermatosis, zinc-responsive dermatosis, pemphigus foliaceus, metabolic epidermal necrosis, and contact irritants or allergies.

16. Can primary digital hyperkeratosis be managed?

This can be difficult to treat. I have seen dogs that groom the excess keratin themselves. Alternatively, soaking daily in a 50% propylene glycol solution may be attempted. A keratolytic ointment such as Kerasolv (DVM Pharmaceuticals) may also be used.

17. What is ichthyosis?

This is a rare inherited primary keratinization defect that manifests as severe scaling or tightly adherent tannish-gray scales or sometimes feathery keratin projections. Ichthyosis can affect any portion of the body, including footpads and planum nasale. The scales may be constantly

shed or may be tightly adherent to the skin to the point of "piling up." This is often seen in very young dogs.

18. Are any breeds predisposed to ichthyosis?

Ichthyosis appears to be most common in West Highland White Terriers, but has been seen in other breeds.

19. How is ichthyosis diagnosed?

Skin biopsy and histopathology should be done to confirm ichthyosis.

20. Describe different ways of managing this disease.

Frequent bathing is usually recommended. The shampoos should be moisturizing hypoallergenic shampoos or keratolytic shampoos (sulfur/salicylic acids). Moisturizing after-bath rinses or 50% propylene glycol may also be helpful. Occasionally, a weekly regimen of bathing in a sulfur/salicylic acid shampoo, followed by a 20-minute baby oil soak, followed by rinsing in a moisturizing hypoallergenic shampoo, can be of great benefit. Cases of ichthyosis may be difficult to manage.

21. Are there any options besides frequent bathing?

Usually, the shampoos are very helpful, but you can also try oral medications. Retinoic acids may be helpful. Dogs treated with systemic retinoids should be monitored periodically for any potential side effects.

22. What are the most common presenting signs for cases of sebaceous adenitis?

The clinical signs may be different in different breeds. Differences in appearance are evident between short- and long-hair coated breeds (see questions 23 and 24). In both coat types the lesions are often complicated by secondary infections. The usual age of onset is young adult to middle-aged. The clinical signs are usually symmetric and most commonly affect the face, head,

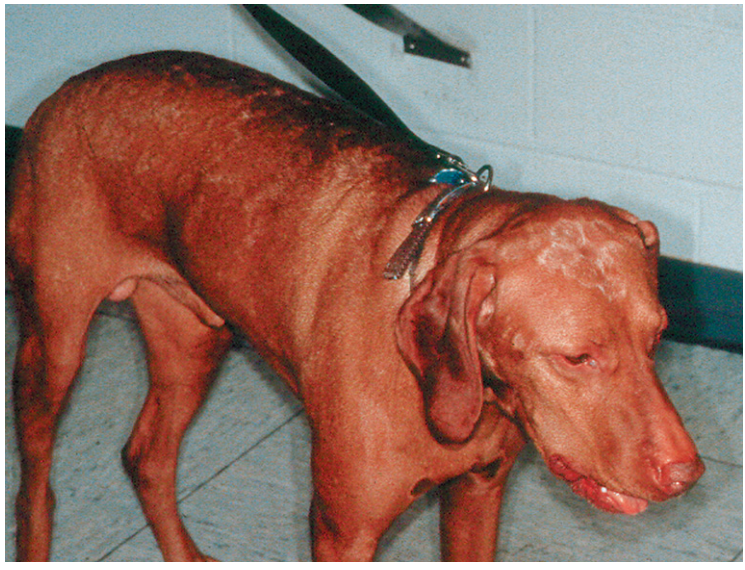

Figure 11-2 Note circular areas of scaling and alopecia on the head and trunk of a Vizsla with sebaceous adenitis.

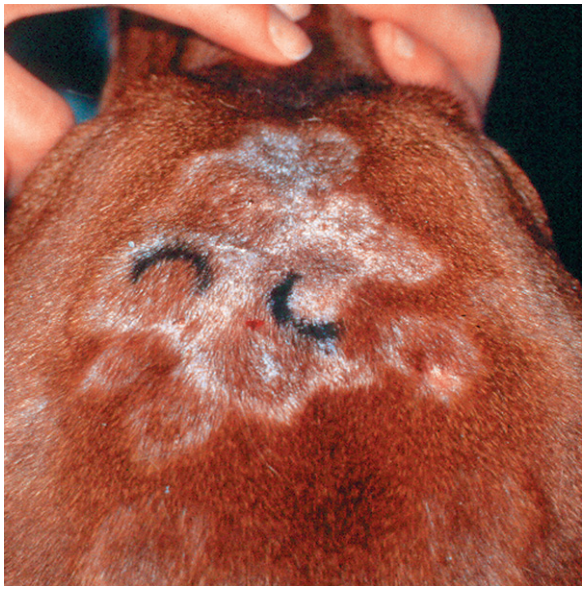

Figure 11-3 Marked circular areas of alopecia on the dorsal head of a Vizsla with sebaceous adenitis.

pinnae, and trunk. Pruritus is generally not evident unless there is a secondary infection. However, occasional cases can be quite pruritic.

23. What is the appearance of sebaceous adenitis in short coated breeds?

Generally, these breeds develop circular areas of scaling and alopecia. The lesions may become large and coalesce. The scaling is usually fine and non-adherent (Figures 11-2 and 11-3).

24. How do the longer hair coated breeds present with sebaceous adenitis?

In Standard Poodles, the initial clinical sign may be a dull haircoat with tightly adherent scales. This is usually followed by alopecia. The remaining haircoat often loses its "crimp" (Figures 11-4 and 11-5). Akitas also start with a dull haircoat and tightly adherent scales; this progresses to a patchy alopecia. Akitas may also present with concurrent signs of systemic illness, such as weight loss, lethargy, and fever. Numerous other breeds may be affected by sebaceous adenitis; their clinical signs generally will fit into one of these two categories.

25. Describe the best method of diagnosing sebaceous adenitis.

As mentioned previously, basic diagnostics need to be done to rule out other differential diagnoses. The final diagnosis is based on skin biopsy and histopathology. The hallmark is an absence of sebaceous glands in multiple skin sections. There may be a great deal of variation in the histopathology and a trained dermatopathologist should be consulted to obtain a correct diagnosis.

26. What treatments work best for sebaceous adenitis?

As in other types of keratinization disorders, the best means of therapy is usually shampoo and rinses. Mild cases may be controlled with keratolytic shampoos and emollient rinses. Fifty percent to 70% propylene glycol in water has been used as a spray or rinse once daily, then decreased to two to three times per week as needed for maintenance. As mentioned in question

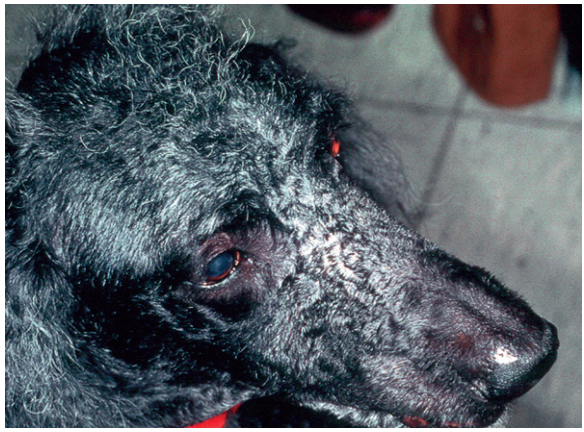

Figure 11-4 Note tightly adherent scaling and incomplete alopecia on the head of a Standard Poodle with sebaceous adenitis.

Figure 11-5 Tightly adherent scaling, alopecia, and loss of crimp in the trunk haircoat of a Standard Poodle with sebaceous adenitis.

20, using shampoos followed with baby oil soaks often works well. Additionally, oral omega 3 and omega 6 fatty acids are often used as dietary supplements and in topical sprays and rinses.

27. Are there any other possible oral therapies?

Yes, oral retinoids are a possibility. Viszlas and Poodles tended to respond best to isotretinoin. Akitas responded best to etretinate in previous studies; however, etretinate is no longer available. Acitretin may be used as a replacement for etretinate. Cyclosporine has also been used with variable responses in treating sebaceous adenitis.

28. What is the long-term prognosis of sebaceous adenitis?

Rarely, a case of sebaceous adenitis may go into remission. Most cases require lifelong therapy to maintain clinical improvement. The owners must realize that this is not a curable disease and will typically require long-term management. Sebaceous adenitis is inherited as an autosomal recessive trait in Standard Poodles; thus, affected dogs should not be bred.

29. Describe epidermal dysplasia of West Highland White Terriers.

The primary feature of this condition is a dysplastic epidermis associated with a *Malassezia* infection developing at an early age. These usually present as a greasy seborrhea that becomes pruritic. Pruritus is present primarily on the face, ears, feet, and ventral surface of the body. This disease was initially thought to be a congenital disorder. However, recent reports have hypothesized that the epidermal changes may just be a hypersensitivity reaction to *Malassezia* or a result of excessive skin trauma after pruritus.

30. How is a diagnosis of epidermal dysplasia made?

Again, a basic dermatological workup should be done. Skin biopsy specimens submitted for histopathology will demonstrate the presence of epidermal dysplasia. Histologic findings include a hyperplastic perivascular dermatitis with epidermal dysplasia. Parakeratotic hyperkeratosis is usually present and *Malassezia* may be observed in the surface keratin.

31. How is epidermal dysplasia treated?

Emphasis should be placed upon identifying any potential underlying hypersensitivity diseases (parasitic allergies, food allergies, atopy). Additionally, shampoos with effectiveness against *Malassezia* should be tried, but may not always be particularly helpful. Often systemic therapy for *Malassezia* using oral itraconazole or ketoconazole will be required to alleviate pruritus. Systemic antifungal agents should be used at the lowest dosage possible to keep the infection under control. Dosages and side effects of itraconazole and ketoconazole are discussed in Chapter 20. Many dogs affected by epidermal dysplasia have ultimately been euthanized due to poor response to therapy.

32. What is Schnauzer comedo syndrome?

This is a localized keratinization disorder that has only been recognized in Miniature Schnauzers. Its typical presentation is multiple comedones that may progress to papules or small crusts located along the dorsal midline.

33. How is the diagnosis of Schnauzer comedo syndrome made?

If lesions are restricted to the back in a Miniature Schnauzer, then this is the likely diagnosis. However, you will still need to rule out other causes of folliculitis and comedo formation (e.g., demodicosis, dermatophytosis, staphylococcal folliculitis, hyperadrenocorticism, hypothyroidism, etc.) and obtain skin biopsies for histopathology.

34. What is the most effective treatment for Schnauzer comedo syndrome?

Treatment depends on the severity of the disease process, and this varies tremendously. Thus, treatment also varies. Some dogs do not require any treatment. Many dogs will benefit from daily wipes with one of the "antiseptic" wipes now available in veterinary medicine (Malaseb pledgets, DVM Pharmaceutics; Malacetic Wipes, Dermapet) or frequent antiseborrheic shampoos (benzoyl peroxide products). Synthetic retinoids may be used for severely affected dogs.

35. What is the cause of the severe "greasy kitten syndrome" in Persian cats?

Persian cats can be affected with a primary hereditary seborrhea oleosa (PHSO). Affected kittens may have a dirty appearance that is apparent as early as 2 to 3 days of age. Initially the haircoat is curly and pasted together by keratoseborrheic material that adheres to the surface of the

skin and hairs. Eventually the whole body becomes scaly and oily with a rancid odor. Ceruminous otitis externa is another common feature of this disease.

36. How are kittens with PHSO managed?

PHSO is an incurable disease. Many breeders euthanize affected kittens soon after birth. Mildly affected cats can be suitable house pets if their owners are willing to invest the time in lifelong management of the disease. Affected cats should be clipped to keep the haircoat short. Regular bathing (frequency may vary from every day to once monthly depending on the severity of the cat's condition) with a mild dishwashing detergent (e.g., Joy, Sunlight, Palmolive) followed by a sulfur/salicylic acid veterinary shampoo will help to control the odor and scaling. Isotretinoin therapy may be helpful in some cases; this synthetic retinoid is used at a dose of 2 mg/kg orally every other day until the seborrhea is under control and then tapered to one dose weekly.

37. Is PHSO the cause of the "dirty face syndrome" seen in adult Persian cats?

No, PHSO is a distinct syndrome from that of idiopathic facial dermatitis (IFD) of Persian cats (Figure 11-6). The lesions of IFD are confined to the head and neck region and consist of a black exudate that encrusts the hairs of the periocular, perioral, nasal fold, and chin regions. The etiology of IFD is currently unknown; however, the later age of onset (range 4 months to 4 years, median 12 months, for IFD versus from birth for PHSO) and distinct regional location (facial for IFD, generalized for PHSO) plus differing clinical appearance makes it unlikely that the two diseases are related. No satisfactory treatment regimen has been identified for IFD. Current treatments are aimed at minimizing secondary infections and relieving pruritus. Gentle cleansing with medicated wipes (Malaseb pledgets, DVM Pharmaceuticals; Malacetic wipes, DermaPet) may be helpful in some cases.

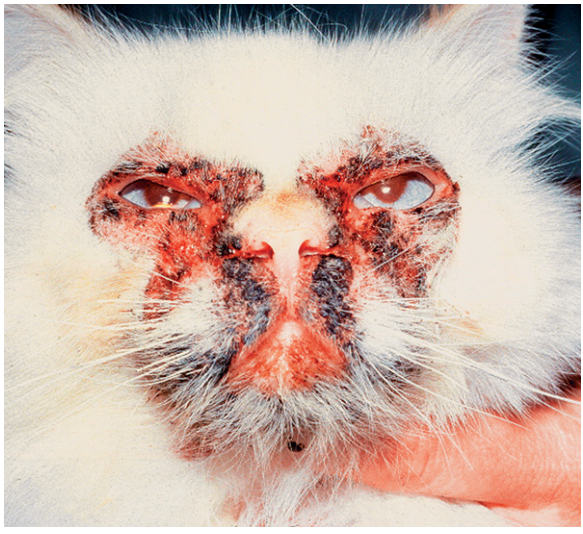

Figure 11-6 Adult Persian with idiopathic facial dermatitis. (Courtesy of Dr. Karen Campbell.)

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12. DISORDERS OF HAIR AND HAIR GROWTH

Daniel O. Morris, DVM, DACVD

1. Dog and cat owners are often concerned about alopecia in their pets. Other than endocrinopathies, what disorders should I be looking for?

While it is true that many "symmetric" alopecias in dogs are endocrine-related, there are several important disorders that are due to hair shaft or hair follicle defects. In cats, the most common cause of symmetric alopecia is over-grooming (or hair pulling) due to pruritus. Congenital and acquired alopecias that result from hair shaft or follicular disorders are a heterogeneous group with a variety of known (or unknown) etiologies. This "group" of conditions is much more common in dogs than in cats.

2. Which congenital conditions are possible?

Congenital alopecias appear to be quite rare, and may involve the entire body or very specific regions. Of course, some breeds have been developed for generalized alopecia—consider the Mexican Hairless, Chinese Crested, American Hairless Terrier, and the feline Sphinx! However, generalized alopecia or hypotrichosis may occur as a genetic mutation in any breed of dog or cat, and puppies and kittens of various breeds have been reported in the veterinary literature. Skin biopsy specimens may reveal defects in just the hair follicles, while others have more extensive ectodermal defects (abnormal claws, adnexal glands, etc.). If hair follicles are not present histologically, or are severely reduced or defective, you may assure your client that regrowth of hair will not occur.

3. Are color-linked alopecias due to the same type of defect?

No…which is good news for some cases. Color-linked alopecias are due to hair-shaft breakage at or below the level of the skin. The hair follicles are still capable of producing hair shafts in most cases (especially younger animals), so therapeutic intervention may be useful. There are two types of color-linked alopecias described in dogs: black hair follicular dysplasia (BHFD) and color dilution alopecia (CDA; also known as "color mutant alopecia").

4. Are BHFD and CDA similar in appearance and diagnostic features?

CDA has been reported in 11 breeds (most commonly in blue or fawn Dobermans) and causes alopecia and follicular plugging in the blue or fawn (black or brown dilute) areas only. Onset of hair loss is tardive (occurring after birth) and usually develops between 4 and 18 months of age. BHFD has been reported in 14 bi- or tri-colored breeds, and results in alopecia of the

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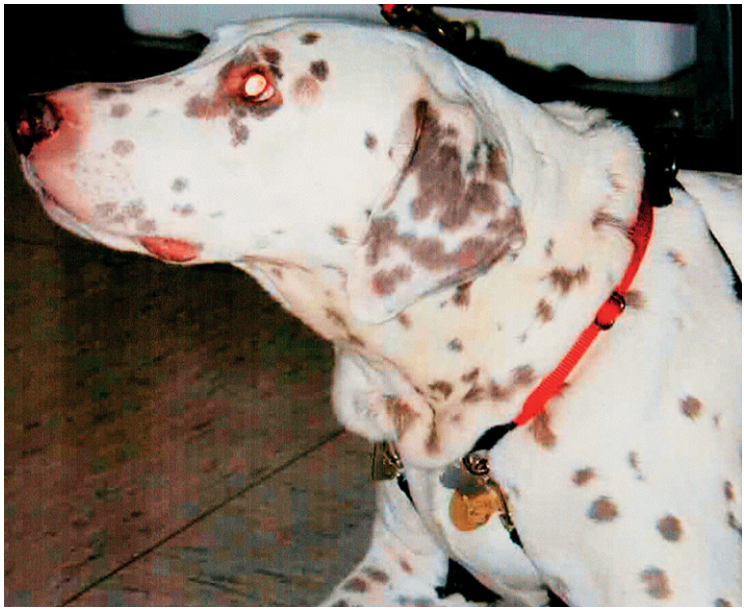

Figure 12-1 A 7-year-old Dalmatian with black hair follicular dysplasia. Note the complete absence of hair in the areas of pigmented spots (although the skin itself is normal), while the white hair is completely normal in texture and density.

black-haired areas only (Figure 12-1). Abnormal haircoat is usually evident by 4 weeks of age. I have also recognized these conditions in solid-colored breeds (Chesapeake Bay and Labrador Retrievers, respectively).

Familial disorders of hair shaft pigmentation, where melanin clumping in the hair shaft results in weakness and breakage, are found in both BHFD and CDA. Autosomal recessive modes of inheritance have been suggested in several reports where pedigree analysis was available. Microscopic examination of plucked hairs will reveal large clumps of melanin within the hair cortex, which may result in fractures or distortion of the hair cuticle. Because the age of onset and restriction of hair loss to the color dilute or black areas *only* are hallmarks, biopsy is often not necessary. However, the pathologist will typically report similar pigment clumping in hair shafts, as well as distorted hair follicles (i.e., follicular dysplasia) in many cases.

In CDA, the hair loss is often accompanied by dry seborrhea and bacterial folliculitis (papules and pustules). Fibrosis of hair follicles can eventually result, which prevents regrowth of hairs. In older animals, complete alopecia of color dilute areas is common, often with severe secondary seborrhea. BHFD is not typically associated with problematic folliculitis, although alopecic areas may be mildly scaly.

5. Are BHFD and CDA treatable?

For some individuals with CDA, there is no effective treatment for the alopecia. Secondary follicular plugging, seborrhea, and staphylococcal infections require lifelong management with topical therapies (benzoyl peroxide shampoos followed by moisturizing rinses), and systemic antibiotics as required to treat infections. Our most effective therapy, a synthetic retinoid (vitamin A derivative) marketed under the trade name Tegison, is no longer available. Some dogs will

respond to the newer synthetic retinoid Soriatane, but this has not been as effective as the original Tegison in the experience of many dermatologists. The dosage of Soriatane may be variable (1-4 mg/kg/day orally) and the drug is quite expensive. Recently, anecdotal reports of CDA and BHFD responding to oral melatonin have surfaced. Because oral melatonin seems to have a very low side-effect profile, its use on a trial basis may be warranted.

6. Tell me more about melatonin!

Melatonin is a hormone secreted by the pineal gland that plays a role in photoperiod-related hair growth and coat color in many mammals (i.e., winter coat develops when melatonin increases, and spring shedding occurs with decreasing levels of melatonin). It also has a role in reproductive development and function, is a potent antioxidant, and has oncostatic properties. Studies performed at the University of Tennessee have shown that melatonin decreases the circulating levels of adrenal sex hormones. It has been used successfully in a wide variety of alopecic diseases in which the underlying etiologies are unknown or incompletely known, some of which may be related to sex hormone imbalances. I typically administer melatonin at a rate of 3 mg orally every 8 hours in small breeds, 6 mg orally every 8 hours in medium-sized breeds, and 9 mg orally every 8 hours in large breeds. Once hair regrowth has occurred, try to decrease the frequency to once-daily or every-other-day administration. Hair loss usually recurs when treatment is halted (with the permanent follicular disorders). This compound has also been used in the treatment of alopecia X, cyclical flank alopecia, pattern alopecias, post-clipping alopecia, and follicular dysplasias (see Chapter 39).

7. What is follicular dysplasia?

Follicular dysplasia simply means "abnormal development of hair follicles," and is primarily a histologic term that we also use in the clinical setting to describe a group of hair growth abnormalities. As mentioned previously, there are color-linked dysplasias (CDA and BHFD) as well as non–color-linked dysplasias. The latter may be classified as either cyclical or structural follicular dysplasias.

Cyclical dysplasias are thought to represent interruptions of the normal hair follicle cycle, which may resolve spontaneously after one or more shedding cycles of the rest of the haircoat. The most common cyclical dysplasia is often referred to as "seasonal flank alopecia" or "canine recurrent flank alopecia" (CRFA).

CRFA typically occurs over the flanks and mid-lateral thorax ("saddle region") of dogs, and results in marked hyperpigmentation. The alopecia may be unilateral or bilateral. It may recur predictably each year, or may skip a year. It may progress to permanent alopecia, or disappear forever after one or more seasons. Most dogs lose hair in the fall and regrow in the spring/summer. Some do just the opposite. The disease is most common in Boxers, English Bulldogs, and Airdale Terriers, but many breeds have been affected (Figure 12-2). The complete etiology remains unknown. Although similar clinical lesions have been noted in isolated cases of hypothyroidism, hyperadrenocorticism, and ovarian imbalances, hormonal deficits have not been documented in this disease entity. The most plausible etiology is an abnormal response of hair follicle receptors in the flank region to a yet unknown mediator (which may be pineal gland dependent), aggravated by the changing photoperiod.

Diagnosis of CRFA is made when there is a history of cyclical recurrence, or when endocrinopathy has been ruled out (i.e., when a dog is presented during the first episode), and the skin biopsy reveals the characteristic atrophy of hair follicles with comedo formation (resembling an inverted foot).

Treatment is unnecessary for most cases in which hair regrowth occurs spontaneously. CRFA is a cosmetic problem only; however, many owners will request intervention or hope to prevent recurrence in subsequent years. Melatonin has been used successfully for this purpose both orally and parenterally. Because the parenteral forms are difficult to obtain, I typically use the oral over-the-counter products that are available in the United States.

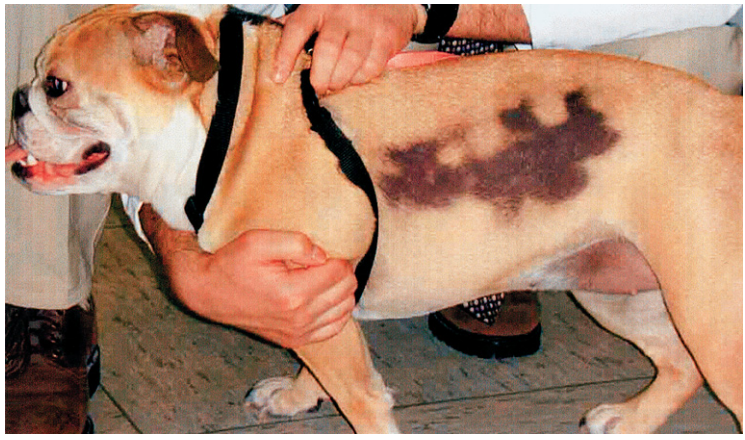

Figure 12-2 A 3-year-old English Bulldog with canine recurrent flank alopecia. Note the extensive hyperpigmentation of the skin in the alopecic areas over the "saddle region." Complete hair regrowth was achieved with the onset of lengthening daylight hours.

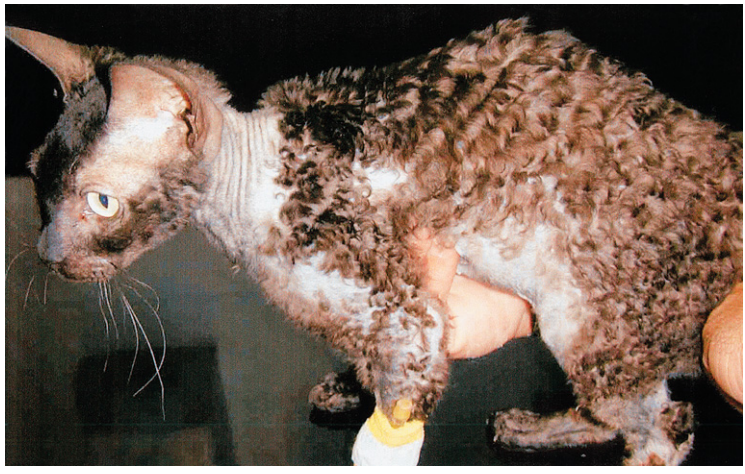

Figure 12-3 A 2-year-old Devon Rex cat with follicular dysplasia affecting the neck and ventral surface. The cat was presented to the teaching hospital for non-cutaneous disease that was unrelated to its alopecia.

Structural dysplasias are a mixed bag of conditions that occur in a myriad of breeds, and remain to be more completely classified. In at least one breed (the Irish Water Spaniel), investigators have reported hormonal and possibly nutritional factors to be involved, so it is becoming less clear where these alopecic diseases fall…are they true developmental defects of the hair follicles, or multifactorial conditions that may respond to diet or hormonal therapies? There are no uniformly successful therapies reported for non–cyclical/non–color-linked follicular dysplasias. The heritability of these conditions is also largely unknown, although there have been several groups of "related" breeds reported to develop them. The most common groups noted are Siberian Huskies/Alaskan Malamutes; curly coated breeds (Irish Water Spaniels/Portuguese Water

Dogs/Curly-Coated Retrievers); and red or black bi-colored breeds (Doberman Pinschers/Miniature Pinschers/Manchester Terriers). Many other seemingly unrelated breeds have also been reported anecdotally or formally in the veterinary literature. Of the cat breeds, only the Cornish Rex has been formally reported, but I have observed several cases in the Devon Rex as well (Figure 12-3).

8. What is pattern alopecia?

Also known as "pattern baldness," there are several forms of pattern alopecia reported in dogs. Whether these forms share pathophysiologic mechanisms with each other, or with human pattern baldness, is not completely known. There are three types of pattern alopecia that are currently recognized in dogs.

Pinnal alopecia of Dachshunds: This occurs predominantly in males and begins between 6 and 9 months of age. Progression to complete pinnal alopecia is complete by 8 or 9 years of age. The skin typically becomes extremely hyperpigmented and the pinnal vasculature is prominent.

Ventral pattern alopecia: This is most common in dachshunds, but also seen in Chihuahuas, Whippets, Greyhounds, Boxers, Italian Greyhounds, Boston Terriers, Manchester Terriers, and Miniature pinschers, among others. The age of onset is typically around 6 months, and the alopecia occurs on the postauricular areas, the entire ventrum (from neck to tail), and the caudomedial thighs. Residual fine hairs often remain in the alopecic areas. The condition is more common in females than males.

Pattern alopecia of curly coated breeds: This occurs in American Water Spaniels and Portuguese Water Dogs, and affects some combination of the ventral/lateral neck, caudomedial thighs, rump, flanks, and tail. The typical age of onset is 6 months.

The diagnosis of pattern alopecia is based upon the signalment, history, and typical clinical signs/pattern. The primary differential diagnosis is follicular dysplasia (especially for the curly coated breeds). The skin biopsy specimen may show miniaturization of hairs, with otherwise normal adnexae, however, this is very difficult for the pathologist to assess, and the biopsy may be read as "normal" in many cases. In the Irish Water Spaniels, histologic changes more typical of CRFA and color dilution alopecia were reported. Of course, it is possible that the curly coated breeds are expressing a different clinical problem that the smooth coated breeds; nomenclature is not yet precise.

In smooth coated dogs, treatment of pattern alopecia is most often achieved successfully with oral melatonin. I have treated many dogs of different breeds successfully in this manner. Again, once hair regrowth has occurred, try to decrease the frequency to once daily or every-other-day administration. My experience has been that most individuals will require daily dosing. Hair loss recurs when treatment is halted.

9. Is pattern baldness the cause of alopecia that occurs on the caudolateral thighs of racing Greyhounds?

"Bald thigh syndrome" of racing Greyhounds is histologically distinct from pattern alopecia. Rather than showing miniaturization of follicles and hairs, the follicles are typically dilated and filled with keratin and hairs. These should appear as comedomes grossly. Histologically, the pathologist may report that many of the follicles are in catagen arrest or describe prominent tricholemmal cornification. The histologic changes are suggestive of endocrinopathy, but a large study of necropsy specimens (adrenal glands, thyroid glands, and skin) from affected dogs failed to document definitive adrenal or thyroid disease. Curiously, this condition resolves when the Greyhounds are no longer actively racing.

10. What other types of acquired alopecia are common?

Perhaps the most common form of acquired alopecia that I see on referral is post-clipping alopecia. This is characterized by a prolonged period of alopecia following clipping for (usually) surgical procedures, or any other reason that necessitates shaving to the level of the skin

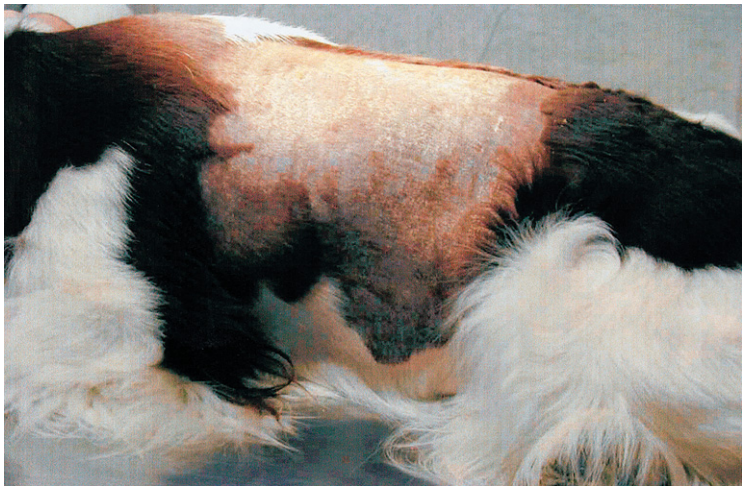

Figure 12-4 A 5-year-old English Springer spaniel with post-clipping alopecia that has persisted for 8 months following a surgical shave. Note the sharp borders between the alopecic area and normal coat, with clipper blade marks evident. As is often the case with post-clipping alopecia, the exposed skin has developed dry scale.

(Figure 12-4). It may also be seen on the legs where hair is shaved for catheter placement. Affected breeds tend to have dense, heavy coats (especially "northern" breeds) and include Siberian Huskies, Alaskan Malamutes, Samoyeds, Keeshonds, Chows, and German Shepherds, although other breeds can be affected. Mild scaling may accompany the alopecia, but hair beyond the alopecic areas is normal. This may persist for as long as 12 months to 2 years, depending on the follicular cycle of the individual. It is now known that some of the "northern" breeds have very long telogen (resting period) cycles, and therefore may have prolonged periods of naturally occurring hair growth arrest, with a cyclical shedding occurring only once a year or every other year. Therefore, if such a dog is clipped at the beginning of a cycle, the alopecic period can be quite protracted.

The diagnosis of post-clipping alopecia is made by ruling out endocrinopathies (such as hypothyroidism, hyperadrenocorticism, and alopecia X) if other supportive clinical signs are present. The skin biopsy may show diffuse catagen arrest of hair follicles, however, caution is warranted in interpreting the presence of these "flame follicles," as they appear to be a normal occurrence in some of the predisposed breeds. Localized regrowth of hair (in tufts) may occur in areas of skin trauma (such as the biopsy sites).

While this condition is purely a cosmetic problem, it is understandably upsetting to the pet owner. Melatonin may be useful in some cases, although I have been routinely disappointed in treatment of my cases.

11. Clients often ask me about the sparsely haired areas in the temporal areas of cats. Is this truly a concern?

Many short-haired cats will have a noticeably sparse hair coat in the areas between the pinnae and eyes. While referred to as "feline preauricular alopecia" by dermatologists, this is not truly a pathogenic condition. It is completely normal and clients should be reassured that there is nothing that should be (or can be) done. However, this is also an area commonly affected in cases of facial pruritus due to allergic or parasitic diseases and crusting dermatoses such as dermato-

phytosis and pemphigus foliaceus. Therefore, if evidence of inflammation (excoriations, folliculitis, crusts, scale, etc.) is present, diagnostic tests such as scrapings, fungal culture, skin biopsy, and allergy diagnostics should be considered.

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13. DISORDERS OF COLLAGEN AND ELASTIN

Jennifer L. *Matousek*, DVM, MS, DACVD

1. What is Ehlers-Danlos syndrome (EDS)?

The Ehlers-Danlos syndromes are a group of rare hereditary connective tissue disorders characterized by decreased tensile strength of affected tissues. Molecular and biochemical advances have led to the definition of nine types of EDS in people (Table 13-1). This classification is based on clinical signs, modes of inheritance, and underlying biochemical defects. Most types of EDS are characterized by defects in collagen fibrillogenesis that result from mutations in genes coding for fibrillar collagen (types I, III, V) or for enzymes (e.g., type I procollagen-N-peptidase) that catalyze the post-translational modification of collagen fibrils. These hereditary collagen disorders cause skin fragility and hyperelasticity in small (cats, dogs, rabbits, mink) and large animals (horses, cattle, sheep).

2. Two forms of Ehlers-Danlos syndrome have been described in cats. Briefly identify and describe the cause of each form.

Dermatosparaxis is an autosomal recessive form of EDS that correlates with EDS type VIIC in people. It is caused by a deficiency of type I procollagen-N-peptidase, which leads to an accumulation of partially processed type I procollagen. Dermatosparaxis has been documented in Himalayan cats.

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Table 13-1 ***Classification of Human Ehlers-Danlos Syndrome***

TYPE OF EHLERS-DANLOS	INHERITANCE	BIOCHEMICAL DEFECT
I Gravis II Mitis	Autosomal dominant	Type V collagen mutation
III Familial hypermobility	Autosomal dominant	Not known
IV Arterial	Autosomal dominant	Type III collagen mutation
V X-linked	X-linked recessive	Not known
VI Kyphoscoliosis	Autosomal recessive	Lysyl hydroxylase deficiency
VII Arthrochalasia multiplex Type A, B	Autosomal dominant	Type I collagen mutation
Type C Dermatosparaxis	Autosomal recessive	Type I procollagen-N-peptidase mutation
VIII Periodontal	Autosomal dominant	Not known
X Other	Autosomal recessive	Possible defect in fibronectin

There is an autosomal dominant form of EDS that correlates best with EDS type I-II. This may be caused by a mutation in the gene for type V collagen. The homozygous form is probably lethal. There is no breed predisposition.

3. List breeds of dogs and cats affected by Ehlers-Danlos syndrome.

Canine

Beagle, Boxer, Dachshund, English Setter, English Springer Spaniel, Fila Brasiliero, Garafiano Shepherd, German Shepherd, Greyhound, Irish Setter, Keeshond, Manchester Terrier, mixed breeds, Red Kelpi, Saint Bernard, soft-coated Wheaton Terrier, Toy Poodle, Welsh Corgi

Feline

Domestic longhair, domestic shorthair, Himalayan

4. Describe the dermatologic signs associated with Ehlers-Danlos syndrome.

Cutaneous fragility and hyperextensibility (Figure 13-1) are the major dermatologic features of EDS. After minor trauma, animals can have large, gaping wounds accompanied by minimal hemorrhage. Animals with extremely fragile skin can tear their skin during normal grooming processes. The wounds tend to heal with wide, "cigarette paper" thin scars.

5. Are there any noncutaneous signs that can be associated with Ehlers-Danlos syndrome?

Periodontal disease, epicanthal folds, subcutaneous hematomas, hygromas, coincidental hernias (inguinal hernia), and ocular changes (microcornea, sclerocornea, lens luxation, and cataracts) have been reported in dogs.

Other than one report of a cat with a coincidental perineal hernia, noncutaneous signs of EDS have not been reported in cats.

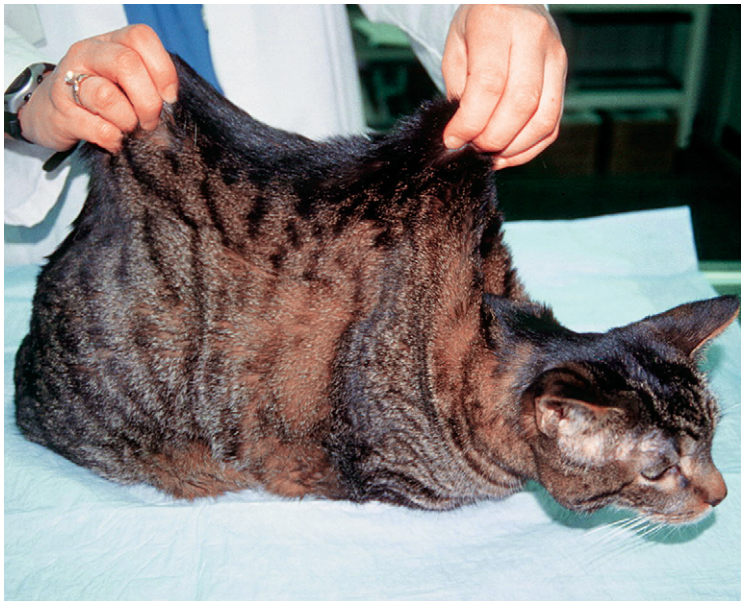

Figure 13-1 Note the skin hyperextensibility in this 11-year-old cat with Ehlers-Danlos syndrome. This cat's EI was 25%.

6. **List differential diagnoses for Ehlers-Danlos syndrome.**
   - Feline acquired skin fragility
   - Cutis laxa

7. **How do you calculate a skin extensibility index (EI)?**
   EI = vertical height of skin fold ÷ body length (occipital crest to tail base) × 100

8. **What is the normal skin extensibility index for dogs? For cats?**
   Normal dogs: less than 14.5%
   Normal cats: less than 19%
   EI values above these levels are consistent with a diagnosis of EDS (Figure 13-1).

9. **Describe histopathologic changes found on skin biopsy specimens from an animal with Ehlers-Danlos syndrome.**
   Histologic changes related to EDS tend to be subtle, so it can be helpful to compare samples from the patient to those of a normal animal. Some animals with EDS do not have identifiable histopathologic abnormalities. Histopathologic findings consistent with EDS include changes in the amount of collagen present (e.g., low collagen content, large spaces between fibers), abnormal size and shape of the collagen bundles (e.g., fragmentation of the fibers), and altered orientation of the collagen (e.g., disorientation of the fibers, collagen fibers whorled around blood vessels).
   Masson's trichrome stain can be used to further evaluate collagen for defects. Collagen fibers normally stain uniformly blue with Masson's trichrome, whereas abnormal fibers contain segmental red staining defects that are birefringent in polarized light.

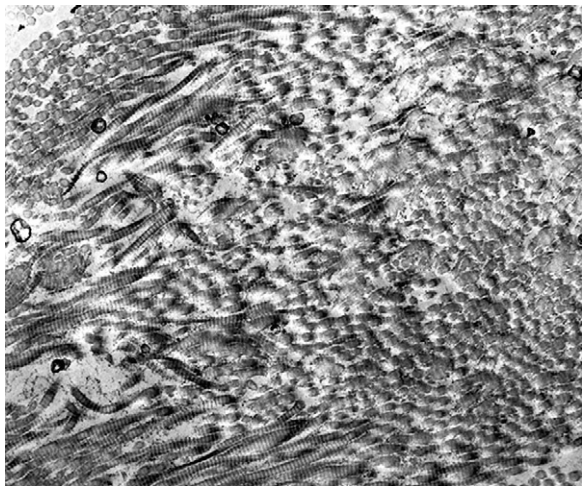

Figure 13-2 This transmission electron microscope photo (10,000×) demonstrates haphazard collagen fibril orientation in a cat with Ehlers-Danlos syndrome.

10. What other tests can be done to confirm a diagnosis of Ehlers-Danlos syndrome?

- Scanning or transmission electron microscopy findings include loosely woven collagen fibers with a twisted appearance (Figure 13-2). The typical banding pattern of fibrillar collagen may be diagonal instead of perpendicular to the length of the collagen fiber. Also, on cross-section, the collagen fibers may be abnormally shaped ("hieroglyphics") or there may be a bimodal distribution of large and small fiber diameter sizes.
- Advanced molecular and biochemical studies that can be on tissue include electrophoresis, enzymatic assays, amino acid analysis, cell culture, mRNA analysis, and tensile strength measurements.

11. Are there any treatments available for animals with Ehlers-Danlos syndrome?

Unfortunately, because of its hereditary nature, there is no specific treatment available for EDS. Anecdotally, vitamin C supplementation has been beneficial in a few dogs. Wounds should be cleaned and sutured promptly. Because the tissue is fragile and may be friable, suggestions to improve the success of closing cutaneous wounds in EDS veterinary patients include using a small taper point needle with swaged suture and placing sutures 5 mm from the wound edge. Additionally, cruciate sutures were used in one case, and were found to be superior to simple interrupted or mattress sutures.

There is an increased incidence of wound dehiscence and delayed wound healing in patients with EDS. Delayed wound healing may be the result of infection, hematoma formation, sutures tearing through skin, or wound dehiscence after the wound appears healed and the sutures are removed. Systemic antibiotics may help prevent secondary infections after wounds occur.

12. What advice should you give to an owner regarding the care of an animal with Ehlers-Danlos syndrome?

- Animals with EDS can have a normal lifespan, but those with excessively fragile skin may have multiple complications that lead to euthanasia.
- It is essential to avoid handling affected dogs and cats roughly.
- Animals should not be allowed to roam freely.

- Onychectomy should be performed in feline patients and cats living in the same household.
- Wounds should be promptly cleaned and sutured.
- Animals with EDS should not be used for breeding purposes because of the heritable nature of the disease. Additionally, mating and parturition could result in serious trauma to the animal.

13. What is cutis laxa?

Cutis laxa (a.k.a. generalized elastosis, dermatochalasia) is a systemic defect in copper metabolism that results in low levels of ceruplasmin and serum copper. Copper is a critical co-enzyme for lysyl oxidase, an important enzyme involved in the synthesis of collagen and elastin. Cutis laxa was formerly classified as EDS type IX. Although cutis laxa has not been reported in small animals, it is an important differential diagnosis for animals with cutaneous laxity. In humans, autosomal dominant, autosomal recessive, and X-linked recessive forms of inheritance exist.

Clinically, the skin is loose and hangs in redundant folds, giving people the "appearance of a Bloodhound." The skin is hyperextensible, but cutaneous fragility, bruisability, and poor wound healing are not significant features. Depending on the type of cutis laxa, patients may also be predisposed to hernias (inguinal, hiatal), cardiovascular disease (mitral valve prolapse, aortic aneurysm), musculoskeletal abnormalities (hooked nose with a long philtrum, joint hypermobility, thoracic malformations, carpal stenoses), and gastrointestinal abnormalities (diverticula, rectal prolapse). Histologically, the dermal elastic fibers (seen with special stains, such as Vernhoeff's or acid orcein and Giemsa) are sparse, fragmented, and clumped.

14. Differentiate between the terms cutaneous asthenia, dermatosparaxis, and Ehlers-Danlos syndrome.

Cutaneous asthenia should be reserved for diseases that affect both collagen and elastin (e.g., cutis laxa).

Dermatosporaxis ("torn skin") should be limited to disorders that are caused by a type I procollagen-N-peptidase mutation (EDS type VIIC).

Ehlers-Danlos syndrome is a group of connective tissue disorders that are characterized by the reduced tensile strength of affected tissues (see Question 1 for details).

15. Name two inherited collagen disorders that affect German Shepherd Dogs (GSD) and their crosses.

- Hereditary disorder of footpads in GSD
- Focal metatarsal fistulation of GSD

16. What is the cause of the hereditary disorder of footpads in GSD?

Because of clinical and histopathologic similarities, it has been proposed that the hereditary disorder of footpads in GSD is similar to familial vasculopathy in GSD. The precise etiology of both disorders is unknown.

17. Describe the clinical signs of the hereditary disorder of footpads in GSD. How would you diagnose this disease?

Affected puppies are usually a few weeks to a few months old, and multiple pups in a litter can be affected. There appears to be no sex predilection.

The footpads of all feet are affected, particularly the metacarpal and metatarsal pads. The footpads are softer than normal, and may be swollen, with depigmentation, ulceration, and crusts. The footpads are often painful, which may lead to lameness. These dogs are otherwise healthy.

A diagnosis is made with biopsies of the footpads. Histopathologic changes include a diffuse, deep dermatitis (lymphoplasmacytic or neutrophilic) to panniculitis with multifocal areas of collagen degeneration.

18. Is there an effective treatment for the hereditary disorder of footpads in GSD?

There is no effective treatment for the hereditary disorder of footpads in GSD. Fortunately, although the footpads remain soft, the ulcers often heal spontaneously within a few months if the animal receives proper wound management. Antibiotics, glucocorticoids, and topical therapies have not been beneficial.

19. What systemic disease has been associated with the hereditary footpad disorder of GSD?

Renal amyloidosis has been reported in some dogs, often occurring around 2 to 3 years of age.

20. What is the cause of focal metatarsal fistulation of GSD?

The cause of focal metatarsal fistulation of GSD is unknown. Some studies have shown that affected dogs have increased antibody levels against type I and type II collagen.

21. What are the clinical signs associated with focal metatarsal fistulation of GSD?

Affected animals are usually diagnosed at 2 to 8 years of age. Focal metatarsal fistulation of GSD appears to be more common in males than in females. Often, both rear legs are affected. Lesions are present on the central plantar surface of the metatarsus proximal to the metatarsal pad. Although the metatarsal area is the most commonly affected site, lesions can also occur in the metacarpal area. The lesions may begin as smooth, cystic structures that progress to well-demarcated fistulae with serosanguinous discharge and deep fibrous tracts. These lesions may be asymptomatic, or the owner may notice the dog licking the affected areas. The dogs are otherwise healthy, and do not have other cutaneous lesions.

22. List differential diagnoses for a GSD with unilateral focal metatarsal fistulation.

- Focal metatarsal fistulation of GSD
- Foreign body
- Deep bacterial pyoderma
- Fungal infection (for example, blastomycosis)
- Neoplasia

23. How is focal metatarsal fistulation of GSD diagnosed?

- Consistent clinical appearance (particularly if bilateral lesions are present)
- Cytologic examination reveals pyogranulomatous inflammation, and possibly intracellular bacteria. Before the lesions fistulate, they are sterile. After the lesions fistulate, secondary bacterial infections (often with *Staphylococcus intermedius*) are common.
- Biopsy specimens and histopathologic studies reveal a deep, nodular to diffuse pyogranulomatous dermatitis to cellulitis with fibrosis and fistulous tracts.
- Antinuclear antibody test results are negative.

24. Describe a treatment plan for animals with focal metatarsal fistulation of GSD.

The lesions often resolve with medical therapy, but in many dogs they will recur. Prednisone 1.1 to 2.2 mg/kg orally every 24 hours results in resolution within 14 to 28 days in most dogs. Topical steroids and vitamin E 200-300 IU orally twice daily may also be useful. The combination of tetracycline and niacinamide has been successful in some dogs, and has the advantage of fewer long-term side effects compared to systemic glucocorticoids. Antibiotics are useful in treating secondary bacterial infections. Surgical debridement of the fibrous tracts and fistulae may provide temporary resolution. Spontaneous resolution has been reported, but treatment is recommended.

25. What is nodular dermatofibrosis?

Nodular dermatofibrosis is a skin condition characterized by multiple cutaneous collagenous nevi. In some dogs, particularly GSD, nodular dermatofibrosis is a cutaneous marker for internal

disease. These animals have renal cystic disease, renal cystadenocarcinoma, or uterine leiomyoma. Additionally, small intestinal polyps have been described in a few dogs. In this syndrome, the collagenous nevi are firm, 0.5-5 cm subcutaneous nodules that are nonpruritic. The nodules are usually located on the limbs and the head, and may be difficult to see. An autosomal dominant mode of inheritance is suspected in GSD.

26. List the three theories proposed for the relationship between nodular dermatofibrosis and renal cystic disease.

- The dermatofibrosis is a paraneoplastic syndrome, and arises secondary to renal neoplasia.
- The animals have inherited the tendency to develop these two diseases, independent of each other.
- The animals have inherited a disorder that leads to simultaneous fibrosis of the skin and kidney parenchyma. The renal fibrosis causes an outflow obstruction, which progresses to renal tubule cyst formation, renal cystadenomas, and renal cystadenocarcinoma.

27. Has nodular dermatofibrosis been described in breeds other than GSD?

Yes, nodular dermatofibrosis has been reported in a Boxer, a Golden Retriever, and a few mixed-breed dogs.

28. What tests would you consider using to diagnose a dog with nodular dermatofibrosis?

Skin biopsy and histopathologic studies are indicated to diagnose the skin lesions. A complete blood cell count, biochemical profile, urinalysis, and imaging of the abdomen (radiography, ultrasonography, computed tomography) are indicated to investigate the possibility of renal cystic disease, renal cystadenocarcinoma, and uterine leiomyoma. If internal abnormalities are detected, further procedures (excretory urogram, nephrectomy, ovariohysterectomy) may be indicated.

29. What is the prognosis for animals with nodular dermatofibrosis?

There is currently no treatment for nodular dermatofibrosis, and the use of medications and chemotherapy has not been extensively reported. Complications of cystic renal disease (e.g., ruptured cysts and subsequent peritonitis, renal tumor metastasis) are a common cause of death or euthanasia in animals with this syndrome. In general, the lifespan does not seem to be significantly shortened, with an average age at death of approximately 9 years.

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14. INHERITED VESICULOBULLOUS DISORDERS

Christine A. Rees, DVM, DACVD

1. What is a vesicle?
A vesicle is a blister less than 1 cm.

2. What is a bulla?
A bulla is a large blister that is usually 2 cm or more in diameter.

3. So, what is a blister?
A blister is a sharp, well-demarcated, elevation of the skin (epidermis) that is filled with a clear liquid. These blisters can be located within the skin (intraepidermal) or just below the skin (subepidermal).

4. What is an inherited vesiculobullous disorder?
An inherited vesiculobullous disorder is characterized by vesicles and bullae on the skin that show up at a young age (usually less than 2 years old). This problem occurs because there is a genetic or inherited component to its pathogenesis.

5. Name some examples of inherited vesiculobullous disorders in animals.
- Epidermolysis bullosa
- Dermatomyositis
- Idiopathic ulcerative dermatosis in Shetland Sheepdogs and Collies
- Canine benign familial chronic pemphigus
- Mucous membrane pemphigoid

6. What is epidermolysis bullosa?
Epidermolysis bullosa (EB) is a condition in which there is structural irregularity of the anchoring substances of the skin (epidermis). The inherited forms of EB can be divided up into four categories: epidermolysis bullosa simplex, epidermolysis acquisita, junctional epidermolysis bullosa, and dystrophic epidermolysis bullosa. All of these forms have been reported in animals.

7. What are the breeds and types of EB that can occur in small animals?
See Table 14-1.

8. What is similar between the various forms of inherited epidermolysis bullosa?
The types of skin lesions and their location are similar regardless of which type of epidermolysis bullosa you are dealing with. Rarely are actual vesicles or bullae seen, because these lesions are so fragile. Instead the skin lesions consist of erosive to ulcerative lesions. These

Wenstrup RJ: Heritable disorders of connective tissue with skin changes. In Freedburg IM, Eisen AZ, Wolff K, et al (eds): *Fitzpatrick's dermatology in general medicine*, ed 5. New York, 1999, McGraw-Hill, pp 1835-1847.
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Table 14-1 ***Breeds Affected by Different Types of EB***

TYPE OF EB	BREEDS AFFECTED
EB simplex	Collies, Shetland Sheepdogs
EB acquisita	Great Danes
Junctional EB	Mongrels, Toy Poodles (lethal form), Beaucerons, German Shorthaired Pointers, Siamese cats
Dystrophic EB	Akitas, Beaucerons, Golden Retrievers, domestic shorthaired cats, Persian cats

skin lesions are usually located over the bony prominences of the face, on the pinna, and pressure points of the limbs and/or footpads. Skin lesions may also be present in the oral cavity as well as around the claw bed. Some animals will also lose their claws (onychomadesis).

9. How do you diagnose EB?

The best way to diagnose EB is to perform a skin biopsy. If the nail bed and/or nail is affected, then samples of skin around the claw and the claw itself should be collected by biopsy and submitted for histopathology.

The results of the biopsy will differ depending on which type of EB is present:

EB simplex will have separation of the skin (cleft formation) that occurs through the basement membrane zone and includes the hair follicles. No inflammation is present unless ulceration is present.

EB acquisita initially has subepidermal blistering with no dermal inflammation. However, many dogs with EB acquisita have subepidermal abscessation that occurs secondary to the intense neutrophilic inflammation that is present. The clefting that occurs in the skin most commonly occurs below collagen IV in the lamina densa of the epidermal basement membrane.

Junctional EB will have subepidermal separation with little or no subjacent dermal inflammation.

Dystrophic EB has a sub-basilar dermoepidermal separation on histopathologic studies. Ultrastructurally, this separation occurs beneath the lamina densa with a reduction in the numbers of anchoring fibrils.

10. How is EB treated?

No treatment to cure an animal of EB exists. Treatments involve symptomatic care (i.e., treating secondary bacterial and/or fungal infections). If possible, trauma should be eliminated or minimized because skin lesions in frictional areas develop in these dogs.

11. What is dermatomyositis?

Dermatomyositis (DM) is a devastating inherited inflammatory disease of the skin and/or muscle, which commonly afflicts Collies, Shetland Sheepdogs and their crosses. Other breeds that have been reported to be affected include Beauceron Shepherds, Welsh Corgis, Lakeland Terriers, Chow Chows, German Shepherd Dogs, and Kuvasz. Although this disease is not classically considered to be a vesiculobullous disorder, cases of a vesiculobullous form of DM have been reported. The skin lesions more classically seen with DM include: alopecia with or without erythema; scaling; and crusting of the face, ears, legs, and tail tip (Figures 14-1 to 14-3). One or more of these areas of the body may be affected. In addition, some dogs may have

Figure 14-1 Tail of a dog with dermatomyositis that demonstrates the typical "rat tail" appearance.

muscular involvement. Sometimes this muscle involvement is so pronounced that it results in muscle atrophy. Other cases may suffer from megaesophagus, with the end result of aspiration pneumonia. In milder cases, the dogs may appear to be sloppy eaters, or have a strange, high stepping gait.

12. When do the skin lesions associated with DM occur?

Most skin lesions develop within the first few years of life, but dogs as old as 8 years of age have been reported to have DM. Whether these adult-onset cases are a different subset of DM or whether these dogs had a mild form of DM that was not recognized earlier in the dog's life remains to be determined.

13. What are the genetics behind DM?

In Collies, the mode of inheritance has been determined to be an autosomal dominant with incomplete penetrance. The incomplete penetrance means that there are triggering factors such as stress, viruses, heat cycles, or pregnancy that trigger genetically predisposed dogs to express DM. Another report suggests a similar mode of inheritance may occur in the Shetland Sheepdog. The mode of inheritance for DM in other breeds of dogs has not been determined.

14. How is DM diagnosed?

DM is diagnosed with skin and muscle biopsies. If muscle involvement is present, then electromyography (EMG) should be performed. The histologic findings of a dog with DM include: scattered hydropic degeneration of the surface and follicular basal cells, mild perivascular to interstitial dermatitis in which lymphocytes, plasma cells and histiocytes predominate. Mild pigmentary incontinence may be present in the superficial dermis. Follicular atrophy and peri-

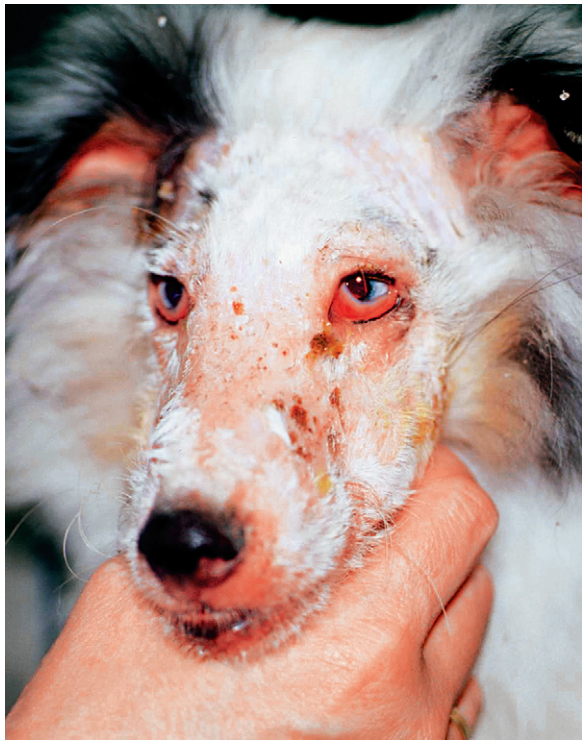

Figure 14-2 Face of dog with dermatomyositis that shows the classic facial pattern with some hair loss, crusting, and erythema.

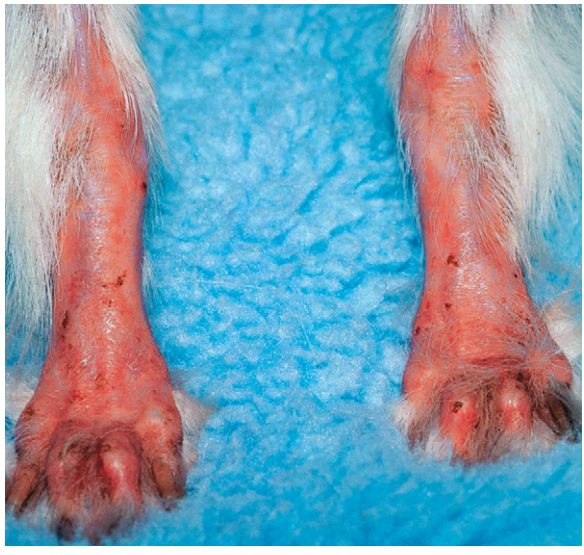

Figure 14-3 Alopecia and erythema on the distal legs of a dog with dermatomyositis.

follicular fibrosis are common. Vasculitis may be present. Muscle biopsy shows a mixed inflammatory exudate accompanied by muscle fiber necrosis and atrophy. The results of EMG are abnormal and show positive sharp waves and fibrillation potential in the muscles of the head and distal extremities.

15. How is DM treated?

Several different treatment options are available. I prefer pentoxifylline (Trental, Aventis, Kansas City, Mo.) with or without vitamin E for a 3-month trial period as the treatment of choice.

- Steroids: Steroids were commonly used to treat DM. However, this treatment is associated with adverse effects when used for extended periods. The complications associated with steroids are recurrent skin and/or urinary tract infections, demodicosis, polyuria, polydipsia, polyphagia, panting, pot-bellied appearance, and thin skin. Anecdotal reports have suggested that thromboemboli develop in some dogs, resulting in a life-threatening situation. Prednisone or prednisolone is most commonly used at a dosage of 1 to 2 mg/kg every 24 hours.
- Pentoxifylline (Trental, Aventis, Kansas City, Mo.): Pentoxifylline is a rheologic drug with immunologic properties. This drug increases blood flow through blood vessels and decreases inflammatory mediators, such as tumor necrosis factor alpha and interleukin 1. Trental has also been shown to stimulate wound healing by stimulating collagenase. It is important that the namebrand, Trental, be used. When generic forms of pentoxifylline have been used, they have been shown to be either ineffective or associated with side effects (profuse vomiting and diarrhea). The drug dose in the literature varies from as little as one 400-mg pentoxifylline tablet regardless of body size every 48 hours to as high as 25 mg/kg every 12 hours. A lower dose but more frequent administration, 10 to 15 mg/kg orally every 8 hours, has also been proposed. Based on my experience, a dosage of 20 to 30 mg/kg orally every 12 hours is recommended for treating DM. Trental should always be given with food. Response to therapy is usually seen within 1 to 3 months.
- Azathioprine (Imuran, AAI International, Wilmington, NC) is an immunosuppressive antimetabolite drug that has been used by some veterinary dermatologists to treat DM. Azathioprine targets rapidly proliferating cells, with its greatest effects on cell-mediated immunity and T lymphocyte–dependent antibody synthesis. The dosage used is similar to that used for treating other immune disorders (azathioprine 2.2 mg/kg every 24 to 48 hours, orally). The problem with this drug is its many side effects. The side effect most commonly seen with azathioprine is bone marrow suppression (anemia, leukocytopenia, thrombocytopenia). Other side effects reported with azathioprine use include vomiting, diarrhea (with or without blood), liver problems, pancreatitis, dermatitis, and alopecia. Animals need to be closely monitored with bloodwork when on azathioprine.
- The immunostimulant drug Immunoregulin (Neogen, Tampa, Fla.) consists of a killed bacteria (*Propionibacterium acnes*) preparation. This is an injectable medication; according to label directions it is injected intravenously twice weekly, then weekly, then monthly. Side effects occasionally occur after an injection and include lethargy, pyrexia, chills, and inappetence. Anaphylactic shock reactions have also been reported. If the drug is given outside of the vein, local tissue inflammation (swelling) will occur. Long-term Immunoregulin use has been associated with hepatitis, vomiting, diarrhea, inappetance, malaise, pyrexia, polydipsia, and acidosis.
- Antioxidants (vitamin E) have been used topically and systemically to treat canine DM. Vitamin E stabilizes lysosomes, reduces prostaglandin E_2 synthesis, and increases interleukin 2 production, which results in both anti-inflammatory and immunostimulatory effects. No known side effects have occurred with either topical or systemic vitamin E when used at recommended doses. Topical vitamin E is typically applied to the affected skin lesions once or twice daily. Systemic vitamin E is administered at a dosage of 200 to

800 IU every 24 hours. This treatment is usually used in conjunction with another therapy for DM.

16. What is idiopathic ulcerative dermatosis in Shetland Sheepdogs and Collies?

This dermatologic disorder is an ulcerative condition of unknown etiology. The current thought is that idiopathic ulcerative dermatosis in Shetland Sheepdogs and Collies is an autoimmune disorder. Therefore, some authors believe that a more appropriate name for this condition would be vesicular cutaneous lupus erythematosus.

17. What are the clinical signs for idiopathic ulcerative dermatosis in Shetland Sheepdogs and Collies?

Skin lesions develop in middle-aged to older dogs. Although this condition has been reported in Collies, it appears to be more prevalent in Shetland Sheepdogs. No sex predilection occurs but skin lesions will recur or get worse when intact female dogs are in estrus. These skin lesions are very painful when they become secondarily infected.

18. What types of skin lesions are associated with idiopathic ulcerative dermatosis?

The initial lesions are vesiculobullous lesions, which can coalesce and ulcerate. The lesions tend to have distinct borders between normal and abnormal skin.

19. Where are the lesions located?

The lesions of idiopathic ulcerative dermatosis are most commonly located in the groin and axillary regions. Other lesion locations include the eyelids, pinnae, oral cavity, external genitalia, anus, and footpads.

20. How do you diagnose idiopathic ulcerative dermatosis?

A biopsy of the skin is the only way to diagnose idiopathic ulcerative dermatosis. A skin biopsy specimen shows hydropic degeneration of basal cells and extensive individual keratinocyte apoptosis, which extends into the stratum spinosum. In severe cases, blisters will form at the dermoepidermal junction. In the dermis, there is superficial perivascular to partially lichenoid dermatitis. Interface folliculitis is often present with no follicular atrophy.

21. How do you treat idiopathic ulcerative dermatosis?

The cyclic nature of this disease makes it difficult to manage. Sunlight and trauma can exacerbate skin lesions. Therefore, affected dogs should be protected from these situations. If a secondary infection occurs, these dogs need to be treated with antibiotics. Glucocorticoids with or without azathioprine, a combination of tetracycline and niacinamide, and vitamin E and pentoxifylline have all been reported to be effective.

22. What is canine benign familial chronic pemphigus?

Canine benign familial chronic pemphigus is a defect in the skin that causes problems with cellular cohesion among skin cells (keratinocytes) (Figure 14-4). Because of this lack of cellular cohesion, vesiculobullous lesions develop easily when the skin is traumatized. The exact skin defect is not known but it is thought to involve the desmosomes.

23. Are there any breeds of dogs that are predisposed?

Canine benign familial chronic pemphigus has been reported in English Setters and their crosses and Doberman Pinschers.

24. What is the mode of inheritance for this syndrome in dogs?

Canine benign familial chronic pemphigus has been found to be inherited in an autosomal

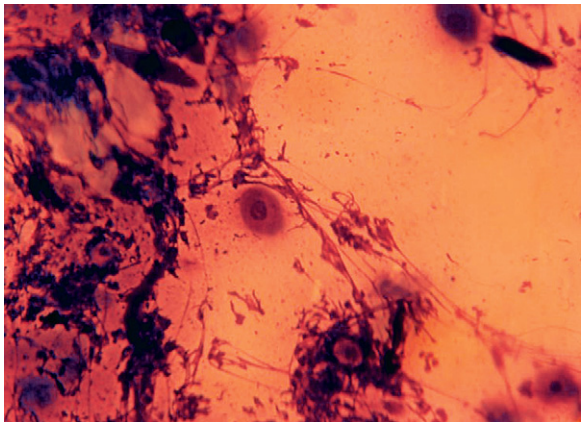

Figure 14-4 Cytology preparation from a dog with pemphigus showing the presence of acantholytic keratinocytes and neutrophils.

dominant fashion in English Setters and their crosses. The exact mode of inheritance in Doberman Pinschers is not known.

25. What types of skin lesions are seen with canine benign familial chronic pemphigus?

Early skin lesions associated with canine benign familial chronic pemphigus are alopecia, erythema, and slight scaling. As the disease progresses, these lesions show increased scaling and crusting. With time these skin lesions can develop into plaques. Although vesicopustules or vesiculobullous lesions can occur, they are rarely seen.

26. What are the locations of the skin lesions?

Lesions occur in dogs at about 6 months of age and occur over pressure points on the limbs, on the ventral chest, or on the pinnae.

27. What is the best way to diagnose canine benign familial chronic pemphigus?

A skin biopsy is the only way to accurately diagnose canine benign familial chronic pemphigus. Skin biopsy specimens show acanthosis with orthokeratotic and parakeratotic hyperkeratosis and marked, diffuse, multifocal areas of acantholysis of the lower and middle portions of the epidermis and follicular outer root sheath. The acantholysis is so marked that the appearance of the affected epidermis appears similar to a dilapidated brick wall. Acantholytic dyskeratotic keratinocytes may be visible.

28. How do you treat dogs with benign familial chronic pemphigus?

In humans, management consists of treating the secondary infections with or without topical corticosteroids and avoidance of trauma. Because the lesions in dogs are asymptomatic and localized, no treatment has been attempted.

29. What is mucous membrane pemphigoid?

This is an autoimmune vesiculobullous disorder that has been reported in a 1-year-old, intact male Australian Shepherd.

30. What are the clinical signs associated with mucous membrane pemphigoid?

The one reported case of mucous membrane pemphigoid had a history of lethargy, lymph-

adenomegaly, swollen joints, and fever, which resolved with trimethoprim-sulfamethoxazole treatment. Several weeks after antibiotic treatment, generalized erythroderma developed that progressed into vesicles, erosions, and crusts in the mouth, around the eyes and nose, and on the ears.

31. How is mucous membrane pemphigoid diagnosed?

Mucous membrane pemphigoid is diagnosed with biopsy. On histopathology, large subepidermal vesicles and focal neutrophilic subepidermal microabscesses are seen. With immunohistochemistry staining, circulating IgG autoantibodies targeted against a 97-kD antigen in the lower lamina lucidia are present.

32. How do you treat mucous membrane pemphigoid?

No treatment recommendations can be found in the literature. However, it would seem reasonable that if the owner wanted to treat his or her pet then treatments used to treat other autoimmune conditions can be tried.

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15. MISCELLANEOUS CONGENITAL AND HEREDITARY DISORDERS

Jennifer L. *Matousek*, DVM, MS, DACVD

1. What breed of dog is affected by idiopathic cutaneous mucinosis?

Shar Pei

2. List some differential diagnoses for cutaneous mucinosis.

Shar Pei
Hypothyroidism
Acromegaly
Alopecia mucinosa

adenomegaly, swollen joints, and fever, which resolved with trimethoprim-sulfamethoxazole treatment. Several weeks after antibiotic treatment, generalized erythroderma developed that progressed into vesicles, erosions, and crusts in the mouth, around the eyes and nose, and on the ears.

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Hypothyroidism
Acromegaly
Alopecia mucinosa

3. What are the clinical signs associated with idiopathic mucinosis?

Often, the animal has exaggerated skin folds, particularly on the head, ventrum, and limbs. Additionally, vesicles composed of mucin may be seen.

4. How do you diagnose idiopathic cutaneous mucinosis?

- Rule out other causes of mucinosis (particularly hypothyroidism).
- A skin biopsy should be done to rule out other depositional diseases (i.e., collagen, etc.).
- Skin histopathology is consistent with excessive mucin in the dermis and there are no other significant abnormalities.
- Thick, clear, sticky material can be removed from the vesicles.

5. How would you treat idiopathic cutaneous mucinosis?

- This is a cosmetic disorder that does not require treatment.
- Some dogs have been reported to "outgrow" the disorder, with its resolving around 2 to 5 years of age.
- Prednisone can be used to decrease mucin deposition (e.g., 2.2 mg/kg orally every 24 hours for 6 days, then taper over 1-2 months).

6. What is congenital hypotrichosis?

Congenital hypotrichosis is a disorder that occurs as a result of an ectodermal defect. In some animals, only the hair follicles are affected, whereas others also have abnormal dentition or tear production.

7. List dog and cat breeds that have been affected by congenital hypotrichosis.

Dogs: American Cocker Spaniel, Belgian Shepherd, German Shepherd, Poodles, Whippet, Beagle, French Bulldog, Rottweiler, Yorkshire Terrier, Labrador Retriever, Bichon Frise, Lhasa Apso, Basset Hound

Cats: Birman, Burmese, Siamese, Devon Rex

8. What is the age of onset of alopecia in animals with congenital hypotrichosis?

Most animals are born with alopecia, which may progressively worsen over a few months. Some animals are born with a normal haircoat that is lost within a few weeks to months.

9. Is there a gender predilection for congenital hypotrichosis?

Male dogs appear predisposed, but there is no apparent gender predilection in cats.

10. What is the typical pattern of alopecia in animals with congenital hypotrichosis?

Alopecia of the temporal region, ear pinnae, caudal dorsum, and entire ventrum (Figure 15-1).

11. How is congenital hypotrichosis diagnosed?

A diagnosis can be made based on history, clinical signs, and skin histopathologic findings (decreased number or small hair follicles, decreased number or small sweat and sebaceous glands, and arrector pili muscles). If the history is not known, tests to rule out endocrinopathies are indicated.

12. What breed of dog is affected by lethal acrodermatitis?

Lethal acrodermatitis is an autosomal recessive syndrome that affects Bull Terriers.

13. Although the cause of lethal acrodermatitis is not known, what common feature is involved in the pathogenesis of the disease?

Bull Terriers with lethal acrodermatitis have abnormal zinc and copper metabolism, but do not respond to high-dose zinc therapy.

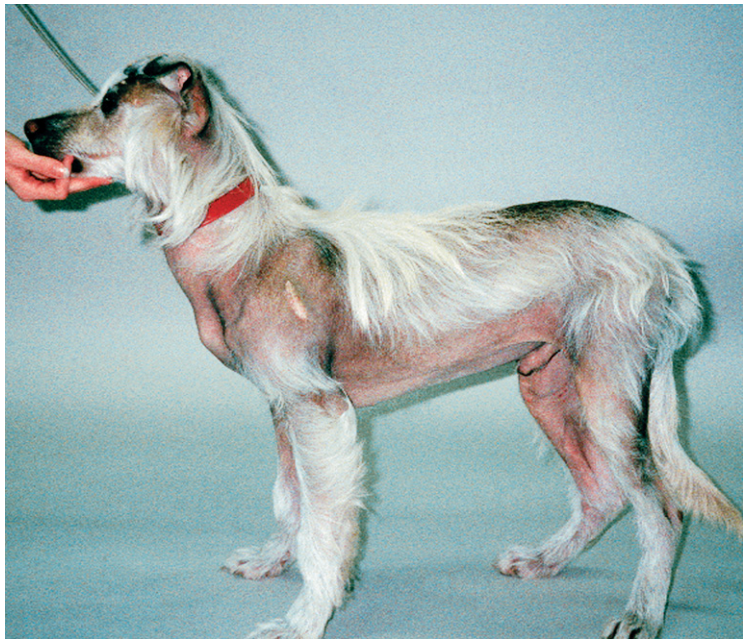

Figure 15-1 A dog with congenital hypotrichosis. Note the alopecia of the temporal region, ear pinnae, caudal dorsum, and ventrum.

14. Describe the clinical symptoms of lethal acrodermatitis.

- Onset noted at an average of 7 weeks of age
- Skin pigmentation is lighter than normal (Figure 15-2)
- Weakness
- High-arched palate makes it difficult to suckle and eat ("messy eaters")
- Retarded growth, skeletal deformities (vertebral abnormalities, abnormal skull and carpus)
- Splayed digits with flat feet
- Paw pads are hyperkeratotic and may fissure (Figure 15-3)
- Ulcers and crusts occur primarily on the face and paws, but can occur anywhere
- Paronychia and onychodystrophy
- Secondary cutaneous infections (bacterial folliculitis, *Malassezia* yeast dermatitis, Candidiasis, dermatophytosis)
- Diarrhea
- Respiratory infections
- May have ocular abnormalities (cataracts, persistent pupillary membranes, corneal opacities)

15. How is lethal acrodermatitis diagnosed?

- Consistent clinical signs in a Bull Terrier puppy
- Skin biopsy specimen shows diffuse and marked parakeratotic hyperkeratosis, crusts, hydropic degeneration of keratinocytes in the upper epidermis, intraepidermal pustules, superficial perivascular dermatitis
- Serum zinc or copper is low or normal
- No classic complete blood cell count, biochemistry, or urinalysis changes

Figure 15-2 Two Bull Terrier puppies with lethal acrodermatitis. Note their light haircoat, stunted growth, and splayed feet.

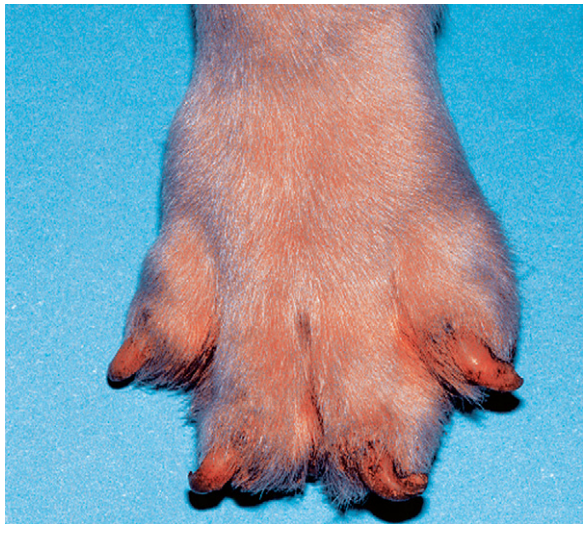

Figure 15-3 Hyperkeratosis of the paw pads in a Bull Terrier puppy with lethal acrodermatitis.

16. What is the average survival time for a puppy with lethal acrodermatitis?
7 months

17. List treatment recommendations for a Bull Terrier with lethal acrodermatitis.
- Treat secondary bacterial or yeast infections
- Try zinc supplementation
- Recommend against breeding the dam, sire, and littermates

18. Describe canine acral mutilation syndrome?
Canine acral mutilation syndrome is a rare sensory neuropathy, in which affected dogs mutilate their extremities. The disorder is probably inherited in an autosomal recessive manner.

19. What breeds of dogs are affected by canine acral mutilation syndrome? Is there a gender or age predilection?
Breeds: German Shorthaired Pointer, English Springer Spaniel, English Pointer
Gender: no predilection
Age: 3-5 months old

20. List the clinical signs in a puppy with acral mutilation syndrome.
- Affected puppies may be smaller than littermates.
- The puppies chew and lick their paws.
- Paws may be swollen with ulceration and paronychia (Figure 15-4).

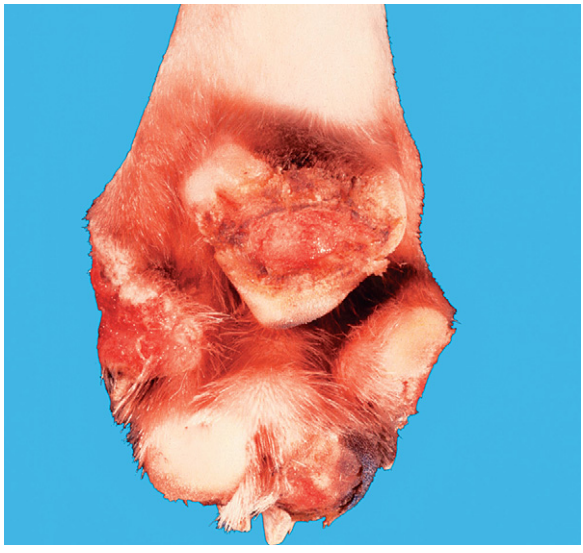

Figure 15-4 Self-induced ulceration and partial amputation of the digits in a puppy with acral mutilation syndrome.

- Autoamputation of the digits may occur.
- There is a loss of temperature and pain sensation in the paws, and possibly in the proximal legs and trunk.
- The hindlimbs are often more severely affected than the forelimbs.
- Dogs have normal proprioception, tendon reflexes, and motor functions.

21. How is acral mutilation syndrome diagnosed?

A presumptive diagnosis of acral mutilation syndrome can be made based on the breed, clinical signs, and history. Histopathology of the nerve tissue (typically performed at necropsy) provides a definitive diagnosis.

22. Are there any treatments available for acral mutilation syndrome?

Attempts to prevent self-mutilation (Elizabethan collars, bandages, sedation) are often ineffective. Most of these animals are euthanized. Be sure to inform the owners that the dam, sire, and littermates should not be bred.

23. What is the cause of persistent scratching in Cavalier King Charles Spaniels?

Cerebellar tonsil herniation with syringomyelia (may be similar to Chiari type 1 malformation in people).

24. How old are the dogs that are affected by persistent scratching in Cavalier King Charles Spaniels?

These dogs are typically 6 months to 2 years old when the pruritus is first noticed.

25. What is the distribution of scratching in Cavalier King Charles Spaniels with persistent scratching?

These dogs have pruritus over the neck or shoulder area.

26. How do you diagnose a Cavalier King Charles Spaniel with persistent scratching from cerebellar herniation?

- Rule out other causes of pruritus.
- Magnetic resonance imaging of the brain.

27. Is there a treatment available for Cavalier King Charles Spaniels with persistent scratching?

- Surgical correction of the herniation should help.
- Some dogs have been treated with dexamethasone or acetazolamide.
- In some dogs, treatment is not necessary.

28. What is urticaria pigmentosa?

Urticaria pigmentosa is a rare cutaneous manifestation of systemic mastocytosis (mast cell hyperplasia that can affect any organ). It has been reported in the dog and cat (Sphinx, Devon Rex, Siamese breeds of cats).

29. What clinical signs are consistent with urticaria pigmentosa?

Multifocal macules, papules and crusts on the head, face, neck, and ventrum. Often these lesions are asymptomatic.

30. Can you treat animals with urticaria pigmentosa?

Yes, Siamese and Sphinx cats have reportedly responded to corticosteroid and antihistamine administration. Be sure to rule out all other diseases (particularly miliary dermatitis and the associated underlying causes).

31. Cutaneous and renal glomerular vasculopathy (CRGV) has been reported in which dog breed?

Primarily Greyhounds, but it is uncertain as to whether there is truly a genetic predisposition to CRGV. Recently, CRGV was reported in a Great Dane.

32. What is the nonprofessional's term for CRGV of Greyhounds?
Alabama rot.

33. What is the proposed etiologic agent of CRGV of Greyhounds?
Shiga-like toxins from *Escherichia coli*, possibly from eating raw meat.

34. Describe the clinical signs associated with CRGV of Greyhounds.
Systemic signs in approximately 25% of affected dogs:
- Pyrexia
- Anorexia, vomiting, and diarrhea
- Lethargy
- Polydipsia, polyuria
- Ascites, ventral edema
- Acute renal failure, possibly with anuria or oliguria

Cutaneous signs:
- Well-demarcated ulcers on the limbs (especially hindlimbs), and occasionally on the trunk
- Pitting edema of the limbs

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Section IV
Parasitic Skin Diseases

16. ARTHROPOD PARASITES

Robert Kennis, DVM, DACVD

1. How are arthropods different from insects?

Insects have three pairs of legs, three segments (head, thorax, abdomen), and wings. Arthropods have four pairs of legs, with the head and thorax, or the head, thorax, and abdomen fused together. No wings are present on arthropods.

2. What is the importance of *Dermanyssus gallinae* to small animals?

This is a bird and poultry mite that may parasitize small animals. Exposure is usually associated with aviaries or chicken coops. Only the larval forms of the mite will feed on animals. After consuming a blood meal, the larvae appear red. The mites may cause clinical symptoms associated with pruritus. Diagnosis is usually easy using tape preparations. Treatment involves avoidance of the source of the mites.

3. Give the name, regional distribution pattern, and clinical findings associated with the cat fur mite.

The cat fur mite is *Lynxacarus radovsky* (Figure 16-1). It has been reported as parasitizing domestic cats in Hawaii, Texas, and Florida. The clinical findings are usually mild and include

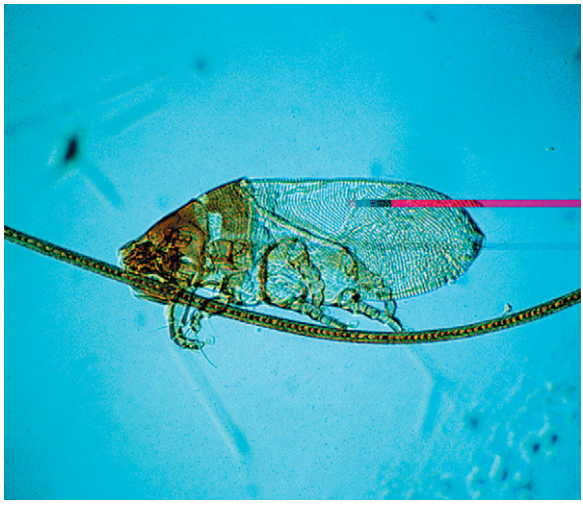

Figure 16-1 *Lynxacarus radovsky*, the cat fur mite.

increased scale, alopecia, and pruritus. It is uncommon to find these mites on normal healthy cats. The fur mites are host-specific and non-zoonotic.

4. Describe the life cycle of chigger mites; include clinical findings associated with parasitism.

Harvest mite is a synonym commonly used to describe these mites. Only the larval stage is parasitic because the adult mites feed on decaying vegetation. The eggs are laid in the soil and hatch into six-legged larvae. Larvae are red or orange and can be seen with the naked eye. After feeding, they drop to the ground and molt to become nymphs and later adults. They can parasitize a myriad of mammals including humans. Bites can be pruritic or non-pruritic; papules, pustules, crusts and scaling may ensue. Trauma-induced alopecia is usually present in animals with pruritus. Identification of the mites can be made using skin scrapings or tape preparations for microscopic evaluation. Chiggers are most common in the late summer and early fall seasons. Keeping the pets from roaming infested environments is the best preventative. Killing the larval mites is usually easy with commonly used topical insecticides approved for dogs and cats.

5. What is the life cycle of the common ear mite *Otodectes cynotis*?

The life cycle is completed in about 3 weeks. An understanding of the life cycle is important for treatment purposes. Eggs hatch in less than 1 week into the six-legged larval stage. The larva feeds for about 1 week and then hatches into a protonymph, which has eight legs. The protonymph molts into a deutonymph which is sexually undetermined. An adult male nymph approaches the deutonymph and attaches end to end. If a female mite is produced, copulation occurs and she becomes egg-bearing. If a male mite is produced after attachment, then there is no physiologic consequence and they are free to attach to another deutonymph.

6. Give three reasons for the diversity of clinical symptoms associated with ear mite infestations.

1. Ear mites are surface feeders and may be irritating. As inflammation ensues due to localized trauma, there are increases in the amount of sebum produced along with blood and ear mite feces, creating an occlusive otitis externa.
2. The host may produce antibodies against mite antigens, leading to hypersensitivity reactions.
3. Ear mites are not always confined to the ear canal. On cats, ear mites may be found on the back feet and claws due to scratching the ear canals. On dogs, the mites may be present on the face and neck and occasionally the posterior half of the body. Ectopic mites may or may not be associated with pruritus.

7. List the two common species of house dust mites and give a brief description of their clinical significance.

The two common species are *Dermatophagoides pteronyssinus* and *D. farinae*. They are present in the environment and their exoskeletons and feces may be responsible for inducing hypersensitivity reactions in dogs and cats (and humans).

8. What are the common species of *Cheyletiella* mites?

There are three common species of *Cheyletiella* mites. Each has its own preferred host but may parasitize other species. All *Cheyletiella* mites have zoonotic potential. *C. yasguri* is the canine mite, *C. blakei* is the feline mite, and *C. parasitovorax* is the common rabbit mite. These are large surface-dwelling mites that feed on surface debris and are sometimes referred to as walking dandruff. They are obligate parasites that do not live for extended periods off the host. Because these mites move about, they tend to be highly contagious among in-contact animals. The clinical symptoms are variable, although pruritus is usually present. Scaling is frequently present with a dorsal distribution pattern. With continued exposure, a hypersensitivity reaction may occur that is associated with intense pruritus.

9. Describe the different methods for identifying *Cheyletiella* mites or their eggs.

Cheyletiella mites lay their eggs on the hair shaft. These nits resemble lice eggs and must be differentiated from them for successful treatment. The eggs of *Cheyletiella* are smaller and more loosely attached to hairs compared to the firmly cemented hairs of lice. There are several diagnostic methods that are available to detect adult mites on animals. More than one should be used to achieve an accurate diagnosis because any diagnostic tool may yield false-negative results. A handheld lens may be all that is necessary to see the mites on the skin surface. Acetate tape–collected samples are a useful diagnostic method for finding the mites or eggs. Plucked hairs placed in mineral oil (trichogram) may lead to the demonstration of eggs. A fecal examination can be very useful in cats as they tend to groom the eggs and mites off the body. The single most useful diagnostic tool is the flea comb. Large amounts of scale can be collected and deposited onto a glass slide, coated with mineral oil, for microscopic evaluation. Broad, superficial skin scrapings may also be beneficial. Unfortunately, clipping the hair may be necessary to obtain successful scraping samples. Because this is a contagious problem, all contact animals, symptomatic or not, should be evaluated. I prefer to treat all contact animals.

10. List the common names sometimes used to describe demodicosis.

Demodectic mange, red mange, and follicular mange are all common names for demodicosis.

11. What are the four life stages of *Demodex canis*, and why is it clinically important to be able to differentiate these stages?

The life stages consist of egg, larva, nymph, and adult. The larval stage contains three pairs of legs and the nymph has four pairs of legs. The adult stage also contains four pairs of legs. It is clinically important to identify the life stages to monitor the success of treatment. Demodicosis can be a very difficult disease to resolve. Once treatment is instituted, skin scrapings should be evaluated monthly. If it is becoming apparent that there is a prevalence of juvenile stages, then it may be appropriate to assume that the mites are reproducing in spite of treatment. It can also be assumed that the survivors may be developing resistance to the treatment. Modification of the treatment may be indicated. Besides evaluating for juvenile stages, it is important to identify whether the mites are alive or dead. Live mites may indicate the need to modify the treatment protocol.

12. How do dogs get *Demodex* mites?

Demodex mites are a part of the normal flora of the skin and ear canals. Mites are transferred from the bitch to offspring within a few days of birth. *Demodex* mites are first found on the muzzle and feet due to close contact with the dam during nursing. Lesions beginning on the muzzle and feet are a common distribution pattern in those dogs developing manifestations of demodicosis. No mites are present on dogs born by cesarean section and isolated from the mother and littermates. Likewise, stillborn puppies do not have *Demodex* mites.

13. What are the common clinical findings associated with localized demodicosis in the dog?

Although there are no finite definitions for what constitutes a localized form of demodicosis, a reasonable starting point includes lesions that can be easily treated with topical spot treatment. In general, the lesions begin when the dog is younger than 2 years of age. Alopecia with inflammation occurs most commonly. As the hairs fall out, comedones (plugged hair follicles) may develop. Papules, pustules, and epidermal collarettes may also be present. The lesions associated with localized *Demodex* are usually not pruritic. However, if a bacterial infection is also present, then pruritus may occur. Because the differential diagnoses for these clinical symptoms include bacterial infection (bacterial folliculitis), dermatophytosis, and demodicosis, a skin scraping, cytology, and fungal culture must be performed. It is not uncommon for more than one of these clinical problems to be present concurrently in a young dog.

14. Generalized demodicosis usually starts at less than 2 years of age. What is the clinical significance of adult-onset, generalized demodicosis?

Adult-onset generalized demodicosis usually has an underlying cause. Endocrine disorders such as hypothyroidism and hyperadrenocorticism must be ruled out. Medications that cause immune suppression such as corticosteroids and antineoplastic drugs can also be an underlying cause for the development of adult-onset demodicosis. It is important to remember that chronically administered topical corticosteroids may cause enough immune suppression to be the cause of generalized demodicosis. Malignant neoplasia is an additional differential diagnosis. All adult dogs that present with generalized demodicosis should have appropriate laboratory blood work to look for an underlying cause. In many cases, an underlying cause for adult-onset demodicosis may not be found. This should not preclude treatment.

15. Why does demodicosis develop in some dogs and not in others (even among littermates)?

A simple answer to this question does not exist. The prevalence of demodicosis in certain breeds, and the fact that avoidance of breeding affected dogs decreases the prevalence of disease, has led to the suggestion that this problem is an autosomal recessive disorder; however, while the predisposition to develop demodicosis is likely hereditary, the actual development of clinical disease may involve multiple factors (i.e., multifactorial). It has been shown that dogs with pyoderma and *Demodex* produce serum factors that are immune suppressive, thereby propagating the problem. One hypothesis is that affected dogs have a specific T-cell defect leading to an insufficient cell-mediated delayed hypersensitivity response against *Demodex* mites. Ongoing research is being performed to further clarify these questions.

16. What are the advantages and disadvantages of the various diagnostic methods used to identify *Demodex* mites?

The most commonly used diagnostic procedure to look for *Demodex* is the deep skin scraping. The advantage is that it is quick and easy. The disadvantages include minor discomfort to the patient and the likelihood of a false negative scraping in chronically inflamed or lichenified skin. Plucking hairs for a trichogram is another diagnostic method. The advantage is that it is quick and easy and not as messy as a skin scraping. The disadvantages include the fact that there may not be any hairs to pluck in a chronic *Demodex* lesion and there is some discomfort to the patient. Performing a biopsy is a very important procedure, especially in chronically inflamed tissues. The disadvantages include the cost of the procedure, the time (shipping and handling) to get results, and the necessity of using localized or generalized anesthesia. In cases where *Demodex* mites are suspected yet not supported by trichogram or deep skin scrapings, doing a biopsy is an extremely useful procedure. Many of these cases are complicated by deep bacterial infections which should be evaluated by bacterial culture and sensitivity testing. Taking an extra skin biopsy and submitting it for macerated tissue culture is the optimum method of obtaining samples for culture of deep infections.

17. What are the two major species of feline *Demodex* mites? How do they differ in their clinical presentation?

The two major species of feline *Demodex* mites are *Demodex cati* (Figure 16-2) and *Demodex gatoi* (Figure 16-3). *Demodex cati* is a long slender mite that resembles *Demodex canis*. These are follicular mites so the clinical symptoms include alopecia and occasionally comedones. Pruritus is not a common feature of this species of *Demodex*. The identification of *D. cati* should prompt a search for an underlying cause of the problem. Immunosuppressive diseases (feline leukemia, feline immunodeficiency virus), hyperthyroidism, neoplasia, or other chronic wasting diseases such as feline infectious peritonitis should be considered. These mites are usually associated with older cats unless one of the aforementioned immunosuppressive viruses is present. *Demodex gatoi* is a short "stumpy" appearing mite. These mites are surface dwelling, living in the epidermal pits. Usually, cats infested with *D. gatoi* present with a chief complaint of pruritus.

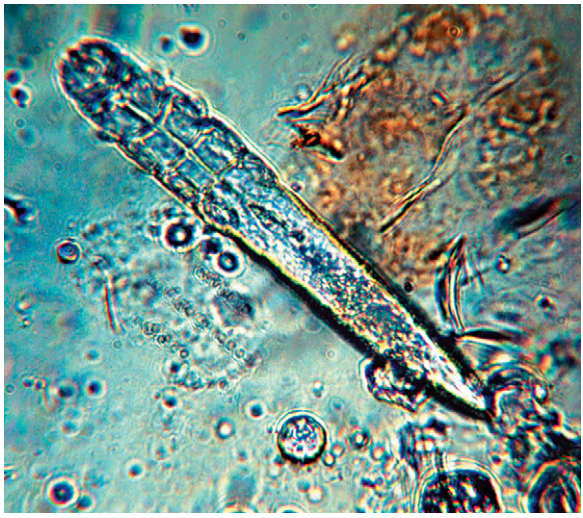

Figure 16-2 *Demodex cati* in a skin scraping from a cat with follicular mange.

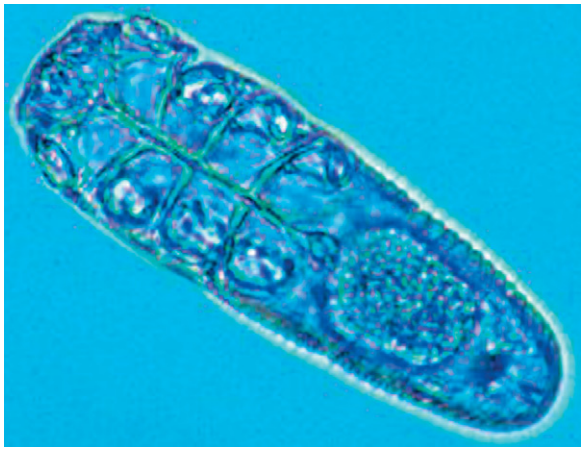

Figure 16-3 *Demodex gatoi* in a skin scraping from a cat with pruritus and symmetric alopecia.

Because cats that are pruritic tend to groom in a symmetric manner, they may present with symmetric alopecia resembling an endocrinopathy. *D. gatoi* is contagious and all cats in the household must be treated. It is possible to have asymptomatic carriers. When looking for either species of mite, it is important to use the correct technique. *Demodex cati* is a follicular mite, so deep skin scrapings are appropriate. *D. gatoi* is a surface mite, so broad superficial skin scrapings are needed. When evaluating for asymptomatic carriers of *D. gatoi*, clipping the hair before scraping may be necessary.

18. Describe the clinical symptoms of dogs infested with *Sarcoptes scabiei* var. *canis*.

The chief complaint is intense pruritus. The initial distribution pattern of pruritus includes the elbows, hocks, and ears; especially the margins of the ears. Over time, the distribution pattern

will include the entire ventrum and sometimes the face. Dogs with scabies usually are not pruritic on the dorsum. Scabies has been described as a rash that itches. Intense erythema may be present as a primary lesion. As the animal traumatizes the lesion, excoriations, increased scale (seborrhea), lichenification, hyperpigmentation, and secondary pyoderma may occur.

19. How long does it take for clinical symptoms to develop once a dog is exposed to scabies mites?

The incubation period is unknown. Most dogs that are infected will begin itching within a few days, but the symptoms are mild. Three to 4 weeks later, intense pruritus develops, suggesting a delayed hypersensitivity reaction.

20. What are the diagnostic methods available to diagnose scabies mites?

The diagnostic method of choice is multiple superficial skin scrapings. It is common to scrape dozens of locations and not recover any mites or eggs. A single mite or egg is diagnostic for scabies. In many cases, the diagnostic method may be response to treatment using an avermectin drug highly effective in the treatment of scabies. Enzyme-linked immunosorbent assay (ELISA) testing for antibodies in serum to scabies mites has been evaluated from a research standpoint but commercial testing is not currently available in the United States. An argument against using ELISA testing is that it may be cheaper to treat based upon clinical symptoms and history. Nonetheless, a diagnosis can help with prognosis and zoonotic concerns.

21. Feline scabies is associated with the mite *Notoedres cati*. What clinical features make it different than scabies in a dog?

Feline scabies infestations are commonly associated with pruritus, scaling, and crusting of the head and face. Superficial skin scrapings tend to recover myriads of *Notoedres* mites. Because of the prevalence of mites, it is common for all in-contact animals and humans to be infested. Dogs tend to harbor fewer mites, making them less likely to spread the mites throughout the household.

22. What are the common ticks that affect dogs and cats?

Ticks are generally divided into soft ticks and hard ticks. Argasid (soft-bodied) ticks are considered to be more primitive, produce fewer offspring, and inhabit the dens or kennels of the host. Ixodid (hard-bodied) ticks are highly parasitic and infest the open habitat of the host.

Otobius megnini is the only soft-bodied tick of importance to small animals. It is commonly known as the spinous ear tick. The clinical symptoms associated with this tick range from asymptomatic infestations to clinical otitis externa with concurrent pruritus.

Rhipicephalus sanguineus is known as the brown dog tick. It can survive inside kennels and homes, leading to potentially severe infestations. The dog is the primary host but it may parasitize other species.

Dermacentor variabilis is known as the common dog tick. It is commonly found along the Atlantic Coast region. Although the principal host of the adult tick is the dog, the principal host of the juvenile tick is the mouse.

Dermacentor andersoni (Rocky Mountain wood tick), *Dermacentor occidentalis* (West Coast tick), *Ixodes scapularis* (black-legged tick), *Ixodes dammini* (deer tick), and *Amblyomma maculatum* (Lone Star tick) are ticks that have been known to parasitize dogs and cats. They may be locally important and may transmit a variety of bacterial, protozoal, and rickettsial diseases.

23. Describe the general life cycle of hard-bodied ticks.

The life stages consist of egg, larva, nymph, and adult. Most ticks require three separate hosts, but a tick may complete its cycle on a single mammalian species. The larva and nymph feed for several days before dropping off to molt. Off-host time periods are variable and may last several months. The adult can lay several thousand eggs at one time and may live for over 1 year. In general, the life cycle is completed in 1 year.

24. What are the common diseases transmitted by ticks?

Ticks are responsible for transmitting several rickettsial, bacterial, and viral diseases and can also cause tick paralysis. *Ehrlichia canis*, Rocky Mountain spotted fever, anaplasmosis, *Babesia*, tularemia, and St. Louis encephalitis may also be encountered. Species of *Ixodes* ticks transmit *Borrelia* spp., the bacterium responsible for causing Lyme disease.

25. What are the clinical symptoms associated with venomous spider bites?

Brown recluse spider bites are frequently associated with pain and tissue necrosis. It is difficult if not impossible to prove the true etiology of many lesions resulting from spider bites. Risk factors for potential exposure may help to rule in spider bites as a cause of the necrosis. It is advisable to collect a biopsy skin sample from affected tissues. Important differential diagnoses include other venomous creatures such as snakes, scorpions, and lizards as well as caustic, chemical, or thermal burn, vasculitis, bacterial pathogens, and adverse drug reactions.

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17. INSECTS

Cecilia A. Friberg, DVM, DACVD

1. What is an insect?

An insect is a type of arthropod. Insects are a very large, varied group of animals containing more than 800,000 species. More specifically they have three body segments and three pairs of legs, although some insects have lost one or two pairs of legs and replaced them with wings (for example, cockroaches, ladybugs, ants, bees, wasps, moths, butterflies, fleas, flies of all kinds, and beetles). Some of the other chapters address dermatosis related to insects such as fleas, other arthropods, and suspected allergic manifestations of these such as canine eosinophilic furunculosis and flea allergy dermatitis.

2. What types of reactions are seen with insect allergy?

Reactions can result from either direct tactile stimulation of the insect, pain or irritation from insect bite/sting, or from an allergic reaction triggered by insect antigens (substances capable of eliciting an allergic reaction). Behaviors triggered by insects can include pruritus, irritation, or restlessness. Other clinical manifestations include those resulting from allergic reactions: urticaria (hives), angioedema (regional swelling), anaphylaxis (uncommon to rarely seen cases), and inflammation (often evidenced by pruritus, erythema and warm skin). Allergic reactions may be localized to the area where the insect exposure occurred, or may be seen as systemic reactions. Specific diseases that may result from insect exposure include eosinophilic furunculosis of the face and feline mosquito bite hypersensitivity. More difficult to classify nonspecific clinical signs

24. What are the common diseases transmitted by ticks?

Ticks are responsible for transmitting several rickettsial, bacterial, and viral diseases and can also cause tick paralysis. *Ehrlichia canis*, Rocky Mountain spotted fever, anaplasmosis, *Babesia*, tularemia, and St. Louis encephalitis may also be encountered. Species of *Ixodes* ticks transmit *Borrelia* spp., the bacterium responsible for causing Lyme disease.

25. What are the clinical symptoms associated with venomous spider bites?

Brown recluse spider bites are frequently associated with pain and tissue necrosis. It is difficult if not impossible to prove the true etiology of many lesions resulting from spider bites. Risk factors for potential exposure may help to rule in spider bites as a cause of the necrosis. It is advisable to collect a biopsy skin sample from affected tissues. Important differential diagnoses include other venomous creatures such as snakes, scorpions, and lizards as well as caustic, chemical, or thermal burn, vasculitis, bacterial pathogens, and adverse drug reactions.

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such as restlessness and itching can be confused with other types of allergic disorders such as food allergy and atopy, or even bacterial and fungal infections.

3. Should insects be expected to be found in conjunction with the allergic reaction?

While finding an insect helps in making a definitive diagnosis, it is not always possible to find one. A very small number of insects or small amount of antigen may be sufficient to trigger an allergic reaction in a sensitized animal. In these cases the insects may not be seen. Many cases of insect allergy are only tentatively diagnosed, and further evidence for the diagnosis is based on response to insecticidal therapy, that is, when insecticidal control measures are taken the reactions are minimized, and symptoms return when these measures are stopped or reduced.

4. Do the insects always have to bite to cause allergies?

Not necessarily. Non-biting insects such as cockroaches, moths, and flies may cause allergies by other mechanisms. Body parts or shed material from the insects may serve as environmental allergens and cause a reaction in the same way that pollens trigger allergies (through inhalation or direct cutaneous absorption).

Many studies of allergies in humans have shown reactions to cockroaches and caddis fly wings. Butterfly, moth, housefly, and honeybee body dust provocation test reactions have been detected in rare cases of occupational allergies. In entomologists, occupational arthropod dermatitis may occur in as many as one third of workers.

These studies have not been replicated in dogs and cats, so the definitive cause and effect is still speculative. However, because of their inquisitive nature in chasing "bugs," dogs and cats may have higher exposure rates than humans.

5. Can insect allergies be controlled by using insecticides and insect repellents?

Insecticides and repellents may help with allergies resulting from insect bites. If allergies are due to inhalation of insects or contact with insect parts, then repellents and insecticides may not be as helpful. Also, treating one time is rarely enough to solve the problem. Insecticides and repellents have a finite functional time span and need to be reapplied to the pet and environment on a regular basis.

6. Can the topical spot-on products be used to control insects?

Several types of these products are available on the market. Some have been well tested, and others have very limited information. Fipronyl and imidocloprid are well-tested adulticides; the insects must come into direct contact with these ingredients before the products work to kill the insect. This may allow some insects enough time to bite the host (thus producing the allergic reaction). Combination products, for example imidocloprid and permethrin, are new and may be more helpful in preventing bites because the permethrin component has a repellent activity.

7. How much do we really know about insect allergies in dogs and cats?

Flea allergy has been well studied, but allergies to other insects are less well understood. Mosquito bite hypersensitivity in cats has also been well documented, but there is less information available about allergies associated with non-biting insects. One study from California showed that 5% of atopic dogs had reactions only to insects, and not to pollens, fleas, or dust mites. Clinical signs in these dogs resembled those of atopic dermatitis. Many studies have been done in allergic humans to correlate insect antigens with allergic disease; however, these types of studies have not yet been performed in cats and dogs.

8. Do insect growth regulators (IGRs) have any effect on insects other than fleas?

This depends on where the insects are reproducing. These products affect the life stages before the adult form. If IGRs are used in the areas where the development is occurring, then they will halt the life cycle. However, IGRs will not have any effect on the adult mosquito, for

example, if the IGR is being used in the home and the mosquitoes are reproducing in some area outside. Care must also be taken so that non-pesky insects are not harmed. Not all insects are bad, and some of these chemicals may kill "good" insects too. Manufacturer's guidelines must be adhered to.

9. Which diseases are most commonly seen in conjunction with insect transmission?

Insects can transmit diseases as well as produce allergic disease. In the United States, heartworm disease is the most widespread insect-borne disease in dogs. More recently West Nile virus has emerged as a new, but still rare, insect-transmitted disease in companion animals. The virus is obtained by mosquitoes feeding on infected wild birds. The infected mosquitoes then bite and transmit the disease to humans and animals. Immunocompromised and sick animals are likely to be at higher risk of clinical disease, but because this is a newly described disease in domestic animals and is still rare, it has not yet been fully described.

10. How is pediculosis diagnosed?

- Pediculosis, lice infestation, may not always be easy to diagnose. Lice are contagious between individuals of the same species, but are very species-specific, so do not transfer among dogs, cats, and humans. Within the species, individual response to pediculosis may vary considerably. Some individuals may appear asymptomatic (although there are probably lice present), and others may appear with severe dermatitis. This variation in reaction may be explained by hypersensitivity. It can be helpful to examine the "asymptomatic" individuals, because the lice may be more easily identifiable on them.
- Diagnosis may also be difficult, because the biting lice move very rapidly, and may be difficult to find and capture. However, the sucking lice are slower and are easier to "catch and identify." Acetate tape may be the easiest method for their capture, by actually adhering them to the sticky surface of the tape. Identification can be done by visualization under low power on a standard microscope. Often lice infestation can be indirectly diagnosed by noting eggs cemented onto hairs. *Cheyletiella* mites also cement their eggs to the hair shafts, so these may be confused. Eggs are cemented onto the proximal region of the hair shaft and then move distally with the hair growth. This may be helpful as an indicator of treatment success as fewer eggs are noted on the proximal portions of the hair (Figures 17-1 and 17-2).

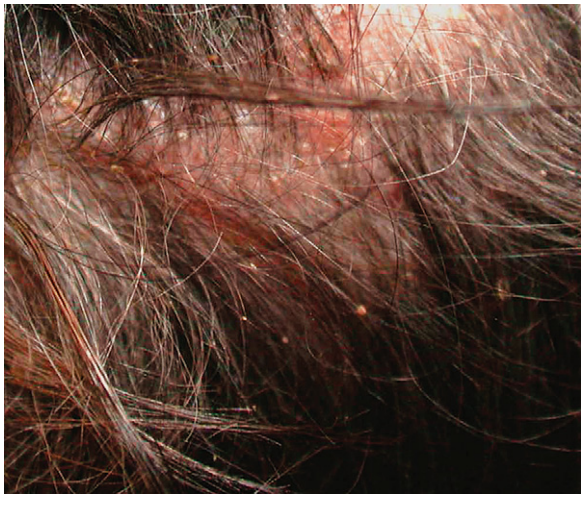

Figure 17-1 Small lice eggs cemented onto hair shafts of a dog.

Figure 17-2 Microscopic view (10×) of these eggs.

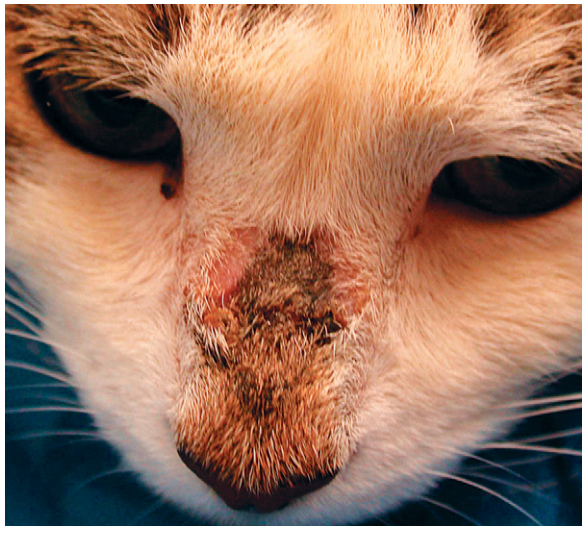

Figure 17-3 Feline mosquito bite hypersensitivity on the sparsely haired skin.

11. How long can lice survive off the host?

There are two classes of lice: biting and sucking. The sucking lice *(Anoplura)* are obligate parasites that feed on their hosts by taking regular blood meals. These lice do not survive well off the host more than 24-36 hours. The biting lice (*Mallophaga*) are not blood feeders—they feed on dead skin and fragments of hair or feather. Adult life span can vary from 1 to several months. Lice can be transferred by fomites (e.g., grooming equipment); direct contact with an infected animal may not be necessary for the spread of lice.

12. How is mosquito bite hypersensitivity in cats diagnosed?

This disease is definitively diagnosed based on skin biopsy. Clinical signs may provide a tentative diagnosis. An affected cat is bitten by a mosquito and lesions proceed to develop at the bite site. Lesions progress from wheals to papules to papulocrustous lesions. These lesions are usually located on the face and pinna (since these are sparsely haired regions), but may occur on any site where the mosquito bites, including the footpads. The lesions are variably pruritic among individuals. An affected cat may redevelop lesions if bitten by mosquitoes in the future. Indoor-only cats may also be affected if mosquitoes make their way into the home (Figures 17-3 and 17-4).

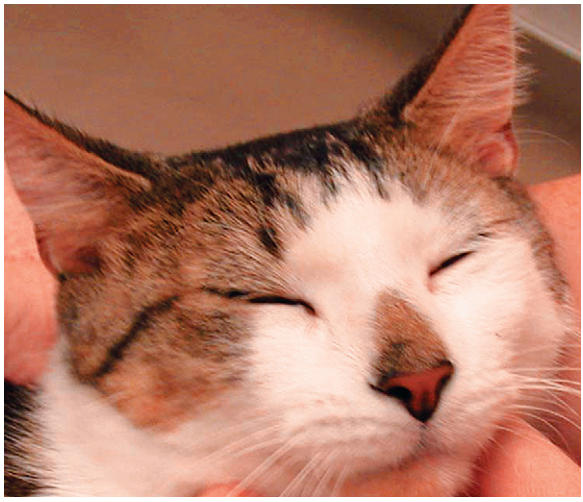

Figure 17-4 Normal hair regrowth after recovery of same cat as in Figure 17-3.

13. How are insecticides used to control biting insects?

This depends on the insecticide. The only insecticides that are repellent are pyrethrins, permethrins, DEET, and Avon Skin-So-Soft. These vary in their toxicity, ability to repel, and concentration needed to be effective. Pyrethroid-type insecticides are not stable in sunlight; therefore, they need to be applied more frequently. Pyrethroids are classified into four generations with the later generations being more UV-resistant. DEET is considered potentially toxic; therefore, its use in domestic animals is not encouraged. Insecticides should be reapplied according to manufacturer's instructions.

14. If only one animal in a group is affected, can an insect problem be ruled out?

Disorders relating to insects cannot be eliminated, especially because if that one animal is hypersensitive to the insects, very little exposure may be necessary to produce clinical signs. The role of the other animals may be very important because if they are sustaining or harboring insects (for example, the nonallergic dog may be a source of fleas, yet have few if any clinical signs because it is not hypersensitive to flea bites). In cases where other animals harbor insects, the clinical signs of the affected animal will not subside unless ALL the animals in the group are treated. This scenario extends to insects other than fleas and should be kept in mind. The allergic animal may also not have the insects easily identifiable (findable) because very small numbers may cause the hyper-reactive skin.

15. What if the owners will not believe that insect hypersensitivity is the problem and are unwilling to follow through with therapy?

Owners may be very difficult to convince of the importance of insecticide therapy because they may not be willing to believe there is a problem unless they see large numbers of insects. Some owners are also intimidated by the amount of work and cost involved in needing to treat all animals, especially if there are several in the household, as well as the environment which may also need to be treated. The importance of thorough treatment cannot be overemphasized. As with all allergies, elimination of contact with the offending antigen is the ideal, yet often unattainable goal. In the case of insect hypersensitivity, this may actually be attainable, but if therapeutic trials are not complete and thorough, then this disease may go undiagnosed and the owners may end

up spending large amounts of money on incorrect diagnoses. On the other hand, if insecticide control is done properly, and response is favorable, then this may be a simple management tool for their pet.

Some owners may understand this once it is explained to them. Another less conventional approach may be to explain to the owner that they may be right, that insect hypersensitivity may not be the problem, but that the only way that they can prove this is to treat the pets and the environment thoroughly and thereby prove that insects were not the problem.

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18. HELMINTH DERMATOSES

Randall C. Thomas, DVM, DACVD

1. What are helminth dermatoses?

Helminths are worm-like parasites that include the cestodes (flat or tapeworms) and nematodes (roundworms). These parasites may be common parasites of the dog and cat, but they are uncommon causes of skin disease. Most cases of helminth dermatoses in the dog and cat occur as abnormal infestation (wrong host), abnormal migration (wrong route of migration), or as a hypersensitivity reaction to the parasite.

2. What is dracunculiasis?

Dracunculiasis is primarily known as a disease of humans living in rural North Africa and India. *Dracunculus medinensis* is the species that primarily affects humans, although it has also been reported to occur in dogs, horses, cattle, and other mammals. *Dracunculus insignis* is a common parasite of raccoons and mink in North America. It has occasionally been reported to infest domestic dogs and other mammals.

3. What are the signs of dracunculiasis in the dog?

Infected dogs may present with single or multiple nodules on the limbs, ventral thorax and abdomen, and head. These nodules may be pruritic or painful, and usually abscess or develop a draining fistula over time. Generalized urticaria and pruritus or pyrexia may develop before fistula formation. Adult female worms can sometimes be seen within or protruding from the ulcerative lesion (Figure 18-1).

4. How do dogs become infested with *D. insignis*?

The intermediate host of *D. insignis* is a small crustacean copepod of the genus *Cyclops*. These crustaceans have a wide distribution in fresh water. The crustacean ingests first-stage larvae

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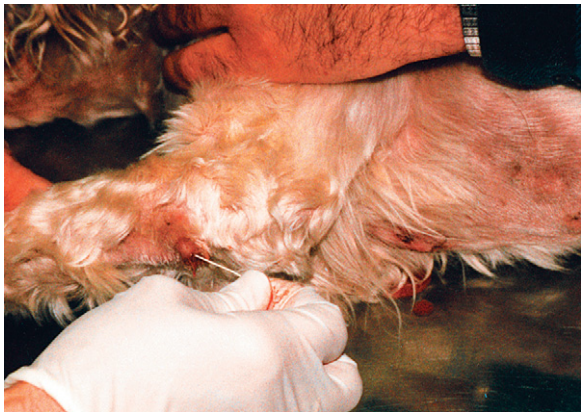

Figure 18-1 Adult *Dracunculus insignis* being extracted from cutaneous nodule on a dog. (Courtesy Rhonda D. Pinckney, DVM, PhD, College of Veterinary Medicine, University of Wisconsin, Madison, Wis.)

that have been released into the water. The larvae molt twice within the copepod to become infective third-stage larvae. Dogs become infected by drinking water containing the *Cyclops*. The infective larvae are released in the gastrointestinal tract and migrate throughout the body.

5. How long does it take for the dog to develop clinical disease?

Development of larvae into adult *Dracunculus* is thought to take 8-14 months. Once fertilized, the females migrate to the subcutaneous tissues and form nodular lesions with shallow ulcers. Exposure to cool water stimulates fistula formation and the female discharges first-stage larvae into the water, completing the life cycle.

6. How is the diagnosis of dracunculiasis made in the dog?

Differential diagnoses for subcutaneous nodules include abscesses or other bacterial infection, foreign body, fungal infection, immune-mediated nodular diseases, parasitic dermatoses, and neoplasia. Visualization of the adult female within the nodule is highly suggestive. Cytology from the nodule or draining tract reveals pyogranulomatous inflammation with first-stage larvae. The larvae may be up to 700 µm long, have striated cuticles, and have a prominent long and pointed tail (Figure 18-2). Visualization of an esophagus within the larvae distinguishes them from the microfilaria of *Dirofilaria* spp. or *Dipetalonema* spp. Histologic examination of excised nodules will reveal pyogranulomatous to eosinophilic, nodular dermatitis and panniculitis with both adult and larval parasites.

7. What is the suggested treatment for dracunculiasis in the dog?

Surgical excision of individual nodules is the treatment of choice. Although numerous medical treatments have been investigated, none has proven reliable. In one dog with marked *D. insignis* infestation, treatment with ivermectin, fenbendazole, and metronidazole did not result in resolution of the infection. A study of *Dracunculus*-infected ferrets indicated that diethylcarbamazine, albendazole, ivermectin, and trichlorfon were all ineffective medical treatments.

8. What is *Pelodera* dermatitis?

Pelodera strongyloides is a free-living nematode, found in damp soil and decaying organic debris. The larvae of these parasites are able to invade the skin of animals by direct contact. In general, this is a disease of poor management. Dogs infested with *Pelodera* are kept in unclean environments (usually on straw) that foster development of this parasite.

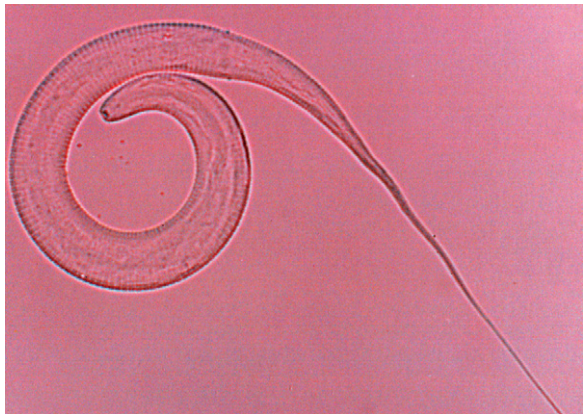

Figure 18-2 Larva of *Dracunculus insignis*. Note striated cuticle, esophagus, and prominent tail. (Courtesy Rhonda D. Pinckney, DVM, PhD, College of Veterinary Medicine, University of Wisconsin, Madison, Wis.)

Figure 18-3 *Pelodera* dermatitis in a mixed-breed dog. This dog was a stray, so its living conditions were unknown.

9. What are the signs of *Pelodera* dermatitis?

Dogs infested with *Pelodera* (also called rhabditic dermatitis) typically have an erythematous dermatitis with papules and traumatic alopecia. Pruritus is variable, but can be intense. Lesions occur in the contact areas of the body, including the ventral abdomen and thorax, feet, legs, and inguinal region. Secondary infection is often present (Figure 18-3).

10. How is *Pelodera* dermatitis diagnosed in the dog?

Pelodera dermatitis may be suspected based on the presence of appropriate clinical signs in conjunction with poor living conditions. Damp straw or hay bedding is most commonly the source. Other differential diagnoses include contact allergic or irritant dermatitis, sarcoptic

mange, or other helminth dermatoses. Larvae can be visualized on skin scrapings from clinically affected areas. Histologic findings include eosinophilic folliculitis and furunculosis with the presence of nematode larvae within hair follicles and dermal pyogranulomas (Figure 18-4).

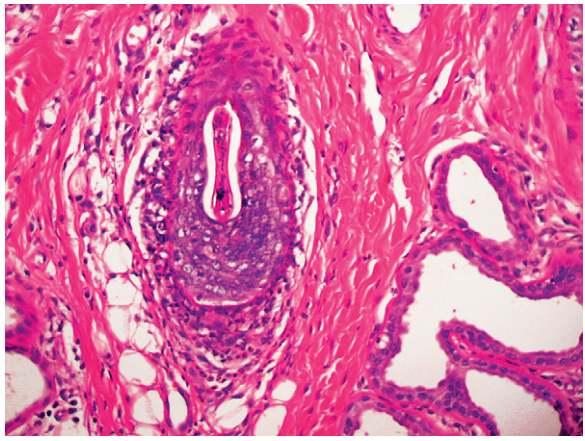

Figure 18-4 *Pelodera* larva within hair follicle in dog from Figure 18-3.

11. What is the treatment of *Pelodera* dermatitis?

This disease is easily treated once diagnosis is made. The parasite is responsive to scabicidal dips, such as phosmet (Paramite) or lime sulfur. Ivermectin may also be an effective treatment. Treatment of secondary bacterial folliculitis and furunculosis is also necessary. Lastly, but most importantly, contaminated bedding materials must be removed from the environment to prevent reinfestation.

12. Is *Pelodera* dermatitis a zoonotic disease?

Pelodera dermatitis has been reported to be a possible zoonotic disease, although this is extremely rare. Because this is a disease of poor sanitation, it is just as likely that humans are infected by contact with the infested environment rather than via direct infection from a dog.

13. What is hookworm dermatitis?

Hookworm dermatitis is a cutaneous reaction to the infestation and migration of the common hookworms of the dog, *Ancylostoma braziliense, A. caninum,* and/or *Uncinaria stenocephala*. Because these are normal parasites of the dog and cat, visible reaction to skin penetration is usually absent. In some cases, a clinically evident dermatitis will develop. Cutaneous lesions may be most frequently associated with *U. stenocephala*, but *Ancylostoma* spp. can also cause hookworm dermatitis. Lesions start as a pruritic, papular dermatitis that may progress to a chronic dermatosis if not recognized and treated.

14. How are dogs and cats exposed to hookworm larvae?

Dogs and cats may be exposed to hookworms by ingestion of or cutaneous penetration by infective larvae. Hookworm dermatitis results from direct cutaneous contact with larvae-infested soil. The larvae migrate through the skin via mechanical undulation. Skin lesions are thought to result from a hypersensitivity to migrating larvae. Hookworm dermatitis is generally a disease of poor sanitation and management. In most cases, dogs are kenneled on grass or dirt that is infested with infective larvae. Sanitary conditions are typically poor.

15. What are the clinical signs of hookworm dermatitis?

Hookworm dermatitis is a pruritic, papular dermatitis that is usually confined to the contact areas of the body. These include the ventral abdomen and thorax, feet, legs, and inguinal regions. With progression, there is generalized erythema and alopecia in clinically affected areas. The skin over pressure points may become erythematous and lichenified. Initially, the footpads and interdigital spaces may have a soft, spongy appearance, but hyperkeratosis occurs with chronicity. Paronychia and onychodystrophy, and interphalangeal arthritis may occur in chronic cases.

16. How is a diagnosis of hookworm dermatitis confirmed?

The distribution of lesions, history of poor management conditions, and presence of hookworm eggs on fecal examination are highly suggestive of this disease. Differential diagnoses include contact allergy or irritant dermatitis, demodicosis, dermatophytosis, *Pelodera* or other helminth dermatoses. Migrating larvae are rarely seen on skin scrapings. Histologic lesions include a hyperkeratotic to spongiotic perivascular dermatitis with a predominance of eosinophils. Tracts left by migrating larvae may be evident, but the larvae themselves are rarely found.

17. What is the treatment of hookworm dermatitis?

As with *Pelodera* dermatitis, this is primarily a disease of poor management, so efforts should be made to improve the overall hygiene of the kennel area. Routine use of anthelmintics is helpful in decreasing the parasite burden in the environment. Secondary infections should be treated with oral and topical antimicrobial agents. Chronic foot and claw lesions may require long-term management. With appropriate anthelmintic therapy and removal from the infested environment, most cases resolve within 2-3 weeks. Symptoms in chronic infections may take longer.

18. What steps can be taken to remove hookworm larvae from the grass or soil?

Ideally, dogs should be removed from areas with larvae-infested soil. If that isn't possible, the kennel/run area should be kept clean and dry, and feces should be removed daily to prevent reinfestation. Occasional treatment of soil or gravel with 10 pounds of borax powder per 100 ft^2 may decrease the larva burden. This, however, will also kill vegetation.

19. Is hookworm dermatitis a zoonotic disease?

Hookworm dermatitis in humans is called cutaneous larva migrans (CLM) or "creeping eruption." It occurs by contact of the skin with sand, soil, or grass contaminated by third-stage hookworm larvae. *Ancylostoma braziliense* is the most common cause of CLM in humans, but *A. caninum, Uncinaria stenocephala*, and many other helminth parasites can cause migratory lesions in humans. CLM can be prevented by ensuring that pets are properly dewormed, and by avoiding direct contact with soil contaminated with dog or cat feces.

20. The clinical signs of *Pelodera* dermatitis and hookworm dermatitis seem similar. How can I differentiate these two diseases?

First of all, both of these disorders are uncommon to rare. Other ventrally oriented, pruritic dermatoses, such as contact allergy/irritant dermatitis, sarcoptic mange, and atopy should be higher on your list of differential diagnoses. Both *Pelodera* and hookworm dermatitis are diseases of poor management, so the conditions in which the pet is kept may make you suspicious of these disorders. With *Pelodera*, a deep skin scrape should reveal the larvae. Larvae are almost never seen with hookworm dermatitis. A positive fecal examination for hookworm eggs would raise the index of suspicion for hookworm dermatitis.

21. Is it common to see skin lesions associated with heartworm disease in the dog?

Skin lesions associated with infestation by *Dirofilaria immitis* are rare. Details of the life cycle of this common canine parasite can be found elsewhere, but adult worms are typically found within the heart and lungs, and larvae within the circulation. There are rare reports of adult

D. immitis causing a nodular dermatitis in the dog. In addition, dogs with circulating microfilaria may rarely develop cutaneous lesions, most likely due to a hypersensitivity reaction.

22. What are the signs of cutaneous dirofilariasis?

Lesions associated with dirofilariasis are typically pruritic papules, plaques, and nodules on the head and limbs, although generalized lesions can develop. These lesions are generally poorly responsive to symptomatic, antipruritic treatment.

23. How is cutaneous dirofilariasis diagnosed?

Diagnosis is based on appropriate clinical signs and a positive heartworm test result. Peripheral eosinophilia may be present. Circulating microfilaria may or may not be detected. Biopsy specimens may reveal microfilaria, but may also only show a nonspecific hypersensitivity reaction.

24. What is the treatment of choice for cutaneous dirofilariasis?

Lesions generally resolve following appropriate treatment for heartworm disease. Treatment of secondary infections may be necessary before resolution of all symptoms.

25. Are there other filarial nematodes that may cause cutaneous lesions?

There are other filarial nematodes that may affect dogs in North America. Besides *D. immitis*, canine infections due to *Acanthocheilonema reconditum (Dipetalonema reconditum)* and *Onchocerca* spp. have been reported. *A. reconditum* has not been reported to cause cutaneous lesions. *Onchocerca* has been rarely reported to cause lesions in the periorbital tissues of the dog. In one recent report, ten dogs from the western United States were described with microfilaria-associated dermatitis. Most of these dogs tested negative for *D. immitis* and *A. reconditum*. It was concluded that a filarioid other than these organisms was the cause. In most cases, the dogs responded to ivermectin therapy.

26. Are there other helminth organisms that may cause dermatitis in the dog or cat?

Certainly, there are many other helminths that may rarely cause skin problems in the dog or cat. *Taenia crassiceps, Habronema* spp., *Lagochilascaris major* and many other organisms have been reported to occur. If single or few nodular lesions occur, then surgical excision is indicated. If multiple nodules or systemic involvement is present, then identification and anthelmintic therapy should be attempted.

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Section V
Infectious Skin Diseases

19. BACTERIAL INFECTIONS

Jennifer L. *Matousek*, DVM, MS, DACVD

1. **How do the microbiota on normal skin contribute to the antibacterial defense mechanisms of the skin?**

The skin is normally colonized by commensal bacteria, yeast, and parasites. The bacteria are located in the stratum corneum of the epidermis and in the infundibulum of hair follicles. The density and composition of bacteria present depends on a variety of factors, such as the presence of water, nutrients, lipids, and the skin surface pH. Resident bacteria compete with other organisms for living space and nutrients, and can produce molecules that are inhibitory to the growth of other microorganisms.

2. **Regarding the normal bacterial inhabitants of the skin, what is the difference between resident and transient bacteria?**

Both resident and transient bacteria can be cultured from normal skin. Resident bacteria have the ability to live and multiply on the skin, whereas transient bacteria do not multiply on the skin. Therefore, resident bacteria tend to persist on the skin for long periods, whereas transient bacteria are only carried on the skin for a short time.

3. **List bacterial species found on normal canine and feline skin, and identify them as residents or transients.**

Please refer to Table 19-1.

Table 19-1 ***Bacteria Found on Healthy Skin and Hair***

	RESIDENT BACTERIA	TRANSIENT BACTERIA
Canine	SKIN *Micrococcus* spp. Coagulase-negative staphylococci *S. epidermidis, S. xylosus* β-hemolytic streptococci *Clostridium* spp. *Propionibacterium acnes* *Acinetobacter* spp. Gram-negative aerobes HAIR *Micrococcus* spp. *Bacillus* spp.	SKIN *Staphylococcus intermedius* *E. coli* *Proteus mirabilis* *Corynebacterium* spp. *Bacillus* spp. *Pseudomonas* spp.

Continued

Table 19-1 ***Bacteria Found on Healthy Skin and Hair—Cont'd***

	RESIDENT BACTERIA	TRANSIENT BACTERIA
	HAIR Gram-negative aerobes (proximal) *Staphylococcus intermedius* (distal) HAIR FOLLICLE *Micrococcus* spp. *P. acnes* *Streptococcus* spp. *Bacillus* spp. *S. intermedius*	
Feline	SKIN *Micrococci* spp. Coagulase-negative staphylococci *S. simulans* β-hemolytic streptococci *Acinetobacter* spp. *S. aureus* *S. intermedius*	SKIN β-hemolytic streptococci *E. coli* *P. mirabilis* *Pseudomonas* spp. *Alcaligenes* spp. *Bacillus* spp. *Staphylococcus* spp.

4. When you find bacteria on the skin, how do you know if it is part of the normal microbiota or if it is causing an infection?

By definition, commensal bacteria that are colonizing the skin do not induce a host reaction. Therefore, isolation of bacteria from intact lesions (e.g., pustules) and the identification of phagocytosed bacteria are evidence of an infection.

5. Name the most common cutaneous bacterial pathogen of dogs.

Staphylococcus intermedius—a coagulase-positive staphylococcus species is most common.

6. Compared to dogs, bacterial folliculitis is uncommon in cats. What bacterial skin disease is most common in cats?

Subcutaneous abscesses are the most common bacterial infection in cats.

7. Differentiate between a primary and a secondary bacterial skin infection.

A primary infection is an infection that occurs in otherwise normal skin. Primary infections are uncommon in small animals. Secondary infections are much more common, and are the result of cutaneous, immunologic, or metabolic abnormalities.

Secondary infections tend to recur if the underlying problem is not identified and corrected.

8. Define and give examples of surface, superficial, and deep bacterial infections.

- In surface bacterial infections, the bacteria secondarily colonize lesions present on the skin surface. Examples include moist pyotraumatic dermatitis and intertrigo.
- In superficial bacterial infections, the bacterial infection involves the skin and hair follicle epithelium. Examples include impetigo, superficial bacterial folliculitis, dermatophilosis, and mucocutaneous pyoderma.
- In deep bacterial infections, the bacterial infection involves the dermis and subcutaneous tissue. Examples include deep folliculitis and furunculosis, cellulitis, pyotraumatic folliculitis and furunculosis, acral lick furunculosis, and subcutaneous abscesses.

9. Describe the clinical appearance of moist pyotraumatic dermatitis lesions (a.k.a. "hot spots").

Moist pyotraumatic dermatitis lesions are well-demarcated areas of erythema, alopecia, and moist dermatitis with proteinaceous exudate in the center of the lesion (Figure 19-1). Hair on the lesion margins sticks to exudative areas. These lesions tend to be painful.

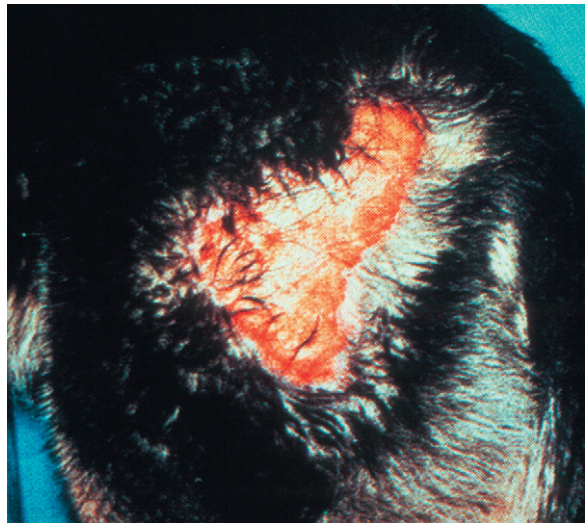

Figure 19-1 This is a German Shepherd Dog with moist pyotraumatic dermatitis on the lateral thigh. Note the well-demarcated area of alopecia, erythema, and crust.

10. What is the cause and pathogenesis of moist pyotraumatic dermatitis?

Moist pyotraumatic dermatitis occurs when an animal traumatizes an area in an attempt to alleviate pain or pruritus. The self-trauma can be triggered by many things, including allergic disorders, ectoparasites, otitis externa, hair mats, and musculoskeletal disorders. The most common cause of moist pyotraumatic dermatitis is flea allergy dermatitis. Other predisposing factors include hot weather and a dense hair coat.

This self-induced trauma causes alopecia, inflammation, exudation, erosion, and ulceration. Moist pyotraumatic lesions then become secondarily colonized with bacteria, most commonly *S. intermedius*. Lesions of moist pyotraumatic dermatitis have an acute onset and can occur within several hours.

11. Propose a treatment plan for lesions of moist pyotraumatic dermatitis.

- Clip and clean the area.
- Because these lesions are painful, sedation may be required.
- Clip hair away from the lesions.
- Remove exudate and debris with a mild antiseptic, such as chlorhexidine or povidone-iodine.
- Apply a topical astringent or antiseptic, such as Domeboro HC (2% aluminum acetate, 1% hydrocortisone).
- Stop the self-trauma. This requires identification and elimination of the underlying cause of pruritus or pain. For example, flea control is indicated for an animal with flea allergy dermatitis.

- Prescribe a topical medication containing both an antibiotic and a mild steroid.
- Some animals benefit from prednisone 1.1 mg/kg orally every 24 hours for 5 to 7 days.
- An Elizabethan collar may be necessary to prevent further self-trauma.

12. What is the significance of "satellite" papules at the margin of a moist pyotraumatic dermatitis lesion?

If papules are present at the periphery of the lesion, a diagnosis of moist pyotraumatic *folliculitis* is more appropriate than moist pyotraumatic *dermatitis*. The papules signify a deeper bacterial infection that requires treatment with systemic antibiotics in addition to the management steps listed previously.

13. What is intertrigo?

Intertrigo is an inflammatory dermatitis that occurs in "skin folds," or areas where the skin surface is in apposition. The presence of skin folds is a breed characteristic in some animals (e.g., Chinese Shar Pei, Persian cat). Skin folds may also be the result of obesity or chronic skin inflammation.

14. What is the pathogenesis of intertrigo?

Intertrigo occurs when two apposing skin surfaces rub together, resulting in frictional inflammation. Additionally, skin folds trap moisture (glandular secretions, tears, saliva, urine), leading to cutaneous maceration. The presence of inflammation and moisture allows secondary colonization of the area with bacteria and *Malassezia* spp. yeast. These organisms do not invade the viable epidermis, but produce metabolic breakdown products that are malodorous and irritating to the skin.

15. List different types of skin folds.

- Body fold (Chinese Shar Pei, Basset Hound, achondrodysplastic dogs, obesity)
- Facial fold (brachycephalic breeds)
- Lip fold (St. Bernard, American Cocker Spaniel)
- Vulvar fold (obesity)
- Tail fold (corkscrew tails)

16. How do you diagnose intertrigo?

Owners often report that the area is malodorous. Physical examination of the skin fold reveals inflammation and purulent exudate (Figure 19-2). In some cases, erosions are present within the fold. Exudate can be collected with a swab, acetate tape, or by making an impression smear with a glass slide. Cytologic studies of the exudate may reveal bacteria, yeast, or inflammatory cells.

In some animals, skin folds lead to other disorders, for example, facial and nasal folds may cause corneal ulceration. Also, vulvar folds may predispose animals to ascending urinary tract infections.

17. What is the treatment for intertrigo?

- Surgical correction of the fold can be curative, but this is often undesirable (e.g., skin folds that are characteristic of the breed).
- Weight loss for obese animals
- Topical astringents (e.g., 2-5% aluminum acetate solution) are useful for removing excess exudate and to decrease moisture.
- Topical antimicrobial agents are useful to decrease secondary colonization. Examples include Malaseb wipes (2% chlorhexidine, 2% miconazole), benzoyl peroxide gels, and mupirocin ointment.
- If the cause of the fold cannot be corrected, topical therapy should be used for long-term maintenance of infections.

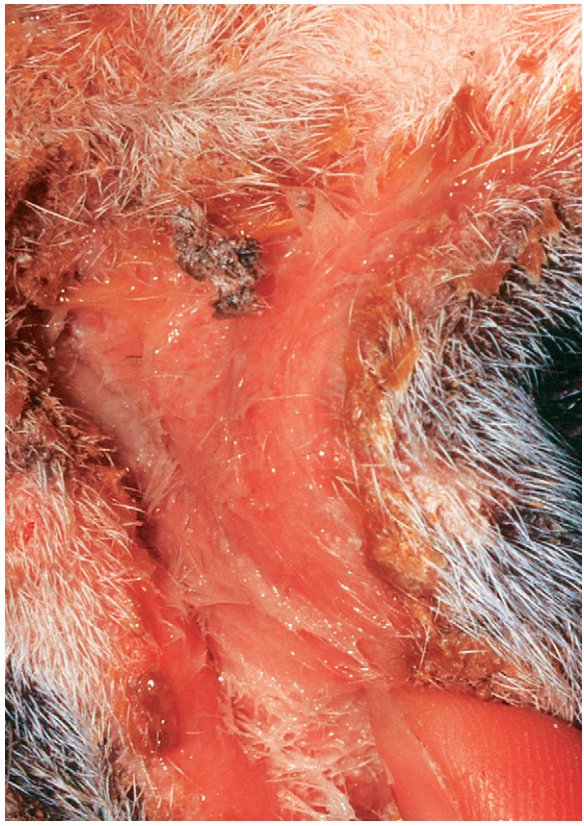

Figure 19-2 This is an English Bulldog with facial intertrigo. Note the erythema and purulent exudate on the surface of the lesion.

18. What is impetigo?

Impetigo is a superficial bacterial infection of sparsely haired areas (e.g., inguinal, axillary) in puppies, and of the dorsal head and neck in kittens. The lesions are nonpainful, nonpruritic, small pustules that do not involve the hair follicles.

19. Describe the pathogenesis of impetigo in puppies and kittens.

Impetigo occurs in animals younger than 1 year of age. In most cases, the infection is secondary, but an underlying cause cannot always be identified. Predisposing causes include endoparasitism, ectoparasitism, poor nutrition, viral infections, trauma, and dirty environments. In cats, overzealous mouthing of the kitten by the queen causes trauma and maceration of the skin.

20. Name the species of bacteria most often associated with impetigo in puppies and in kittens.

Puppies: *S. intermedius*
Kittens: *Pasteurella multocida*, β-hemolytic streptococci

21. How do you treat impetigo?

- Many cases resolve spontaneously, thus simple cleansing may be sufficient.

- Identify and correct predisposing factors.
- Topical therapies:
  - Astringents: 2-5% aluminum acetate
  - Antimicrobial agents: mupirocin ointment, medicated shampoo (e.g., chlorhexidine, ethyl lactate, benzoyl peroxide)
- Systemic antibiotic therapy is not usually indicated unless the animal does not respond to topical therapy and the resolution of predisposing factors.

22. How does bullous impetigo differ from impetigo?

The lesion of bullous impetigo is a large, flaccid pustule. Bullous impetigo is generally seen in adult animals, and its presence suggests that the animal is immune suppressed or has a concurrent endocrinopathy (e.g., hyperadrenocorticism, diabetes mellitus). Bullous impetigo is usually associated with *S. intermedius*, but *Escherichia coli* and *Pseudomonas* spp. have also been identified. Both topical and systemic antibacterial therapies are warranted.

23. Define superficial bacterial folliculitis.

Superficial bacterial folliculitis is a bacterial infection of the superficial portion of the hair follicle and the adjacent epidermis.

24. What species of bacteria is most commonly associated with superficial bacterial folliculitis in dogs? List other species of bacteria that can also be involved.

Most common bacterial species: *S. intermedius*
Others: *E. coli, Proteus mirabilis, Pseudomonas* spp.

25. What are the three most common causes of folliculitis in dogs?

- Staphylococci
- Dermatophytes
- *Demodex* mites

26. List predisposing causes of canine superficial bacterial folliculitis.

- Dermatophytosis
- Ectoparasites (*Demodex*, *Sarcoptes*, *Cheyletiella*, fleas)
- Endocrinopathies (hyperadrenocorticism, hypothyroidism)
- Follicular inflammation (sebaceous adenitis)
- Hypersensitivity disorders (parasitic, environmental, dietary)
- Immunodeficiencies (hereditary, neoplasia, glucocorticoids)
- Keratinization disorders
- Trauma
- Dirty environment
- Local irritants

27. Describe the clinical signs of canine superficial bacterial folliculitis.

The primary lesions are small follicular pustules or papules. Because the pustules are fragile, they tend to be transient and are not always seen. The secondary lesions include epidermal collarettes, crusts, alopecia, hyperpigmentation, and excoriation (Figure 19-3). Pruritus is variable, and the severity is often dependent on the underlying cause.

Short-haired dogs may initially present with papules and crusts, leading to raised tufts of hair and a "bumpy" feeling. As the hair falls out of the infected areas, there are circular areas of alopecia, giving the coat a "moth-eaten" appearance. The first noticeable signs of bacterial folliculitis in long-haired dogs may be a dull hair coat and increased shedding. Some breeds, such as Collies and Shetland Sheepdogs, present with large, coalescing epidermal collarettes that result in large areas of alopecia.

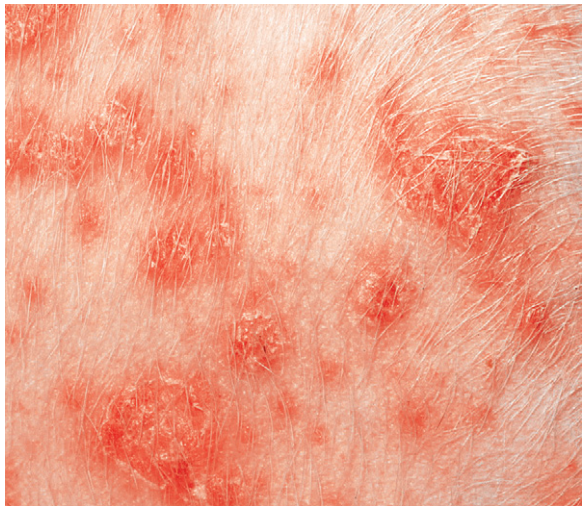

Figure 19-3 This dog has a superficial bacterial folliculitis in the inguinal region. Note the erythematous papules, epidermal collarettes, and crusts.

The distribution of superficial bacterial folliculitis lesions usually reflects the underlying cause. For example, a truncal distribution of lesions is commonly seen in dogs with endocrinopathies.

28. What tests should be performed to diagnose canine superficial bacterial folliculitis?

- Physical examination should reveal consistent lesions (follicular pustules and papules, epidermal collarettes, crusts, alopecia).
- Cytologic evaluation should reveal bacteria and inflammatory cells. Also look for the concurrent presence of *Malassezia* spp. yeast.
- Skin scrapings to investigate the possibility of ectoparasites.
- Dermatophyte test medium culture to evaluate for dermatophytosis.
- Cutaneous bacterial culture for identification of bacterial species and antibiotic susceptibility.
- Biopsies to confirm the diagnosis and to evaluate for underlying causes.

29. When is a cutaneous bacterial culture indicated?

In most cases of superficial bacterial folliculitis, bacterial cultures are not necessary. This is because most superficial bacterial infections are caused by *S. intermedius*, which has a predictable antibiotic susceptibility profile. Therefore, empirical therapy is usually successful. Cultures are indicated when:

- There is cytologic evidence of a mixed bacterial infection.
- The dog is not improving with the administration of an appropriate antibiotic.

30. What additional tests should be considered in a dog that has been diagnosed with superficial bacterial folliculitis?

- Deep and superficial skin scrapes to rule out ectoparasites, particularly *Demodex*
- Fungal culture to rule out dermatophytosis
- Complete blood cell count, biochemistry, and urinalysis to screen for metabolic disease and endocrinopathies
- Thyroid hormone levels or pituitary-adrenal axis testing if indicated

- Intradermal skin testing and/or allergen-specific serum IgE testing for environmental allergies
- Food trials to evaluate for food hypersensitivity
- Skin biopsies with histopathology to evaluate for immune-mediated diseases (pemphigus foliaceus), follicular dysplasias, sebaceous adenitis, etc.

31. Outline a treatment plan for a dog with superficial bacterial folliculitis.

- The dog should receive systemic antibiotics for a minimum of 21 days, and at least 7 days after clinical resolution. An antibiotic with efficacy against *S. intermedius* (Box 19-1) should be selected. Penicillins are poor empirical choices for the treatment of superficial bacterial folliculitis in dogs because *S. intermedius* produces penicillinases.

Box 19-1 *Empirical antibiotics for* S. intermedius

Erythromycin 10-15 mg/kg orally every 8 hr
Lincomycin 20 mg/kg orally every 12 hr
Clindamycin 5 mg/kg orally every 12 hr
Ormetoprim-sulfadimethoxine 27.5 mg/kg orally every 24 hr
Trimethoprim-sulfadiazine 15-30 mg/kg orally every 12 hr
Oxacillin 22 mg/kg orally every 8 hr
Cephalexin 22-30 mg/kg orally every 12 hr
Amoxicillin-clavulanic acid 15-22 mg/kg orally every 12 hr
Enrofloxacin 5 mg/kg per day orally (every 24 hours or divided every 12 hr)

- Shampoos and conditioners can increase the patient's comfort, speed the resolution of an infection, and help prevent future infections. Several antibacterial shampoos (benzoyl peroxide, chlorhexidine, ethyl lactate) and conditioners (chlorhexidine) are available.
- Avoid corticosteroids. Corticosteroids suppress the immune system, predisposing the animal to recurrence of the infection.
- Identify and correct the predisposing causes.
- Educate the owner about the potential for recurrence of the infection, particularly if the underlying causes of the infection are not identified and controlled.

32. What should be done for animals with recurrent cases of superficial bacterial folliculitis?

- Make sure that the patient has received appropriate antibiotic therapy, including an antibiotic effective against *S. intermedius*, the correct dosage, and the proper duration of therapy. Additionally, investigate owner compliance.
- If the infection never completely resolved with appropriate therapy, perform skin biopsies and a bacterial culture and susceptibility testing.
- Ensure that a thorough search for underlying causes has been performed.
- Institute routine bathing with an antimicrobial shampoo.
- Consider using immunomodulators (efficacy is not well documented).
  - *S. aureus* phage lysate (Staphage Lysate) 0.5 mL SC twice a week for 10-12 weeks, then once every 7-14 days for maintenance therapy
  - *Propionibacterium acnes* (Immunoregulin) IV twice a week for 2 weeks, then weekly until the condition resolves, then monthly for maintenance therapy
  - Human interferon alfa-2a (Roferon) 1000 IU/dog PO daily
  - Autogenous bacterins
  - Levamisole 2.2 mg/kg orally every 48 hours
  - Cimetidine 6-8 mg/kg orally three times a day

- Consider extended antibiotic regimens for animals that have failed to respond to adjunctive therapies and the correction of underlying disorders. These regimens may increase the risk of developing bacterial resistance.
  - Pulse-dose therapy is the use of antibiotics at a full dosage every other week.
  - In low-dose continuous therapy, the antibiotic is given at a suboptimal dose (e.g., once daily instead of twice daily).

33. What is the causative agent of dermatophilosis in small animals?

The causative agent of dermatophilosis is *Dermatophilus congolensis*, a gram-positive actinomycete that forms filaments (parallel rows of cocci) in tissues.

Dermatophilosis is rare in small animals, and the organism is thought to come from carrier farm animals. The infectious zoospores are highly resistant, and can persist in crusts for years.

34. Explain the pathogenesis of dermatophilosis.

Moisture is very important in the pathogenesis of dermatophilosis; thus, the disease is rare in dry climates. Conditions that predispose animals to *Dermatophilus* infections include cutaneous trauma, maceration, inflammation, and other infections.

Moisture causes the release of infectious motile zoospores that are attracted to carbon dioxide diffusing from the skin surface. These zoospores germinate and produce filaments that invade the epidermis.

35. Describe the clinical signs of dermatophilosis.

The classic lesion of dermatophilosis is a "paint brush" lesion, characterized by a thick crust embedded with hairs. In early lesions, the crust is associated with green purulent exudate and a bleeding ulcer underneath. In chronic cases, lesions include crusts, scale, alopecia, and hyperpigmentation. Usually, the lesions are distributed along the dorsum, but the face, ears, and feet may also be affected.

36. How is dermatophilosis treated?

- Eliminate any factors that predispose to moisture or trauma
- Remove crusts with topical therapy (povidone-iodine, lime sulfur)
- Systemic antibiotics: ampicillin, cephalosporin, tetracycline, high-dose penicillin

37. What is the pathophysiology of furunculosis?

Furunculosis occurs when an infected hair follicle (folliculitis) ruptures, releasing hair shafts and keratin into the dermis. The result is a foreign body reaction, including tissue eosinophilia and a pyogranulomatous to granulomatous response.

38. List predisposing causes of deep bacterial infections (folliculitis and furunculosis).

Adverse cutaneous drug eruptions, demodicosis and other ectoparasites, dermatophytosis, endocrinopathies (hyperadrenocorticism, hypothyroidism), foreign bodies, immune deficiency or immune suppression (corticosteroids, cancer chemotherapeutics), immune-mediated skin diseases (pemphigus, lupus erythematosus), trauma (pressure, rooting in burrows, rubbing on hard surfaces), pruritus from hypersensitivity disorders (inhalant, dietary, parasitic), or secondary to neoplasia.

39. What bacteria are associated with deep bacterial folliculitis and furunculosis?

S. intermedius is often involved in deep pyoderma, as well as *Proteus* spp., *Pseudomonas* spp., and *E. coli*.

40. Describe the clinical signs of a deep folliculitis and furunculosis.

The lesions of deep folliculitis and furunculosis begin as superficial bacterial infections (e.g., papules, pustules). When the infection breaks through the hair follicle, the lesions progress

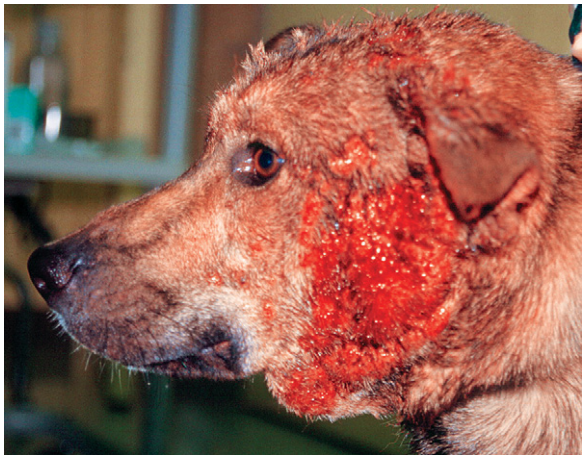

Figure 19-4 This mixed-breed dog has deep folliculitis and furunculosis on the lateral aspect of the face. Note the alopecia, erosions, and hemorrhagic crusts.

to furunculosis, hemorrhagic bullae, fistulas, and ulcers (Figure 19-4). In severe infections, tissue swelling and cellulitis may be present. Pruritus is variable, and often reflects the underlying cause.

Deep folliculitis and furunculosis lesions are usually located on pressure points and on the trunk (rump, thighs, dorsum, ventral abdomen). Additionally, the lesions may be isolated only to one area (nasal, muzzle, pedal, interdigital). Generalized lymphadenopathy is a frequent finding. Some animals may also have a poor appetite, weight loss, and pyrexia. Bacteremia and sepsis are potential systemic complications of a deep pyoderma.

41. List differential diagnoses for an animal with deep folliculitis and furunculosis.

- Parasites: demodicosis, others
- Fungal diseases: dermatophytosis, *Malassezia*, blastomycosis, sporotrichosis, cryptococcosis
- Immune-mediated diseases: pemphigus, lupus erythematosus, etc.
- Foreign bodies: suture or plant material
- Traumatic injuries: fights, gunshot pellets, etc.

42. What types or breeds of dogs are predisposed to developing pedal folliculitis and furunculosis?

- Working or hunting dogs
- Dogs with psychogenic dermatitis: Poodles, terriers, German Shepherds
- Short-coated breeds (sterile pyogranulomas): English bulldogs, Dachshunds, Great Danes, Boxers
- Flat foot shape: Pekinese, some terriers

43. What types or breeds of dogs are predisposed to developing pyotraumatic folliculitis and furunculosis?

Pyotraumatic folliculitis and furunculosis tends to occur in long-coated breeds, for example Golden Retrievers and St. Bernards.

44. What types or breeds of dogs are predisposed to developing nasal folliculitis and furunculosis?

Nasal folliculitis and furunculosis tends to occur in dolichocephalic breeds, such as Collies and German Shepherds.

45. What are the age and breed predispositions for canine muzzle folliculitis and furunculosis?

Muzzle folliculitis (chin acne) is seen most often in young dogs with short coats. Breeds of dogs commonly affected include Boxers, Doberman Pinschers, Great Danes, Mastiffs, English Bulldogs, and Weimaraners.

46. What two qualities of a deep pyoderma lesion help determine the severity of the disease?

- Size—larger lesions are more severe
- Color—darker red ("violaceous") lesions are more severe

47. List tests you would perform to diagnose deep folliculitis and furunculosis in a dog, and procedures you would consider helpful in identifying the underlying cause.

- Physical examination reveals consistent lesions.
- Cytologic evaluation of pustules or purulent exudate should reveal neutrophils and intracellular bacteria.
- Bacterial culture and susceptibility testing is indicated, particularly if there is a mixed bacterial infection.
- Skin cytology for *Malassezia* spp. yeast
- Skin scrape for ectoparasites, particularly *Demodex*
- Fungal culture for dermatophytosis
- Skin biopsies and histopathology to confirm the diagnosis, evaluate for underlying disease, and rule out neoplasia
- Complete blood cell count, biochemistry profile, and urinalysis to evaluate for underlying metabolic disease
- Endocrine testing if indicated (thyroid testing, pituitary-adrenal axis tests)
- Immune function tests if indicated

48. Outline a treatment protocol for a dog with deep folliculitis and furunculosis.

- The dog should receive systemic antibiotics based on culture and sensitivity testing for a minimum of 4-6 weeks, and for at least 3 weeks beyond clinical resolution.
- Lesions should be clipped and cleaned.
- Topical therapy and whirlpool baths aid in the removal of crusts, exudate, and bacteria.
- Localized areas of infection may benefit from topical application of an antiseptic (chlorhexidine, 2-5% aluminum acetate) or antimicrobial creams and ointments (benzoyl peroxide, mupirocin).
- Avoid corticosteroids because they are immunosuppressive.
- Identify and correct the predisposing causes.

49. Deep folliculitis, furunculosis, and cellulitis occur as a familial dermatosis in what breed of dog?

German Shepherds and their crosses

50. Describe a cellulitis lesion.

Cellulitis is characterized by extensive, poorly demarcated tissue edema. The overlying skin is sometimes devitalized (discolored, friable), and may slough.

Crepitance may occur if gas-producing bacteria (*Clostridium* spp., *Bacteroides* spp.) are present. Additionally, bacterial toxins and tissue necrosis may lead to systemic toxicity (depression, fever, malaise).

51. List aerobic and anaerobic bacteria commonly isolated from cellulitis lesions.

The most common aerobic organisms isolated are staphylococci. Occasionally other bacteria are isolated, such as *Pseudomonas* spp. Tissue areas with low oxygen levels are predisposed

to anaerobic infections. The most common anaerobic organisms isolated from cellulitis include species of *Bacteroides, Peptostreptococcus, Fusobacterium, Porphyromonas, Clostridium*, and *Prevotella*.

52. Describe the clinical appearance of an abscess.

An abscess is a nodule that ruptures and has purulent drainage. These lesions are often painful and commonly occur on the tail base, neck, and shoulders.

53. List common causes of abscesses and list aerobic and anaerobic bacteria that are often isolated from abscesses.

Common causes of abscesses include traumatic wounds (especially bite or scratch wounds), foreign bodies, and the extension of deep folliculitis and furunculosis. Immune suppression may be a predisposing factor in some cases.

Common aerobic organisms involved in abscesses include *P. multocida* (bite wounds), *S. intermedius*, and β-hemolytic streptococci. Common anaerobic organisms isolated from abscesses include species of *Bacteroides, Peptostreptococcus, Fusobacterium, Porphyromonas, Clostridium, Prevotella*, and *Actinomyces*.

54. What is the pathophysiology of cutaneous abscess formation?

Bacteria are inoculated into the skin through a traumatic penetrating wound. The surface of the wound heals, trapping the bacteria under the skin. As the bacteria proliferate, an abscess is formed.

55. What laboratory tests are indicated for cats with recurrent subcutaneous abscesses?

Feline leukemia virus and feline immunodeficiency virus tests.

56. Name three differential diagnoses for cellulitis.

- Sterile panniculitis
- Mycobacterial infections
- Neoplasia

57. List several differential diagnoses for an abscess.

- Miscellaneous bacterial organisms: *Nocardia* spp.*, Yersinia pestis,* mycobacterial infections, *Myoplasma* spp.
- Fungal infections: cryptococcosis, blastomycosis, sporotrichosis, dermatophyte kerion
- Foreign bodies
- Sterile panniculitis
- Sterile granuloma
- Neoplasia

58. Outline a treatment plan for a subcutaneous abscess.

Systemic antibiotic therapy based on culture and susceptibility testing. It is important to provide systemic antibiotic treatment for at least 7-14 days after resolution of the clinical signs.

Antibiotics often used for aerobic organisms:

- Clavulanic acid 15-22 mg/kg orally twice daily
- Oxacillin 22 mg/kg orally three times daily
- Cephalexin 22-30 mg/kg orally twice daily

Antibiotics often used for anaerobic organisms:

- Metronidazole 25 mg/kg orally twice daily
- Chloramphenicol 50 mg/kg orally, intravenously, or subcutaneously three times daily (dog), twice daily (cat)
- Amoxicillin-clavulanic acid 15-22 mg/kg orally twice daily

It is very important to provide drainage for focal abscesses. Surgical débridement is beneficial for removing devitalized tissues and providing drainage for the exudate.

Hydrotherapy also improves drainage and promotes healing.

Identify and correct predisposing factors if possible (neutering may help decrease roaming and fighting behavior in male animals).

59. What species of bacteria is acid-fast?
Mycobacteria

60. What is the causative agent of feline leprosy?
Mycobacterium lepraemurium

61. Describe the clinical signs of feline leprosy.
Feline leprosy usually affects young cats, between 1 and 3 years of age. Affected cats have a variety of lesions including nodules, abscesses, plaques, draining tracts, and ulcers. The lesions are usually on the head and limbs. Exposure to mycobacteria occurs in the summer, but because of a long incubation period, many cases are diagnosed in the winter.

62. How is feline leprosy diagnosed?
- Physical examination reveals consistent lesions.
- Cytologic evaluation reveals numerous acid-fast rods.
- It is very difficult to culture these organisms. They require special media (Ogawa yolk medium) and may take months to grow.
- Skin biopsies may reveal few to numerous acid-fast organisms in the tissue.

63. What is the causative organism of canine leproid granuloma syndrome and how is it transmitted?
Canine leproid granuloma syndrome is caused by an unknown species of acid-fast bacteria (mycobacteria). Identification has been difficult because cultures to date have been unsuccessful. Biting flies probably serve as vectors of the disease.

64. Describe the clinical signs of canine leproid granuloma syndrome.
A majority of dogs affected with canine leprosy have short-hair coats. Lesions include nodules, plaques, and ulcers that usually occur on the head, ear pinnae and limbs. Similar to feline leprosy, most cases are diagnosed in the fall and winter.

65. List organisms that cause opportunistic (atypical) mycobacteriosis.
M. fortuitum, M. phlei, M. smegmatis, M. cheloni, M. xenopi, and *M. thermoresistible*

66. Although it is relatively rare in small animals, which small animal is more commonly affected by opportunistic mycobacteria?
Cats are affected more often than dogs.

67. What are the clinical signs associated with opportunistic mycobacteriosis?
Opportunistic mycobacteriosis is characterized by chronic nonhealing wounds, abscesses, ulcers, and draining tracts.

68. In cats, where are lesions of opportunistic mycobacteriosis usually located?
Ventral abdominal or inguinal fat

69. How do you diagnose opportunistic mycobacteriosis?
- Physical examination reveals consistent lesions.

- Cytologic evaluation reveals rare acid-fast rods.
- Culture specimens of these organisms usually demonstrate rapid growth (often within 2-3 days).
- Skin biopsy specimens may reveal a few acid-fast organisms in the tissue.

70. How do you treat cutaneous mycobacterial infections (feline leprosy, canine leproid granuloma syndrome, atypical mycobacteriosis)?

- Spontaneous remission has been reported, but treatment is recommended.
- If possible, wide surgical excision of the lesion should be performed. This may be curative for solitary lesions.
- Systemic therapy is based on culture and susceptibility. If culture and susceptibility is not available, consider:
  - Feline leprosy: dapsone, rifampin, clofazimine
  - Canine leprosy: doxycycline, amoxicillin-clavulanic acid
  - Atypical mycobacteriosis: tetracyclines, clarithromycin, enrofloxacin, clofazimine

71. List mycobacteria that cause disseminated infection (e.g., cutaneous, respiratory, gastrointestinal).

M. bovis, M. tuberculosis, M. avium, M. intracellulare

72. Name three additional bacterial infections characterized by nodules, abscesses, and draining fistulae.

- Actinomycosis is an infection that occurs secondary to wound contamination. Actinomyces (*A. odontolyticus, A. viscosus, A. meyeri, A. horovulneris*) are gram-positive, non–acid-fast, catalase-positive, anaerobic rods that are commensal organisms of the oral cavity and gastrointestinal tract.
- Actinobacillosis is an infection that occurs secondary to trauma and wound contamination. *Actinobacillus lignieresii* is a gram-negative, non–acid-fast, aerobic coccobacillus that is a commensal organism of the oral cavity.
- Nocardiosis is an infection that causes infection through inhalation, ingestion, and wound contamination. *Nocardia* spp. (*N. asteroides, N. nova, N. farcinica*) are gram-positive, partially acid-fast filamentous aerobes that are common soil saprophytes.

73. Name bacterial skin diseases that are potentially zoonotic.

D. congolensis, M. bovis, M. tuberculosis

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20. SUPERFICIAL MYCOTIC INFECTIONS

Karen A. Moriello, DVM, DACVD

1. What are superficial mycotic infections?

Superficial mycotic infections are fungal infections of the skin, hair, and claws. These infections are limited to the surface of the epidermis and outer layers of the hair and claws. Fungal infections of the dermis and subcutaneous tissues are referred to as "intermediate" fungal infections while those that involve the body organs (e.g., lungs) are called "deep" fungal infections.

2. Are there different categories of superficial mycotic infections?

Yes, there are two major categories of superficial mycotic infections. The first group is the dermatophytes such as *Microsporum* and *Trichophyton* species, which use keratin to grow. The second group is the yeasts or yeast-like organisms such as *Candida*, *Malassezia*, and *Trichosporon.*

3. Which of these is the most common?

Ten years ago the answer to this question would have been dermatophytosis, but today the most common superficial mycotic infection in small animal dermatology is *Malassezia* dermatitis. This organism is associated with both otic and skin disease. The second most common superficial mycotic infection is dermatophytosis. *Candida* is a rare infection in dogs and cats and is usually seen in immunocompromised hosts. The most common presentation of candidiasis is a mucocutaneous ulcerative disorder or moist dermatitis. *Trichosporon* is a rare opportunistic agent that causes disease in debilitated and immunocompromised hosts. To date, it has only been seen in cats as a nodular disease involving the nares or at the site of wounds. This is a diagnosis that you stumble upon—it is rare even for a dermatologist to list this in a differential diagnosis when submitting a biopsy specimen of a lump from the nose of a cat. Most of us would be thinking of cryptococcosis, not *Trichosporon*.

4. There are hundreds of mycotic organisms; which ones infect dogs and cats?

More than 25 different species of dermatophytes and six species of *Malassezia* have been isolated from dogs and cats. The most commonly isolated dermatophytes are *Microsporum canis*, *M. gypseum, Trichophyton mentagrophytes,* and *T. verrucosum.* The most commonly isolated *Malassezia* species is *M. pachydermatis;* however, there are a number of other species that have been isolated from cats or dogs including *M. furfur*, *M. globosa* (cats), *M. obtusa*, *M. restricta*, *M. sloofiae*, and *M. sympodialis* (cats).

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5. Which of the 25 species of dermatophytes is most commonly associated with skin disease in dogs and cats?

The most commonly isolated dermatophyte pathogen in both dogs and cats is *Microsporum canis*. It accounts for almost all of the cases of dermatophytosis in cats.

6. Are these diseases a human health concern?

Yes. Dermatophytosis is considered a zoonotic disease. Clients at particular risk for contracting dermatophytosis from an infected pet include children, debilitated individuals, and those with immunosuppression from viral diseases (e.g., human immunodeficiency virus), chemotherapy, or transplant therapy. These individuals should avoid contact with the infected pet until it is cured. In addition, there is some evidence to suggest that *Malassezia* spp. infections may be of zoonotic concern. It is advised that owners wash their hands after treating pets with *Malassezia* otitis or dermatitis.

7. So, is it true that cats are the major reservoirs of infection for *M. canis?* And what about *Malassezia*?

Yes and no. There are two major reservoirs of infection for dermatophytes. The first is a contaminated environment or surface. Infective material can remain viable for weeks to months in the environment, serving as a source of contagion for susceptible hosts. *M. gypseum* is a soil saprophyte and most infections are believed to occur as a result of exposure to contaminated soil. The second "reservoir" of infection is exposure to an infected host or a host that is mechanically carrying a dermatophyte on its hair coat. This is where the cat comes into the picture. *M. canis* does not normally live on the hair coat of cats, or dogs. If you isolate *M. canis* from a cat or dog, it indicates that the host is either infected or mechanically carrying the organism. In either case, a treatment plan needs to be devised to limit exposure to other animals or people. *Malassezia* is found on normal skin, in normal ears, and on the mucosal regions (vaginal, oral, nasal, perianal, anal sac) areas of dogs and cats.

8. What are *Trichophyton* infections?

The reservoir of infection for *T. verrucosum* are cattle. Unfortunately, unless your dog or cat has *T. verrucosum* and has been in contact with cows, you may never find the reservoir. However, here is some food for thought: mice and rodents are commonly infected with *Trichophyton* infections and so are people. In fact, *T. rubrum* is the organism of athlete's foot fungus, and owners playing "footsie" with cats have been known to infect them.

9. How are dermatophyte infections transmitted?

Dermatophytosis is a highly contagious skin disease. Infection can be transmitted from direct animal-to-animal contact, contact with a contaminated object (e.g., brush, blanket, pet carrier), or from contact with a contaminated environment. Human-to-animal infection has been anecdotally reported to happen. Environmental sources of contagion are of particular concern in multiple animal households, catteries, animal shelters, breeding kennels, or veterinary clinics. As previously mentioned, infective material can remain viable for a long time and serve as a source of exposure for animals and people.

10. What factors affect the establishment of a dermatophyte infection?

There many factors that influence the establishment of a dermatophyte infection in a cat or dog. First, exposure must occur. The "critical mass" of infective material or "critical time" of exposure to an infected host is unknown. Many infections may never get established because too little material is present to establish an infection and/or too little contact occurs between an infected and uninfected animal. If infective spores reach the skin surface, an infection may or may not occur. Grooming, especially by cats, effectively removes particulate material (including fungal spores) from the hair coat. Spores may fall off the coat or be mechanically removed via bathing

or other means. Assuming infective material reaches the skin, the fungal spores require a warm humid environment for sporulation; the normally dry arid skin surface is not very hospitable. It is possible that there is more to the lazy sunbathing of cats than most of us think. Animals with pre-existing inflammatory skin diseases (e.g., atopic skin disease), those exposed to chronic moisture and skin maceration (e.g., outdoor dogs or cats wet from the rain, swimming, or bathing), or animals that have concurrent skin diseases that cause microtrauma (e.g., flea infestations) have skin surfaces with environments that favor dermatophyte infections. As a matter of fact, fleas can mechanically carry spores on their bodies and may be a source of contagion in animal shelters, etc. The skin immune system and surface lipids are also important barriers to infection and can be compromised in hosts with underlying medical diseases. One of the reasons that show cats may be more prone to infection is due to all the grooming (much to the cat's disgust) done by exhibitors before the show. The presence of concurrent medical illnesses will make a host more susceptible to infection. Finally, age is an important factor with both the young and old being more susceptible to dermatophyte infections.

11. List the most common clinical signs of dermatophytosis in dogs and cats.

The clinical signs of a dermatophyte infection are pleomorphic and can include any combination of the following:

- Focal or diffuse alopecia: this is caused by the dermatophyte invading the hair follicle and hair shaft
- Broken or stubbly hairs: this is caused by structural damage to the hair shaft
- Scaling and crusting: this may be caused by infection of the stratum corneum and/or a host defense reaction to the invading organism
- Papular or pustular eruption: this is caused by fungal folliculitis
- Variable pruritus

12. Are there any clinical signs of dermatophytosis unique to cats?

YES!!! Cats can show any of the clinical signs listed above, in addition to:

- Non-inflammatory alopecia: cats have a unique relationship with *M. canis* and little or no inflammatory reaction is often visible at the time of examination.
- "Eosinophilic plaque-like lesions": dermatophytosis in cats can be very pruritic and many cats will create areas of self-trauma that mimic those seen in eosinophilic disorders.
- Unilateral lip ulcers: small areas of dermatophytosis infection are common on the muzzle of cats and when lesions occur near the lips, lesions similar to "eosinophilic lip ulcers" may be seen. These lesions may persist for weeks after the infection has resolved.
- Chin acne may be seen and often presents as a "contagious chin acne" syndrome in multiple cat households.
- Severe interdigital or pedal crusting, especially around the claw base
- Diffuse exfoliation and erythema: some cats can have very inflammatory reactions to dermatophyte infections.
- Diffuse hyperpigmentation: hyperpigmentation is uncommon in cats with skin disease; however, it is often seen in cats with dermatophytosis (Figure 20-1).
- Nodular subcutaneous lesions (kerions), especially in Persian cats
- Unilateral or bilateral areas of circular inflammation on the inner pinnae
- Symmetric alopecia or over-grooming syndromes

13. What is the difference between localized and generalized dermatophytosis?

In reality, there is no difference; it's purely a clinical description issue.

"Localized" dermatophytosis describes a clinical presentation in which one or only a few well-circumscribed lesions are visible.

"Generalized" dermatophytosis describes a clinical presentation in which lesions are present over the entire body.

Figure 20-1 Note the hyperpigmentation of the skin of this cat with dermatophytosis.

It is important to remember that these terms refer only to "lesions"; the disease is considered a generalized infection of the skin regardless of how widespread the clinical lesions are.

14. What is an "asymptomatic carrier"?

This term describes cats or dogs that are culture positive, but appear to be free of clinical lesions. "Asymptomatic carriers" fall into one of two groups:

- Culture-positive dogs or cats with subtle active infections
- Culture-positive dogs or cats without active infection (mechanically carriers of spores, most likely culture positive because of exposure to a contaminated environment)

The MOST important thing to remember is that these animals must be treated because they represent a source of infection for people and other animals.

15. What is a kerion reaction?

A kerion reaction is a well-circumscribed, exudative, swollen nodular lesion caused by a dermatophyte infection (Figure 20-2). Kerion reactions are most commonly seen in cases of *M. gypseum* or *T. mentagrophytes* infection and are probably caused by a host-immune response to the organism. Definitive diagnosis is usually made via skin biopsy, as the lesion can resemble areas of deep pyoderma, tumors, or be a suspect area of deep or intermediate fungal infections. Because of the inflammatory nature of these reactions, they usually heal rather rapidly.

16. How is a dermatophyte infection diagnosed?

The patient's history, clinical signs, demonstration of the presence of a dermatophyte associated with the lesions, and a positive response to specific antifungal therapy are all required to make a definitive diagnosis of a dermatophyte infection. On occasion, a physician may make the diagnosis for you because their patient (the pet's owner) has contracted the disease.

17. What laboratory tests can be used to aid in the identification of a dermatophyte infection?

- Wood's lamp examination
- Direct examination of hair and scale for cuffs of ectothrix spores on hair shafts
- Skin biopsy specimen showing fungal folliculitis or furunculosis
- Fungal culture and microscopic identification of the organism

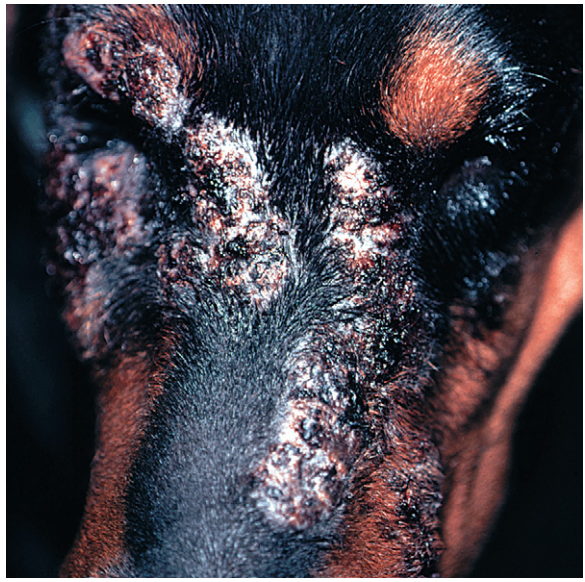

Figure 20-2 Note the inflammatory reaction on the face of this dog. This is a kerion reaction.

18. What are the advantages and disadvantages of each of these diagnostic tests?

A Wood's lamp is an ultraviolet light filtered through a cobalt or nickel filter. It is used to screen lesions for the presence of fungal metabolites that fluoresce apple-green when exposed to the light. The only pathogen of veterinary importance that fluoresces is *M. canis*, and not all strains glow. In addition, topical drugs or shampoos can change or alter the color of the fluorescence. Sebum can give a false-positive test result, as can many bacterial infections of the skin. A positive test result is only suggestive of an infection, not diagnostic. The primary use of this tool is for the selection of hairs for culture or microscopic examination.

Direct examination of hair and scale is done to look for evidence of fungal spores growing in cuffs on the outside of hairs or for fungal hyphae invading hair shafts. It is often positive in human patients, but not so in veterinary patients. Because of the density of the hair coat of dogs and cats and the difficulty associated with finding lesions, it can be difficult for the clinician to find actively infected hairs for examination. The chances of finding infected hairs is increased if Wood's lamp–positive hairs are examined; unless the patient has active lesions that are Wood's lamp–positive, it is not cost effective to perform these examinations. Glowing hairs should be placed in a clearing agent such as 10% potassium hydroxide or chlorphenolac to enhance finding spores and hyphae. Clearing agents cause the background debris to swell, making the spores more refractile. Infected hairs appear swollen, filamentous, and much larger and more disorganized than "normal hairs." A positive test result is diagnostic for a dermatophyte infection, but hairs should still be cultured to confirm the identity of the infective agent.

A definitive diagnosis of a dermatophyte infection can be made via histological examination of a skin biopsy specimen. This is not usually the diagnostic test of choice because less invasive and less expensive tests are often definitive. However, in dogs and cats with unusual presentations of a dermatophyte infection, this may be the ultimate diagnostic test of choice. Unfortunately, the identity of the pathogen cannot be determined from the formalin-fixed tissue specimen. Successful sampling is key and multiple tissue specimens should be submitted (see Chapter 3).

A fungal culture is often considered to be the diagnostic test of choice. It is easy to perform, inexpensive, and will not only diagnose the infection, but also will identify the causative agent.

19. What is the best way to perform a fungal culture?

There are a number of ways to obtain specimens for fungal culture (see Chapter 3):

- Toothbrush culture: A new toothbrush is combed over the hair coat of the animal and/or lesions. This works very well for cats.
- Hair plucking: Hairs from the margins of lesions are plucked in the direction of growth. If the patient is a dog or indoor-outdoor cat, the area should be gently swabbed with alcohol to decrease the number of contaminants collected.

20. What fungal culture medium is best to use?

There are advantages and disadvantages to readily available commercial fungal culture media and containers. The best one to use is cost friendly, user friendly, and readily available.

Fungal culture containers that are easy to inoculate are preferred. Glass jars are easy to store, but are problematic to use. It is difficult to inoculate the surface, especially with a toothbrush. It is also difficult to obtain mycelial samples from the surface for cytological examination. If the lid is screwed on too tightly, the moisture can condense on the inside and bacterial and yeast overgrowth can occur. Petri dishes are easy to inoculate but the plates easily dry out if not sealed with a laboratory wax paper.

Sabouraud's dextrose agar Petri dish plates are commonly used in diagnostic laboratories, however these plates are expensive to purchase and have a relatively short shelf life. The major advantage to this fungal culture medium is that "classic" gross and microscopic morphology will be observed.

The most commonly used medium for in house dermatophyte cultures is Dermatophyte Test Medium (DTM). This fungal medium contains Sabouraud's dextrose agar, antibiotics to inhibit overgrowth of bacteria and yeast, and phenol red, a color indicator. DTM is popular because it contains a color indicator that signals the growth of a possible pathogen. Pathogens use the protein in the medium first, producing the color change. In general, contaminants use the carbohydrate source first and do not produce a color change until after all of the carbohydrate source has been used. The problem is that the color indicator (phenol red) may alter the gross and microscopic appearance of fungal colonies and/or depress macroconidia growth. In addition, some common contaminants will grossly mimic pathogens and turn the media red.

21. Is it practical to perform in-house fungal cultures?

Yes. In-house fungal cultures can be performed using a commercially available plate; many dermatologists prefer Sab-Duets (Bacti-Labs, Mountain View, CA). This fungal plate is comprised of a dual compartment plate with plain Sabouraud's dextrose agar on one side and DTM on the other. With this plate, the clinician has the best of both worlds—an early "alert" system via the DTM and a fungal medium that should produce characteristic colonies for ease in identification of the pathogens. This plate is cost friendly, user friendly, and readily available (Figure 20-3).

22. How do you inoculate fungal culture plates with toothbrushes?

Toothbrush cultures are only practical if a Petri dish or Sab-Duets fungal culture plate is used. The toothbrush should contain hairs in the bristles obtained by combing for at least 2 or 3 minutes through the pet's hair coat. The bristles are gently stabbed onto the surface of the plate and then the toothbrush is discarded.

23. What are the rules of thumb for the interpretation of in-house fungal cultures?

- Pathogens are pale or white in color. If a color indicator is used, a color change will be seen around the culture growth; e.g., red if DTM is used.

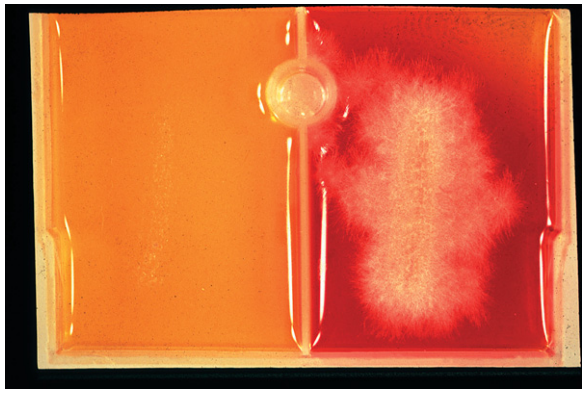

Figure 20-3 A "Sab-Duets" fungal culture plate. Note how easy it is to open and to obtain samples.

- Pathogens are never heavily pigmented; contaminants tend not to cause color changes and many are heavily pigmented or have colored colony growth. Bacteria and yeast produce glistening colonies on the plates.
- Definitive diagnosis is *always* made via microscopic examination. Color changes in the media are not diagnostic of a pathogen or infection. This cannot be stressed often enough.

24. What is lactophenol cotton blue stain and what is it used for?

This is a vital stain that stains living cells. It is used to stain mycelial samples for microscopic examination. The most common technique used to examine fungal colonies is as follows:

- Place a small drop or two of stain on a glass microscope slide
- Take a small piece of clear acetate tape and gently touch the edge of the fungal colony; hyphae and spores will stick to the tape
- Place the tape (sticky side down!) onto the stain, add another drop of stain and coverslip the slide
- Phenol will damage the microscope lens—the coverslip is very important!

25. Okay, so how do you evaluate the cytological fungal specimen?

Early colonies may only show hyphae and no macroconidia or micro conidia. If this is the case, resample the colony in 48-72 hours.

Pathogens are never heavily pigmented and darkly pigmented hyphae or spores are contaminants.

Matching colony and microscopic morphology is used to make a definitive identification of common pathogens. The salient features of common pathogens are described in many dermatology and mycology text books (see Bibliography.)

In most cases, an in-house diagnosis of *M. canis* or *M. gypseum* can be made with ease. *Trichophyton* spp. can be more difficult to culture and identify, and the use of a reference laboratory familiar with veterinary mycology may be needed.

26. In a healthy host, dermatophytosis will self-cure. Why bother with treatment?

It is true; dermatophytosis is a self-limiting skin disease in a healthy host. However, there are many important reasons to treat these animals:

- Treatment will hasten the resolution of the infection and limit the risk of contagion to other animals and people.

- Treatment will aid in decreasing environmental contamination, an important source of infection for people and other animals.
- Dermatophytosis is a zoonotic disease.
- Treatment will eliminate the guesswork out of trying to determine if the animal in front of you is "otherwise healthy."

27. Dermatophytosis infects hairs. Is it always necessary to clip the entire hair coat?

No. Clipping of the hair coat is recommended in dogs or cats with medium or long hair, dogs and cats with generalized or multifocal lesions, and in any animal that is not responding to therapy as expected.

28. Can "localized" dermatophytosis be treated with spot therapy or topical ointments?

No! Although dermatophytosis may appear to be a "localized" infection, it is not. Spores are present throughout the hair coat and it is common to under-recognize lesions. Topical or spot therapy also contributes to chronic infections. Topical ointments are messy, groomed off by the pet, put the owner at increased risk of exposure, and are ineffective.

29. What are the current treatment recommendations for a dog or cat with dermatophytosis?

Clipping

In animals with medium or long hair OR that have generalized infections regardless of hair length, the hair coat should be clipped.

In animals with clinically focal lesions, the infected hairs should be clipped from the margins of the lesion.

Bathing

Bathing in an antifungal shampoo is optional and may paradoxically increase the spread of the lesions by dispersing spores from hairs fractured via scrubbing.

There is no antifungal shampoo available that alone will "cure" a dermatophyte infection.

Bathing may be beneficial in animals with dirty, matted coats in that it grossly removes hair and debris.

Bathing puts the owners at increased risk for exposure to the dermatophyte. Owners should wear gloves and long sleeves during the process.

Topical Therapy

Topical antifungal dips are a useful adjuvant therapy for the treatment of dermatophytosis. In addition they can be used as sole therapy, provided the owner is capable of thoroughly applying the dip. Because this is RARELY the case, topical therapy is not recommended as a sole therapy.

Topical lime sulfur 4 to 8 ounces/gallon twice weekly is effective as a sole therapy; however, few animals (or owners!) can tolerate the required 4 to 8 weeks of therapy. Animals, especially cats, often suffer from conjunctivitis and oral mucous membrane irritation from the dip.

Topical enilconazole is an effective antifungal dip, but it is not available worldwide. It can be irritating.

If lime sulfur or enilconazole is selected as the sole therapy, the pet should be dipped at least twice a week until there are at least three negative culture results at weekly intervals.

Systemic Therapy

Systemic therapy is the treatment of choice for dermatophytosis.

Griseofulvin microsize 25 to 50 mg/kg orally once daily in a fatty meal and itraconazole 5 to 10 mg/kg orally once daily are the most commonly used drugs.

Griseofulvin should not be used in cats unless they are negative for feline leukemia virus and feline immunodeficiency virus because studies have shown that these viral infections may predispose cats to griseofulvin-induced bone marrow suppression.

Complete blood cell counts, ideally, should be monitored before therapy and at biweekly intervals during griseofulvin therapy; however, this is not always possible due to cost constraints or fractious cats.

Liver enzymes, ideally, should be monitored before itraconazole therapy and every few weeks during treatments. This is not always possible due to cost constraints.

Terbinafine and fluconazole can also be used, but there is no evidence to suggest that they are any more effective than griseofulvin and itraconazole.

Ketoconazole is variably effective in the treatment of dermatophytosis; it should be avoided in cats, because they do not tolerate this drug well.

Traditional therapy is to treat daily until three negative culture results at weekly intervals are obtained. Weekly fungal cultures should be obtained starting at week 4 of therapy.

30. Is there a practical way to combine topical and systemic therapy?

Yes. The following plan is often used by the author and is well tolerated by all parties involved:

- Whole body clipping if necessary; otherwise, only infected hairs from lesions are clipped.
- Twice-weekly lime sulfur dips for 3 weeks only
- Systemic antifungal therapy
  - Griseofulvin microsize 25 to 50 mg/kg orally daily OR
  - Traconazole:
    + 5 to 10 mg/kg orally once daily
    + 5 to 10 mg/kg orally daily for 28 days and then on a "week on, week off" schedule until cure (this is especially useful in cats to minimize gastrointestinal upset from the drug).
- Weekly toothbrush fungal cultures starting at week 4 of therapy.

31. How do you treat pregnant animals or puppies and kittens younger than 12 weeks of age?

Pregnant animals should never be given systemic antifungal drugs because these drugs are teratogens, especially griseofulvin. These animals should be treated with topical lime sulfur; it is important to clip the hair coat and dip the animal at least twice a week to minimize infection of newborns. Systemic antifungal drugs should be avoided, if possible, in animals younger than 12 weeks of age; however if the infection is severe and life threatening or euthanasia is a consideration, it may be necessary to use systemic antifungal drugs to save the patient's life. In these situations, use the lowest possible dose of griseofulvin or itraconazole. Topical therapy is preferred in young patients.

32. Are fungal vaccines effective in the prevention or treatment of *M. canis* infections?

To date, there has been no evidence to show that *M. canis* fungal vaccines are protective against challenge exposure to *M. canis* in cats. These vaccines alone will not cure an active infection; however, there is some evidence that their administration may "dampen" clinical signs. The benefit of this "dampening" is unclear but it may be useful in limiting the spread of the infection because fewer active lesions shedding infective material into the environment are present.

33. How is therapy monitored?

Weekly fungal cultures, starting at week 4 of treatment, are performed until the dog or cat has at least two to three negative fungal culture results at weekly intervals.

34. What about environmental decontamination?

Infected animals contaminate their environment as infected hairs and spores are shed. Decontamination recommendations include:

- Isolation of the infected animals until the infection has been resolved; concurrent topical therapy with lime sulfur will hasten recovery and help lessen environmental contamination.

- Elbow grease: Gross cleaning of the environment: vacuuming of debris and dust and aggressive scrubbing of surfaces with detergents. This includes vents, ledges, etc.
- The environment should be disinfected with a 1:10 dilution of household bleach. The target surface needs to be wetted for at least 10 minutes and this needs to be repeated every 2 to 3 days.
- All bedding, rugs, toys, combs, scratching posts, and towels should be destroyed.

35. What about using enilconazole in the environment?

Enilconazole sprays and foggers are used in poultry production units to control molds and fungi. This product is very effective against *M. canis*, but unfortunately is not licensed in the United States for use on cats or in catteries.

36. What about "resistant dermatophyte infections"?

Drug resistance is always a concern; however when most of these situations are carefully and methodically investigated one or more of the following problems is usually found. These problems should be investigated and corrected before changing therapy or assuming there is a "drug resistance" problem:

- Inadequate, ineffective, or inconsistent environmental decontamination
- Inappropriate dose, dosage, or length of therapy with a systemic antifungal drug
- Use of only spot therapy for lesions
- Resistance to clipping of the hair coat in long-haired animals or animals with generalized infections
- Owners stopping therapy too soon; clinical cure will precede mycologic cure by several weeks
- Lack of treatment of all exposed animals; reinfection is occurring from a subclinically infected host

37. If *Malassezia* spp. are part of the normal flora of the skin, how do we know that they are a cause of skin disease?

For years, *Malassezia* spp. organisms were found on skin biopsy specimens of animals with various skin diseases, most notably from those with pruritus and seborrheic disorders. At the time, conventional thinking was that these organisms were "normal flora," were not involved in the disease process, and were to be ignored. Eventually, clinicians started to realize that overcolonization of "normal" skin and ear flora played a huge part in the pathogenesis of many skin diseases. In time, it was recognized that although *Malassezia* organisms are found on the skin and in the ear canal of normal animals, they can cause skin disease.

38. How are *Malassezia* infections transmitted?

Malassezia organisms are found on the normal skin of dogs and cats. It is believed that the skin of kittens and puppies is colonized in the first few days of life via grooming and licking. Currently, *Malassezia* spp. is not considered to be a contagious infection between animals.

39. What skin diseases predispose animals to *Malassezia* infections or overcolonization?

There are a number of well-recognized skin diseases that are associated with secondary *Malassezia* infections (i.e., overcolonization) of the skin. These include atopic dermatitis, recurrent bacterial infections, endocrine disorders (especially hypothyroidism), and keratinization disorders or primary seborrhea.

40. What factors affect the establishment of a *Malassezia* infection?

It is important to remember that *Malassezia* spp. are normally found on the skin and in the ears of dogs and cats. They are usually present in low numbers and without any evidence of concurrent disease. Overcolonization of the skin by *Malassezia* can occur for any number of

reasons, including, but not limited to, the presence of a concurrent bacterial infection, increased skin humidity at the surface or as a result of oppositional skin folds, increased presence of nutrients from the surface of the skin, changes in sebum or hormones, and defects in the skin immune system.

41. What are the most common clinical signs of *Malassezia* infections in dogs?

Dogs can exhibit any combination of the following:

- Pruritus: this is one of the MOST consistent clinical signs. It is likely caused by a hypersensitivity reaction to *Malassezia* antigens, particularly since the number of organisms present can often be disproportionate to the severity of the patient's pruritus.
- Odor
- Erythema
- Waxy, oily debris and scaling of the skin
- Lichenification and hyperpigmentation of the skin, especially in the axillary and inguinal areas
- Papular and pustular eruptions
- Intense pedal and interdigital pruritus with or without waxy debris lodged beneath the claw beds
- Seborrheic otitis externa
- Recurrent otitis externa
- Pruritus ani

42. What are the common clinical signs of *Malassezia* infection in cats?

Malassezia infections are less well described in cats, most likely because this disease is under-recognized. The clinical signs can include any combination of the following:

- Pruritus with or without scaling
- Miliary dermatitis lesions that do not respond to oral antibiotics or glucocorticoids
- Black waxy debris in the ears—ears may or may not be pruritic
- Feline chin acne
- Pedal pruritus and paronychia
- Generalized erythema and scaling
- Follicular plugging in the pre-auricular area

43. How is *Malassezia* dermatitis diagnosed?

The diagnosis is made by a compatible history, clinical findings, and cytologic demonstration of the organism. One of the most important things to remember about the diagnosis of *Malassezia* dermatitis is that it is almost never an "only skin disease." In other words, it is almost always present as a result of some predisposing cause, whether that is obvious or not. The second most important thing to remember is that it is not the number of organisms present per high-power field that is key, but whether or not *Malassezia* organisms are seen in conjunction with compatible clinical signs.

44. How many organisms need to be seen on a cytologic specimen to make a definitive diagnosis of *Malassezia* dermatitis?

Sometimes all it takes is ONE. The organism is found on normal skin and in normal ears and it is hard to know how many organisms per high-power field indicate "infection or overgrowth" vs. normal flora. However, here is where common sense must prevail and not a numbers game. If there is no inflammation or pruritus present in the area sampled, it seems reasonable to conclude that the population of *Malassezia* present is living in harmony with the surrounding tissues. However, if the skin is inflamed and *Malassezia* organisms are easily found, then it seems reasonable to conclude that the population is not living in harmony and may very well be contributing to the patient's symptoms.

45. What is the best diagnostic test for finding *Malassezia* organisms?

The easiest and most cost-effective diagnostic testing technique is to sample symptomatic skin. Impression smears of affected skin can easily be obtained by firmly pressing a new clean glass slide to the skin (be sure to place your thumb directly over the site and press until a "fingerprint" is seen on the slide), heat-fixing the slide (gently flaming the underside for 5 seconds) and then staining it with DiffQuik. Slides are best examined under oil immersion and the organism is often found adhered to keratinocytes. A skin-scraping spatula can be used to scrape cellular debris from between crevices in lichenified skin, interdigital spaces, and/or under claw beds for cytologic examination.

46. What are the pitfalls associated with cytologic testing?

- *Malassezia* organisms can be missed if pressure that is too light is used when performing the impression smears.
- If the owner has washed the dog, it can be difficult to find organisms or the number seen may under-represent the true extent of the overcolonization.
- Forgetting to heat-fix the slides will make it more difficult to find organisms.

47. Is skin biopsy more reliable?

Not as a routine diagnostic test. It is invasive, expensive, and often *Malassezia* organisms are lost during processing because they are found in the most superficial layers of the skin.

48. What is the best treatment protocol for *Malassezia* dermatitis?

There is no one "best" treatment protocol for *Malassezia* dermatitis. All treatment plans must take into account the severity and duration of the disorder, the clinician's experiences with various therapies, what the owner is able and willing to do, what the owner can afford, and any other concurrent skin diseases. In general, successful therapy involves:

- The identification and treatment of any and all concurrent skin diseases or predisposing triggers
- Improving the hair coat hygiene (grooming practices)
- Topical therapy to remove oil and sebum, which act as growth media
- Specific antifungal therapy: topical and/or systemic antifungal drugs

49. How does the treatment of *Malassezia* dermatitis differ from the treatment of bacterial pyoderma?

In many respects it does not differ, except for the fact that systemic antifungal drugs are used instead of systemic antibiotics.

- The hair coat should be clipped to remove any mats or strands of hair matted with oil and debris, which may harbor large populations of organisms.
- The hair coat should be bathed two to three times per week using a cleansing shampoo to remove debris and dirt, followed by a medicated shampoo.
- The medicated shampoo might be an antiseborrheic shampoo or an antifungal shampoo (ketoconazole, miconazole, ketoconazole-chlorhexidine, or selenium disulfide).
- The hair coat should be thoroughly rinsed to remove all shampoo residue because this can be irritating.
- Cats often prefer not to be bathed; however, bathing is recommended if their hair coat is severely matted and/or oily.
- Systemic antifungal drugs should be administered for at least 7 to 14 days past clinical cure. In the "real world," this is usually 21 to 30 days of therapy.
  - Dogs: Ketoconazole or itraconazole 5 to 10 mg/kg orally once daily
  - Cats: Itraconazole 5 to 10 mg/kg orally once daily

50. How are chronic cases of *Malassezia* dermatitis managed?

Recurrent cases of *Malassezia* dermatitis are recurrent because either the underlying disease or trigger has not been identified and treated, or it cannot be cured but only managed (e.g., *Malassezia* secondary to primary disorders of keratinization). In these cases, chronic bathing may be beneficial and/or once- or twice-weekly pulse doses of ketoconazole or itraconazole.

51. How are patients with concurrent bacterial and *Malassezia* dermatitis treated?

The presence of concurrent bacterial and yeast pyoderma is one of the most under-recognized causes of pruritus in dogs, and even cats. Any skin disease that can predispose a dog or cat to a secondary bacterial pyoderma can trigger an overgrowth of *Malassezia* spp. In fact, there is a symbiotic relationship between staphylococci and *Malassezia*. Concurrent treatment of both skin infections is not difficult:

- Attention to grooming and hair coat issues.
- Bathing of the pet two to three times per week. In these cases combined antibacterial and antifungal shampoos are especially helpful.
- Concurrent systemic antibiotic and antifungal therapy; both infections should be treated at the same time.

52. Does antibiotic therapy predispose animals to the overgrowth of yeast? This is the case with candidiasis.

Interestingly, chronic antibiotic therapy has not been associated with an overgrowth of *Malassezia* spp. on the skin.

53. What is a *Trichosporon* spp. dermatitis?

Trichosporon spp. are yeast-like fungi that are normally found in the soil. They can sometimes be isolated from the hair of animals and people. This is an opportunistic organism that most likely causes infection via traumatic introduction into a host that is incapable of eliminating the organism. To date, reports of infections in animals have been limited to cats. It has been reported to cause single to multiple nodular lesions on the skin, nostrils, and at the site of bite wounds. Definitive diagnosis is via skin biopsy and the key finding is a pyogranulomatous inflammatory infiltrate with fungal elements. Isolation of the organism for culture requires a tissue sample, best obtained via skin biopsy. This organism is sensitive to ketoconazole and itraconazole; the latter is recommended in cats, because it seems to be better tolerated. A thorough search for an underlying cause is warranted.

54. A skin biopsy specimen is obtained from a nodule on the face of a cat. The report reveals pyogranulomatous inflammation with pleomorphic fungal elements that "most likely represent yeast or yeast-like organisms." Fungal culture is recommended. What is the best method to collect a specimen for culture and what organisms should you tell the reference laboratory to culture for?

In pyogranulomatous skin diseases, infectious agents are often found in small numbers. Therefore, a tissue block collected via skin biopsy should be submitted for culture. If the lesion is superficial and small, a skin biopsy punch may collect an adequate amount of tissue for culture. If the lesion is large, a wedge of tissue collected with a scalpel blade is recommended; the organisms are often cultured from the subcutaneous fat or deep dermis and skin biopsy punches often collect too superficial a sample. The laboratory should culture the tissue on Sabouraud's dextrose agar and be alerted for opportunistic mycotic infections such as *Paecilomyces*, *Trichosporon* spp., and *Geotrichum* spp.

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21. DEEP MYCOSES

Karen L. Campbell, DVM, MS, DACVIM, DACVD

1. What is a "deep" mycosis?

Deep mycoses are infections with fungal organisms that invade deep into the skin; many produce skin lesions secondary to systemic infections. These are in contrast to the superficial fungal infections, which only invade the keratinized tissues of the epidermis and hair shafts. Deep mycoses may be acquired through direct inoculation, ingestion, and/or inhalation of spores. Deep mycoses are often further subdivided into subcutaneous fungal infections and systemic fungal infections.

2. Which fungal pathogens are most commonly associated with subcutaneous infections in cats and dogs?

- *Sporothrix*
- Chromomycoses
  - Phaeohyphomycosis (*Brachycladium spiciferum, Drechslera spiciferum, Phialemonium obovatum, Pseudomicrodochium suttonii, Xylohypha bantiana*, and others)
  - Chromoblastomycosis
- Mycetomas
  - Eumycotic (*Pseudoallescheria boydii, Curvularia geniculata, Acremonium hyalinum, Phialemonium curvatum*)
  - Actinomycotic (*Actinomyces, Nocardia*)—note, these are bacteria that result in clinical lesions similar to those produced by fungi
- Zygomycoses
  - Mucorales (*Rhizopus, Mucor, Absidia, Mortierella*)
  - Entomophthorales (*Conidiobolus, Basidiobolus*)
- Rhinosporidiosis (*Rhinosporidium seeberi*)

3. How are subcutaneous fungal infections acquired?

These infections are acquired by traumatic implantation of spores from the environment. In most cases, the infections remain localized, involving only the skin and subcutaneous tissues.

4. What are the clinical signs associated with subcutaneous fungal infections?

Most cases present with solitary nodules or draining tracts that are most commonly found on the face or limbs.

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Most cases present with solitary nodules or draining tracts that are most commonly found on the face or limbs.

5. How is the diagnosis of a subcutaneous fungal infection confirmed?

Cytologic evaluation of fine needle aspirates or impression smears demonstrates pyogranulomatous inflammation. Depending on the species, the fungi may form tissue grains, may appear as thick-walled yeast-like bodies (some are found intracellularly within phagocytic cells; others are extracellular), or may form hyphae. Some fungi are pigmented while others are not. Diagnosis is confirmed by submitting tissue biopsy specimens for histopathology and fungal culture. Caution is warranted because some organisms are also pathogenic for humans.

6. How are subcutaneous fungal infections treated?

Where feasible, wide surgical excision followed by antifungal chemotherapy is the treatment of choice for most infections. Antifungal agents have variable efficacy. Ideally drugs for treatment should be selected based on in vitro susceptibility testing. Antifungal drugs that may be effective include ketoconazole, itraconazole, fluconazole, amphotericin B, and potassium iodide.

7. What is the most common subcutaneous fungal infection in dogs and cats?

Sporotrichosis is the most common of the subcutaneous fungal infections. *Sporothrix schenckii* is ubiquitous in the soil, on thorned plants (especially roses), in hay, and in sphagnum moss, and may be carried on the paws of cats. Cats are most likely to acquire the infection from punctures by the teeth or claws of another cat. Dogs usually acquire this infection from puncture wounds from thorns or wood splinters.

8. What is the treatment of choice for sporotrichosis?

The traditional treatment for sporotrichosis is oral potassium iodide. Dogs are treated with 40 mg/kg every 8 to 12 hours, given with food. Cats are more sensitive to iodide toxicity and are treated with 20 mg/kg every 12 to 24 hours, given with food. Signs of iodide toxicity include ocular and nasal discharges, dry scaly hair coat, anorexia, vomiting, diarrhea, depression, twitching, weakness, and collapse. Itraconazole is better tolerated by most animals and is given at a dose of 5 to 10 mg/kg orally every 24 hours. Treatment should be continued for 30 days after clinical cure. Humans are at greatest risk of acquiring the disease from cats and should wear gloves at all times when handling an infected animal.

9. Cryptococcosis is a common opportunistic fungal infection in immunosuppressed humans. How common is it in dogs and cats?

Cryptococcus neoformans is an ubiquitous encapsulated yeast found in the soil and is found in large numbers in soil contaminated with pigeon droppings. It rarely causes disease in dogs but is the most common deep mycosis in cats. Siamese cats may be at increased risk of disease. Cats infected with feline leukemia virus and/or feline immunodeficiency virus are at increased risk and may have more severe disease.

10. What are the clinical signs of cryptococcosis in cats?

- Cutaneous lesions are most common on the face, pinnae, and paws and consist of multiple papules, nodules, ulcers, and draining tracts (Figure 21-1).
- Upper respiratory signs include sneezing and nasal discharge; many cases have a polyplike mass visible within the nares or a firm swelling over the bridge of the nose (Figure 21-2).
- Lymph nodes may be enlarged and in some cases will abscess.
- Blindness—chorioretinitis, granulomas that result in retinal detachment, optic neuritis.
- Neurologic signs: seizures, ataxia, paresis.

11. How is a diagnosis of cryptococcosis confirmed?

- Aspirate specimens or impression smears from nodules or nasal masses contain large numbers of yeast organisms. An India ink stain will demonstrate the thick capsule of the yeast (Figure 21-3).

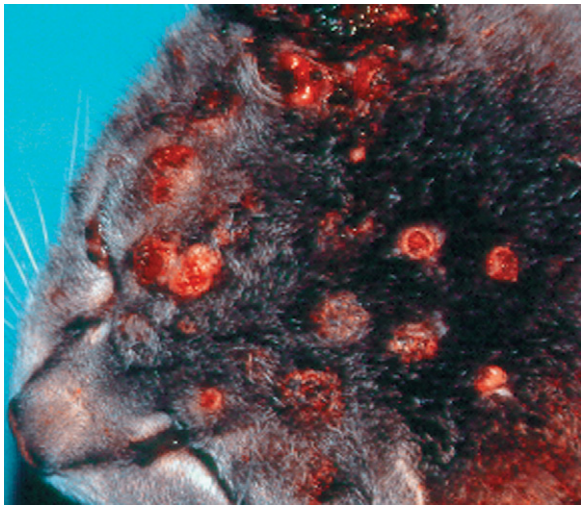

Figure 21-1 Cutaneous nodules associated with cryptococcosis in a cat.

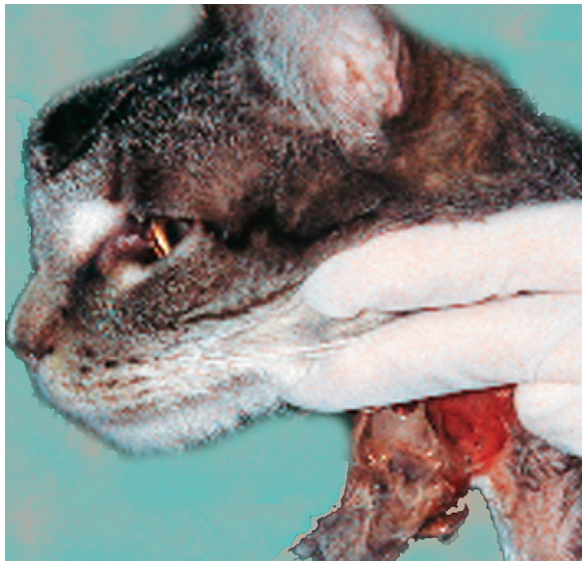

Figure 21-2 Cat with cryptococcosis. Note the swelling over the nose and the abscessed lesion on the ventral neck. (Courtesy Dr. Jennifer Matousek.)

- Latex agglutination or enzyme-linked immunosorbent assay detects cryptococcal capsular antigens in the serum. The magnitude of the titer may correlate with the extent of the infection (may be useful in monitoring response to treatment).
- Biopsies and cultures can also be used to identify the organisms.

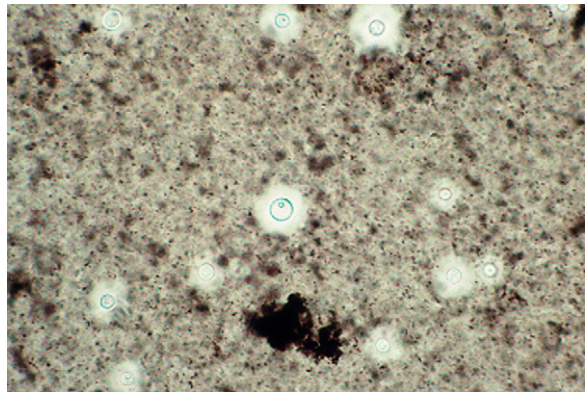

Figure 21-3 India ink–stained impression smear from a cutaneous nodule. Note the thick capsule characteristic of *Cryptococcus neoformans.*

12. What are the drugs of choice in treating cryptococcosis?

- Itraconazole: 10-15 mg/kg orally once daily or divided twice daily. Capsules should be given with a fatty meal to maximize absorption; liquid suspensions can be given on an empty stomach.
- Fluconazole: 50 mg/cat orally every 12 hours; this is preferred over itraconazole if there are ocular or nervous system signs as it has better penetration into the cerebrospinal fluid.
- Flucytosine: 25-30 mg/kg orally every 6-8 hours is given in addition to itraconazole or fluconazole if the infection is not responding well.

Monitor biochemical profiles monthly.

Monitor capsular antigen titers every 2 months. Continue treatment for 2 months after the titer is non-detectable, and continue to monitor titers for another 6 months because relapse is common.

13. What are the cutaneous manifestations of blastomycosis? What other clinical signs are usually associated with this infection?

Direct implantation of the organism may result in a primary skin infection with papules, nodules, plaques, draining tracts, and subcutaneous abscesses (Figure 21-4).

Cutaneous lesions are most commonly associated with dissemination from a primary respiratory infection. The cutaneous lesions may be single or multiple papules, nodules, plaques, draining tracts, and subcutaneous abscesses. Lymphadenomegaly is common. Other clinical signs include fever, coughing, dyspnea, ocular disease (corneal edema, uveitis, chorioretinitis, retinal detachment, glaucoma, blindness), prostatitis, and lameness (osteomyelitis).

14. What are the risk factors predisposing to infection with *Blastomyces dermatitidis*?

- Soil type: sandy, acidic with moisture, the presence of wildlife and frequent soil disruption all favor the growth of *B. dermatitidis*
- Geographic "hot beds" in the United States include the Missouri, Illinois, Mississippi, Tennessee, Ohio, and St. Lawrence river valleys and basins
- Young (2-4 years) male dogs of large and sporting breeds
- Fall months

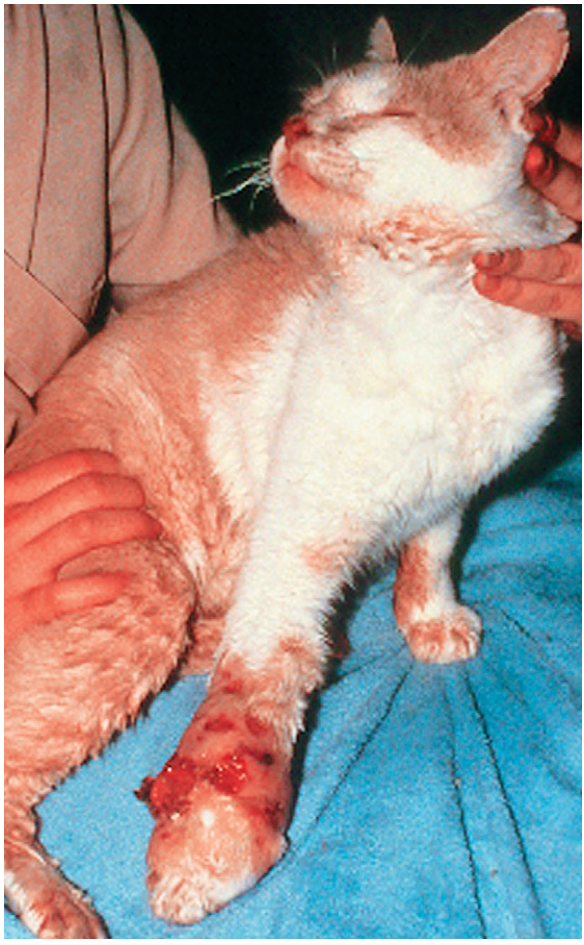

Figure 21-4 Draining tracts associated with blastomycosis in a cat.

15. How is the diagnosis confirmed?

Cytologic examination of impression smears or fine needle aspirates are often diagnostic due to the presence of round to oval yeasts (5-20 µm diameter) with broad-based budding. The cell walls are double-contoured and refractile (Figure 21-5).

Organisms may also be found on tracheoalveolar lavage or in tissue biopsies.

Thoracic radiographs generally show a generalized interstitial to nodular infiltrate and tracheobronchial lymphadenomegaly.

Do not attempt to culture (zoonotic risk with mycelial forms).

16. What are the drugs of choice for treating blastomycosis?

- Itraconazole: 5 mg/kg orally every 12 hours, given with a fatty meal. Treatment should be continued for a minimum of 60 days and at least 1 month after resolution of all signs of disease. Biochemical profiles should be monitored monthly for evidence of hepatotoxicity.
- Ketoconazole: 10 mg/kg orally every 12 hours, given with food. This is a cheaper alternative; however, it is not as effective (lower response rate and higher recurrence rate).

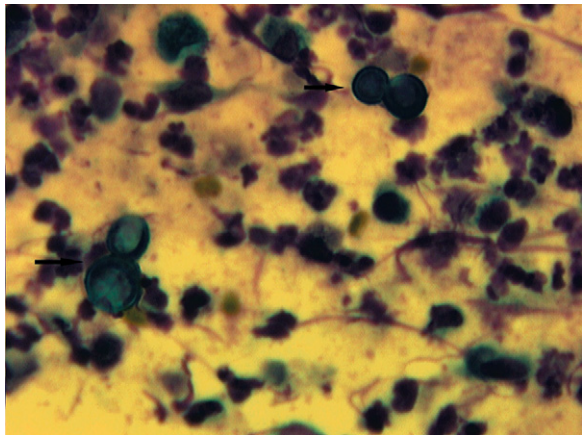

Figure 21-5 *Blastomyces dermatitidis* in an impression smear. Note the refractile, double-contoured, broad-based budding of these yeasts.

- Amphotericin B: 0.5 mg/kg intravenously every other day, monitor closely for nephrotoxicity. Due to the expense and toxicity, this treatment is generally reserved for dogs that do not tolerate or respond to itraconazole.

When pulmonary disease is present (majority of cases!) monitor thoracic radiographs and continue treatment for a minimum of 30 days after resolution of active disease.

17. What are the risk factors associated with histoplasmosis infections?

Bird roosts where soil is rich in bird droppings and old chicken coops are sources of the organism.

Ohio, Missouri, Mississippi, Tennessee, and St. Lawrence river basins are endemic areas.

Young to middle-aged dogs are at highest risk. Most affected cats are younger than 1 year of age.

Pointers, Weimaraners, and Brittany Spaniels may be predisposed to this disease.

18. What are the clinical manifestations of histoplasmosis infections?

- Anorexia, diarrhea, weight loss
- Depression
- Coughing, dyspnea, exercise intolerance
- Ocular discharges, chorioretinitis
- Enlarged lymph nodes
- Cutaneous lesions: papules, nodules, ulcers, draining tracts
- Anemia
- Icterus
- Lameness

19. How is a diagnosis of histoplasmosis made?

- Complete blood cell count: non-regenerate anemia, leukocytosis, occasionally find *Histoplasma capsulatum* organisms in circulating neutrophils and monocytes (buffy coat smear or bone marrow aspirates may increase detection rate)
- Biochemical profile: may have elevations in hepatic enzymes with liver involvement, low serum protein with protein-losing enteropathy
- Thoracic radiographs: diffuse to nodular interstitial pneumonia, enlarged tracheobronchial lymph nodes, older lesions may appear as calcified nodules

- Abdominal radiographs/ultrasonography: splenic, hepatic and mesenteric lymph node enlargement
- Osteolytic bone lesions
- Cytology of skin impression smears, fine needle aspirate specimens of nodules or lymph nodes, bronchoalveolar lavage, hepatic aspirate specimens, rectal scrapings: pyogranulomatous inflammation with intracellular yeasts (2-4 μm diameter found within neutrophils, monocytes, and macrophages) (Figure 21-6).

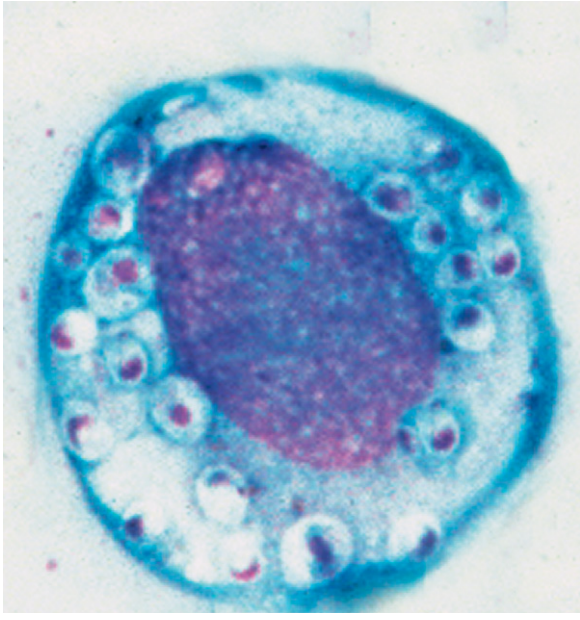

Figure 21-6 *Histoplasma capsulatum* in an impression smear. These yeast organisms are found within macrophages (intracellular).

20. What are the drugs of choice for treating histoplasmosis?

- Itraconazole: 5 mg/kg orally every 12 hours, given with a fatty meal.
- Amphotericin B: 0.5 mg/kg intravenously every other day; this may be the initial drug of choice for dogs with severe gastrointestinal disease. Use until the dog begins gaining weight then switch to itraconazole. Monitor renal function closely.
- Fluconazole: intravenous form is available for use in dogs with severe gastrointestinal disease that are not good candidates for amphotericin B (e.g., renal disease), dose at 5 mg/kg every 12 hours until intestinal absorption improves and then switch to itraconazole.

Continue treatment for at least 1 month after resolution of active clinical disease (monitor thoracic radiographs if pulmonary disease is present).

21. What are the risk factors for coccidioidomycosis infections?

- Sandy, alkaline soils
- High environmental temperature, low rainfall, low elevation
- Lower Sonoran life zone: southwestern United States, Mexico, Central and South America
- Young male dogs (1-4 years old)
- Boxers and Doberman Pinschers are predisposed to disseminated infections.
- Dust storms, digging in the soil, and earthquakes disseminate the spores.

22. What are the clinical manifestations of coccidioidomycosis infections?

- Fever
- Coughing, dyspnea
- Lameness, bone swelling, joint enlargement
- Weakness, paraparesis, back and neck pain
- Seizures
- Uveitis, keratitis
- Lymphadenomegaly
- Cutaneous nodules, ulcers, draining tracts

23. How is a diagnosis of coccidioidomycosis made?

- Complete blood cell count: non-regenerative anemia, neutrophilic leukocytosis
- Biochemical profile: hyperglobulinemia, hypoalbuminemia, azotemia
- *Coccidioides immitis* antibody serologic testing
- Radiographs: interstitial pulmonary disease, osteolytic bone lesions
- Cytology: lymph node aspirate specimens, skin impression smears may contain large spherules characteristic of *C. immitis*.
- Biopsies of skin or bone lesions: granulomatous inflammation with large spherules characteristic of *C. immitis*
- Do not attempt to perform a culture of a specimen because the mycelial form is highly contagious!

24. What are the drugs of choice for treating coccidioidomycosis?

- Itraconazole: 5 mg/kg orally every 12 hours given with a fatty meal
- Amphotericin B: 0.5 mg/kg intravenously every other day; monitor renal function closely
- Fluconazole: 5 mg/kg orally every 12 hours; this is the drug of choice when neurologic signs are present.

Continue treatment for at least 1 month after resolution of active clinical disease; this is considered the most severe of the systemic mycoses and the prognosis is grave to guarded.

25. What cutaneous adverse drug reactions have been reported in dogs treated with itraconazole? What other side effects are seen with this drug?

- Vasculitis followed by skin necrosis and ulceration have been associated with itraconazole administration (7.5% in one report of dogs treated with 10 mg/kg orally every 24 hours).
- Erythema multiforme
- Other reported side effects include anorexia, nausea, and hepatotoxicity. Adverse drug interactions may occur due to inhibition of cytochrome p450 enzymes, which are important in the metabolism of many drugs (ketoconazole is a more potent inhibitor of cytochrome p450).

If side effects are seen, discontinue treatment for 1 week. Most side effects are dose-related; restart treatment at one-half the original dose once adverse signs have abated.

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22. PYTHIOSIS AND LAGENIDIOSIS

Rosanna Marsella, DVM, DACVD

1. What is pythiosis?

Pythiosis is an invasive, ulcerative, proliferative, pyogranulomatous disease of the skin, subcutis, and gastrointestinal tract caused by *Pythium insidiosum*, a fungus-like oomycete in the order Peronosporales of the kingdom Protista. Pythiosis is a form of phycomycosis, which is a complex of pyogranulomatous diseases that also includes conidiobolomycosis and basidiobolomycosis.

2. Where can *Pythium insidiosum* be found?

Pythium insidiosum naturally inhabits wetlands, ponds, and swamps and is endemic in some areas of southeastern United States, where it is referred to as "swamp cancer." Other slang names for pythiosis are Florida leeches and canker.

3. What is lagenidiosis?

Lagenidiosis is a recently recognized canine disease that shares many similarities with pythiosis. *Lagenidium* is another oomycete and the *Lagenidium* species that causes disease in dogs is closely related to *Lagenidium giganteum*, a facultative pathogen of mosquito larvae, currently approved by the Environmental Protection Agency for use in the United States to control mosquito populations. It is reasonable to believe that in the past some cases diagnosed as pythiosis were indeed cases of lagenidiosis.

4. How does infection occur?

For both pythiosis and lagenidiosis, dogs become infected by ingesting or by swimming in contaminated water where the zoospores of these oomyces are present. The zoospores are attracted via chemotaxis to open wounds, even minor scratches. Dogs with gastrointestinal pythiosis often have a history of retrieving objects from water and then chewing on them.

5. Is there any geographical difference in the distribution of pythiosis versus lagenidiosis?

Pythiosis is endemic in states that border the Gulf of Mexico, but has been diagnosed in dogs from southern Indiana, Illinois, Missouri, Kentucky, and Arizona (with no history of travel outside the state). Most cases of lagenidiosis have been reported in Florida and Louisiana, but some cases have been diagnosed in Texas, Tennessee, and Indiana.

6. Is there any breed, gender, or age predilection?

Young male retriever-type dogs are particularly at risk for pythiosis. Dogs with open skin wounds are probably predisposed to acquiring cutaneous disease. German Shepherds seem to be at increased risk for the cutaneous form of pythiosis. Lagenidiosis has been reported in young to middle-aged dogs. At present, no breed predilection has been reported.

7. Is there any seasonality for these diseases?

Yes, most cases seem to occur in the summer and fall in tropical and subtropical climates. Presumably high temperatures and high rainfall are necessary for reproduction, and flooding likely distributes the organism over a wide region.

8. Can people become infected with oomycetes such as *Pythium* and *Lagenidium*?

Pythiosis is very rare in people. So far, there have been only 28 cases of human pythiosis published in the literature and 23 of them were from Thailand. Currently there are no reported cases of lagenidiosis in humans.

9. How does pythiosis manifest in people?

Human pythiosis presents in one of three clinical forms: cutaneous or subcutaneous, systemic or vascular, and ophthalmic (e.g., corneal ulcer or keratitis). A saturated solution of potassium iodide may be effective in the treatment of the subcutaneous form. Surgical removal of the source of infection is the method of therapy for the vascular and ophthalmic forms.

10. Can people get infected directly from dogs?

Although direct transmission from infected animals to humans or other animals has never been reported, it is possible that exudates and contaminated bandages may be a source for zoonotic infections.

11. Can other animals get pythiosis or lagenidiosis?

Yes, pythiosis frequently affects horses and, much more rarely, cats and cows. Currently, lagenidiosis has only been reported in dogs.

12. What are the symptoms of pythiosis in the dog?

The cutaneous form presents with rapidly developing pruritic nodules and draining tracts (Figure 22-1). The nodules rapidly progress into large proliferative masses. Lesions are intensely

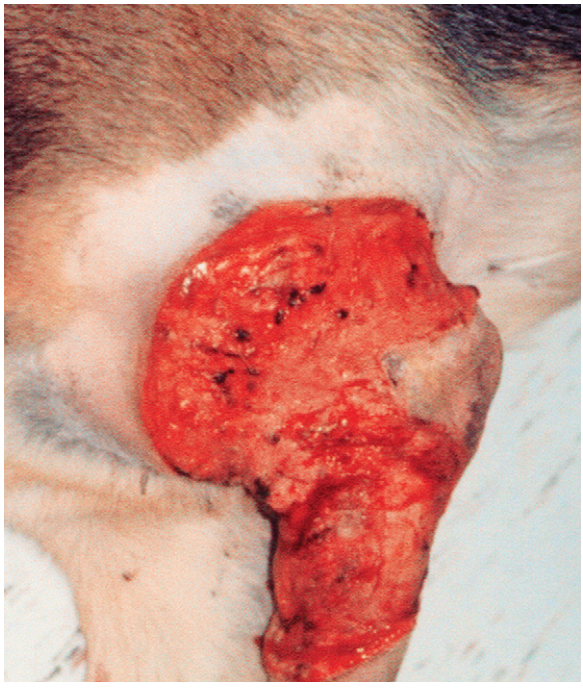

Figure 22-1 Extensive, ulcerated, proliferative lesions due to *Pythium* infection of the ventral chest, axilla, and foreleg of a German Shepherd dog. These lesions had developed over 2 months; the dog was euthanized shortly after diagnosis.

pruritic and, in some cases, the animal licks and chews them to the point of self-mutilation. Initial lesions are often confused with lick granulomas.

13. What are the clinical signs of pythiosis in cats?

Twelve cats with pythiosis have been reported; they presented with subcutaneous masses in the inguinal, tailhead, or periorbital region.

14. What are the symptoms of lagenidiosis in the dog?

Cutaneous lesions of lagenidiosis (Figure 22-2) are similar to those of pythiosis. Regional lymphadenopathy is usually present. In contrast with pythiosis, most dogs with lagenidiosis develop lesions in distant sites (e.g., invasions of distant vessels, lung lesions).

15. How rapid is the development of these diseases?

Pythiosis and lagenidiosis develop very rapidly and lesions can reach considerable size within a matter of days to weeks.

16. How is a diagnosis of pythiosis or lagenidiosis made?

Diagnosis is usually based on clinical signs, in conjunction with supportive histologic findings (pyogranulomatous and eosinophilic inflammation with broad, irregularly branching, infrequently septate hyphae). In contrast to *P. insidiosum*, hyphae of *Lagenidium* can usually be seen on regular hematoxylin and eosin sections. Special staining (e.g., GMS) is necessary to depict *Pythium*. Because these characteristics are not unique, isolation and identification of the pathogen by fungal culture has been traditionally necessary to make a definitive diagnosis.

17. What is the best way to isolate *Pythium* from tissues?

Optimal isolation rates of *P. insidiosum* from infected tissues are achieved by culturing fresh lesions on selective media. For samples that cannot be processed immediately, acceptable handling techniques include storage at room temperature for up to 3 days, refrigeration for up to 5 days, shipping on cold packs, and storage in antibiotic solution, each combined with subsequent inoculation on selective media.

18. What criteria are used to identify oomycetes in a culture?

Size and appearance of the sexual reproductive structures are used for identification. Unfortunately, sometimes these structures are not present in cultures, thus the evaluation of other characteristics may be necessary (e.g., production of biflagellate zoospores in water with plant material). The presence of zoospores does not differentiate between *Pythium* and *Lagenidium*.

19. What diagnostic tests can be done when a culture is not available?

Recently, a polymerase chain reaction technique has been developed to make a final diagnosis of pythiosis or lagenidiosis in absence of a fungal culture in dogs. Both frozen and ethanol fixed animal tissues can be used.

20. Is immunohistochemistry helpful in making a diagnosis?

Specificity of immunohistochemistry is, at this point, questionable; thus, it should not be used to make a final diagnosis.

21. Is there a blood test that can help diagnose pythiosis?

Serology can be used to detect antibodies. An enzyme-linked immunosorbent assay (ELISA) for the detection of anti–*P. insidiosum* antibodies in canine serum has been recently developed. This test appears to be a sensitive and specific test for the diagnosis of canine pythiosis, and may be a useful tool for monitoring response to medical or surgical therapy. More specifically, dogs that develop recurrence after surgery maintain a high level of antibodies,

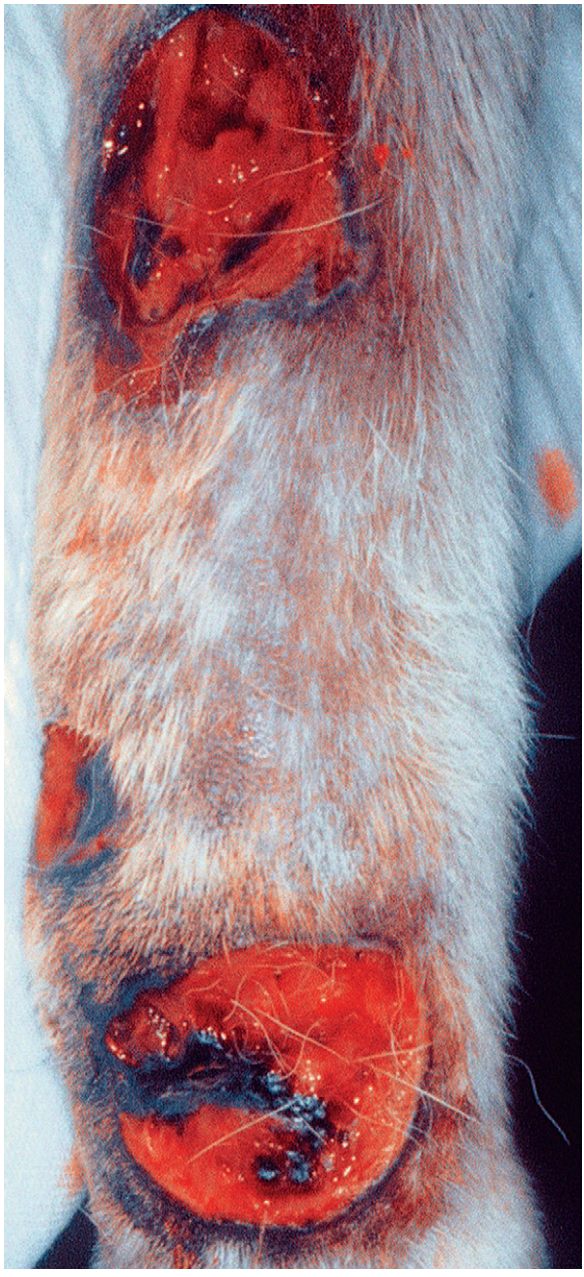

Figure 22-2 Multiple, ulcerated, highly pruritic lesions due to *Lagenidium* infection of the leg of a dog. The lesions had developed over a 1-month period.

whereas dogs that undergo successful resection have a marked decrease of titers 2-3 months after surgery.

22. Is serology helpful in making a diagnosis of lagenidiosis?

Unfortunately, the ELISA currently available has questionable specificity (e.g., normal dogs may test positive and dogs with pythiosis may also have false-positive titers to *Lagenidium*); thus, additional research is needed before ELISA can be used to diagnose and monitor cases of lagenidiosis.

23. What is the recommended treatment for pythiosis and lagenidiosis in dogs?

Wide surgical excision is the treatment of choice for both lagenidiosis and pythiosis, but recurrence is extremely common. Because *Pythium* and *Lagenidium* are not true fungi and do not contain ergosterol in the cell wall, traditional antifungal treatments targeting the synthesis of ergosterol (e.g., ketoconazole) are usually ineffective. Some response may be obtained by combination therapy (e.g., itraconazole and amphotericin B) but the success rate is very low (less than 25%).

24. Is there any other antifungal drug that could have potential application for oomycetes?

Caspofungin is a newly approved drug that targets B-glucan, which is present in the oomycete wall, and thus has the potential of being a successful treatment. Unfortunately, it is extremely expensive.

25. Is immunotherapy (vaccination) successful?

It is in horses but not in dogs. In horses, two vaccines have been developed for use in treatment but neither is commercially available. In a study of 40 horses, immunotherapy was most effective when it was preceded by surgical debridement of the lesions. By itself, the vaccine success rate was 53% but when combined with surgery the success rate increased to 100%.

26. Is topical therapy successful in dogs?

It is not in dogs but it is in horses. Topical amphotericin B (either topical application or local injection) has been reported to be successful for treatment of smaller lesions in horses.

27. What is the prognosis for pythiosis and lagenidiosis in dogs?

Prognosis is guarded to poor in dogs with extensive lesions or lesions than cannot be resected.

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23. MISCELLANEOUS INFECTIONS

Jennifer L. *Matousek*, DVM, MS, DACVD

1. What is the causative agent of feline cowpox infection?

Feline cowpox is caused by an orthopoxvirus that is contagious to cats, dogs, and people. It primarily affects cats in European countries, but there have been sporadic cases in the United States and India.

2. How is feline cowpox virus transmitted?

Cats contract feline cowpox virus by inhalation and through inoculation into the skin. Small mammals (e.g., voles) can serve as reservoirs of the virus. Most cases of feline cowpox virus are diagnosed in the fall, when wild rodent populations tend to be high.

3. Describe the dermatologic signs of feline cowpox virus infection.

The primary site of feline cowpox virus infection is usually an infected wound. Viral replication in the wound leads to viremia and secondary lesions within 10-14 days. During the viremic stage, cats may be febrile and anorexic, but systemic illness (e.g., vomiting, diarrhea, dyspnea, icterus) is otherwise uncommon. Initially, the lesions are classic macular pox lesions, which progress to crusted papules. The lesions are distributed on the face, limbs, paws, and dorsal lumbar areas. Oral ulceration occurs in a small percentage of animals. Spontaneous recovery occurs within 1-2 months in immunocompetent animals.

4. How is a feline cowpox virus infection diagnosed?

A diagnosis of feline cowpox can be made with histopathology, immunohistochemistry, electron microscopy, virus isolation, and serology. Skin histopathology demonstrates eosinophilic intracytoplasmic inclusion bodies.

5. List skin diseases that have been associated with feline leukemia virus (FeLV) and feline immunodeficiency virus (FIV) infections.

- FeLV and FIV: recurrent abscesses, bacterial folliculitis, chronic gingivitis, increased risk of demodicosis
- FeLV: paronychia, poor wound healing, seborrhea, generalized pruritus, cutaneous horns, lymphoma, fibrosarcoma

6. Which canine viral infection is sometimes associated with nasal and footpad hyperkeratosis?

Canine distemper (paramyxovirus)

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6. Which canine viral infection is sometimes associated with nasal and footpad hyperkeratosis?

Canine distemper (paramyxovirus)

7. Name two viral diseases that cause feline upper respiratory disease and oral ulceration.
- Feline rhinotracheitis (α-herpesvirus)
- Feline calicivirus

8. How are papillomaviruses (papovavirus) transmitted?
Direct and indirect contact

9. What is the incubation period for papillomaviruses?
2-6 months

10. List lesions that have been associated with feline papillomaviruses.
- Solitary papillomas
- Hyperkeratotic plaques
- Multicentric squamous cell carcinoma in situ

11. List syndromes that may be associated with canine papillomavirus infections.
- Proven to be caused by papillomaviruses:
  - Canine viral papillomatosis
  - Cutaneous inverted papillomas
- Suspected association with papillomaviruses:
  - Cutaneous papillomas of older dogs
  - Multiple papillomas on the footpads of adult dogs

12. Describe the age predisposition and lesions associated with canine viral papillomatosis.
Canine viral papillomatosis tends to affect young dogs. It is characterized by multiple papillomatous (white-gray, pedunculated, hyperkeratotic) masses (Figure 23-1). These lesions often affect the oral cavity (buccal mucosa, tongue, palate), lips, and eyelids. Papillomas can also occur on haired skin.

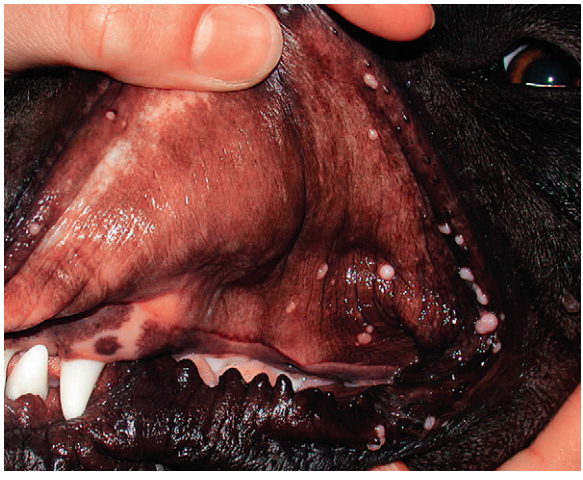

Figure 23-1 A 6-month-old Great Dane with early papillomavirus lesions, seen as multiple white to gray papules in the oral cavity.

13. What is the prognosis for canine viral papillomatosis?

Good, the lesions should spontaneously regress in immunocompetent dogs. Anecdotally, immune stimulants have been reported to speed resolution in some cases.

14. Describe the clinical appearance of cutaneous inverted papillomas.

Cutaneous inverted papillomas are raised, 1-2 cm in diameter, alopecic masses with a central pore. These lesions are most common on the ventral abdomen.

15. Is there an age predisposition for cutaneous inverted papillomas?

Cutaneous inverted papillomas affect animals from 8 months to 3 years of age.

16. Describe the papilloma lesions that can occur on the footpads of young adult dogs (1-2 years old).

Papillomas on the footpads of young adult dogs are firm, horn-like areas of hyperkeratosis. Usually, multiple lesions are present on several paw pads. These papilloma lesions can spontaneously regress, but usually recur.

17. Describe papillomavirus-associated lesions that have been reported in older dogs (3-5 years old).

Cutaneous papillomas have been described in older dogs. These lesions are gray-white pedunculated masses that are usually found on the head or feet (Figure 23-2), and are more common in male dogs. Cocker Spaniels and Kerry Blue Terriers appear to be predisposed to this form of papilloma.

Multiple pigmented plaques or nodules have also been reported.

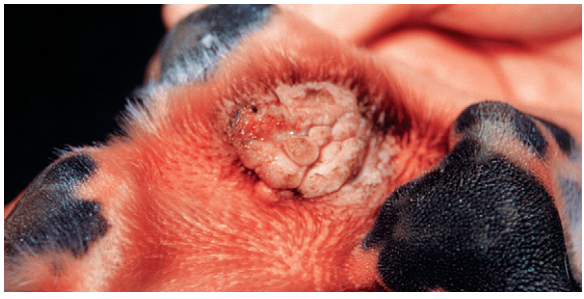

Figure 23-2 Note the raised, white mass with a cauliflower-like surface on the paw of this mixed-breed dog. This is an example of a cutaneous papilloma in an adult dog.

18. How do you diagnose cutaneous papillomas?

- Physical examination reveals the presence of consistent lesions
- Biopsy with histopathology
- Basophilic viral intranuclear or intracytoplasmic inclusion bodies may be present.
- Immunohistochemistry can be used to identify papillomaviruses.
- Electron microscopy

19. What types of treatment are available for papilloma lesions?

- Monitoring without treatment: many spontaneously regress
- Removal: surgical excision, cryosurgery, laser surgery
- Immune stimulation (benefits not proven): interferon, levamisole
- Autogenous vaccination
- Retinoids (cutaneous inverted papillomas)

20. List cutaneous lesions associated with canine Rocky Mountain spotted fever (*Rickettsia rickettsii*).
- Cutaneous erythema
- Edema
- Petechial or ecchymotic hemorrhages
- Vasculitis: cutaneous and oral ulceration and necrosis

21. List cutaneous lesions associated with canine ehrlichiosis (*Ehrlichia canis*).
- Vasculitis
- Pruritic papulocrustous dermatitis

22. What are *Leishmania* spp.?
Leishmania spp. are protozoal organisms.

23. How are *Leishmania* organisms transmitted?
Leishmania spp. are transmitted by sand flies (*Lutzomyia* spp., *Phlebotomus* spp.). Mammals, particularly dogs and rodents, serve as reservoir hosts. Once an animal is infected, macrophages engulf the *Leishmania* amastigotes, which are capable of resisting lysosomal degradation and multiplying within the cell.

24. Which species is more susceptible to infection with *Leishmania* spp., dogs or cats?
Dogs. Cats appear to be relatively resistant to infection.

25. How long is the incubation period in animals infected with leishmaniasis?
The incubation period is long, sometimes lasting weeks to years.

26. What causes the tissue damage associated with leishmaniasis?
Tissue damage is caused by the animal's immune response to the amastigotes, and by immune complex deposition.

27. Leishmaniasis has a worldwide distribution, but is relatively rare in the United States. Which states have been reported to have animals with *Leishmania* spp. infections?
Alabama, Michigan, Ohio, Oklahoma, Texas

28. List systemic signs of leishmaniasis.
- Weight loss
- Lethargy
- Generalized lymphadenopathy
- Hepatomegaly
- Splenomegaly
- Pyrexia
- Muscle wasting
- Keratoconjunctivitis
- Lameness

29. What percentage of animals affected with visceral leishmaniasis have cutaneous signs?
Greater than 80% have cutaneous signs.

30. List dermatologic lesions associated with leishmaniasis.
- Silvery white scale, particularly on head and extremities
- Periocular alopecia ("lunettes")
- Nasodigital hyperkeratosis
- Ulcerative dermatitis
- Paronychia
- Nodular dermatitis
- Secondary bacterial infection
- Predisposition to demodicosis

31. List tests that are available for the diagnosis of leishmaniasis.

- Identification of the organism cytologically (aspirate of tissue)
- Identification of the organism histopathologically
- Immunohistochemistry
- Anti-*Leishmania* antibodies: Indirect immunofluorescent antibody (IFA), enzyme-linked immunosorbent assay (ELISA)
- Polymerase chain reaction (PCR)

32. Does an animal with a high anti-*Leishmania* antibody titer have a better prognosis than an animal with a low titer?

No, a strong humoral immune response is not associated with the resolution of *Leishmania* infection. The cell-mediated immune system is much more important in helping the animal resist the infection, because the amastigotes are engulfed by macrophages where they are able to resist degradation and multiply.

33. What stain is best for identifying *Leishmania* spp. organisms?

Giemsa stain

34. Which tissue aspirate specimens have the greatest chance of yielding amastigotes?

Lymph node and bone marrow aspirate specimens.

35. How is leishmaniasis treated?

Leishmaniasis is currently considered an incurable disease. Clinical remission can be achieved, but dogs remain carriers. The current recommendation for therapy is the use of a combination of meglumine antimonate and allopurinol.

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Section VI
Inflammatory Skin Diseases

24. ATOPY

Pascal Prelaud, DV, DECVD

1. Who was the first dog to be diagnosed with atopy?

Atopy has been described for many centuries in human medicine. For example, one of the most well known cases of spontaneous allergies was the Roman Prince Britannicus. Britannicus was allergic to horse dander; this was a significant problem for him when it was his job to lead a battle. More recently, another famous case of atopy in humans is Richard III, who was allergic to strawberries. Because there are not too many famous dogs (with the exception of Argus, the hound of Odysseus), no reports related to spontaneous allergy in the dog are found in history. The first published clinical case of canine atopy is Lacy.[11] Lacy was a dog living with owners who were allergic to ragweed. They observed symptoms in Lacy comparable to their own disease during ragweed pollen season. They asked their allergist, Wittich, to perform allergy tests. He observed huge reactions to a scratch test with ragweed in this dog. He also did a passive transfer of anaphylaxis on healthy dogs and demonstrated that this allergy was mediated by a heat-labile substance in the serum. Therefore, Lacy's ragweed allergy became the first described case of spontaneous allergy to an aeroallergen in a dog. In addition, Wittich's testing provided the first evidence of the existence of anaphylactic antibodies in the dog and the first canine skin test to be performed using pollen extracts.

2. Is atopy a phenomenon related to societal conditions?

Progression of atopic disease in humans is highly significant in industrial countries. Numerous factors have been implicated, including the lack of infectious stimulation of the immune system during childhood, confined environments, and eating highly processed and hygienic foods. In the dog, no reliable epidemiologic studies have been done to investigate the roles of environmental and socioeconomic factors on the incidence of canine atopy. In this species, the genetic factors seem to be very important because breed predisposition is very clear in most countries.

3. Are atopic dogs the same all around the world?

Yes, the clinical signs of atopy in dogs present all around the world with feet licking, recurrent otitis, and facial or generalized pruritus. In the urban areas of most countries, the main responsive aeroallergen is the house dust mite, *Dermatophagoides farinae* (the role of storage mites is still controversial) (Figure 24-1). However, other important allergenic pollens can vary very significantly: ragweed in northern America, grasses in most countries of the Old Continent, or Japanese cedar in Japan.

4. How is canine atopic dermatitis (CAD) diagnosed?

Since the first cases of atopic dermatitis were described in dogs allergic to pollens and other aeroallergens, it was considered for a long time that the diagnosis of CAD could be made based on the observation of positive allergy test results to aeroallergens. However numerous non-atopic dogs can have positive allergy test results and approximately 20% of atopic dogs have negative

Figure 24-1 The house dust mite *Dermatophagoides farinae* is the main aeroallergen for dogs in urban areas.

test results. This is why allergy testing is now considered as a tool to be used to select aeroallergens for hyposensitization and not to definitely diagnose atopic dermatitis.[1,2] As in human medicine, the diagnosis of CAD can be based on the observation of clinical and historical criteria. This concept was used by Willemse in developing criteria for the diagnosis of atopic dermatitis in dogs (Table 24-1). Willemse adapted the diagnostic criteria that had been proposed by Hanifin and Rajka for human atopic dermatitis.[9] More recently, diagnostic criteria of human AD were reevaluated[7] and the methodology of this work was applied to dog.[8] Five discriminant criteria were defined (Table 24-2). The observation of at least three of these criteria is highly sensitive and specific (> 80%) for the diagnosis of CAD. However, the use of such parameters can lead to misdiagnosis in practice, especially in parasitic diseases such as demodicosis and some cases of sarcoptic mange, but it is more accurate than making a diagnosis of CAD based on results of allergy testing. Requiring three of five of the discriminant criteria allows a very simple diagnostic approach and it is highly accurate if care has been taken to rule out the differential diagnoses of ectoparasites.

5. What is the difference between adverse food reactions and atopy in the dog?

Commonly adverse food reactions and atopic dermatitis are considered as two distinct clinical entities. However, it is often impossible to differentiate between these two diseases based

Table 24-1 ***Willemse's Criteria for the Diagnosis of Canine Atopic Dermatitis***

MAJOR CRITERIA (THREE OR MORE REQUIRED)	MINOR CRITERIA (THREE OR MORE REQUIRED)
• Pruritus • Typical morphology and distribution – Facial and/or digital involvement or – Lichenification of the flexor surface of the tarsal joint and/or the extensor surface of the carpal joint • Chronic or chronically relapsing dermatitis • An individual or family history of atopy and/or the presence of a breed predisposition	• Onset of symptoms before 3 years of age • Facial erythema and cheilitis • Bilateral conjunctivitis • Superficial staphylococcal pyoderma • Sweating • Immediate skin test reactivity • Elevated allergen-specific IgG • Elevated allergen-specific IgE

From: Willemse T: *J Small Anim Pract* 27:771-778, 1986.

Table 24-2 ***Sensitivity and Specificity of Proposed Major Diagnostic Criteria of Canine Atopic Dermatitis (Comparison With All Other Causes of Pruritus)***

Rights were not granted to include this table in electronic media. Please refer to the printed publication.

From Prélaud P, Guaguère E, Alhaidari Z, et al: *Rev Med Vet* 149:1057-1064, 1998.

on an animal's clinical signs.[4] This confusion in diagnosis can be easily solved if CAD is considered as a clinical entity (a clinical syndrome of immunologically mediated pruritus) and adverse food reaction is considered as one of the causes of CAD. With such an option, it is easy to understand that adverse food reaction can be the cause of many different pruritic dermatoses including CAD. This concept has been largely accepted in human medicine. Further more cross reactions between pollens and foods are frequently seen in human beings and recently a case of cross sensitization to tomatoes and Japanese cedar pollen has been described in an allergic dog.[3] Therefore allergy to both aeroallergens and food antigens can be considered etiologic factors that can be involved in different pruritic diseases including CAD. These allergies are not a disease per se but are the underlying causes for the development of clinical lesions in allergic animals.

6. What are the main clinical signs or the chief presenting complaints observed in CAD?

The most common chief complaint is pruritus with scratching or foot chewing and licking. However, there are other clinical signs of CAD that are often overlooked and should be recognized as possible symptoms. One of the most common clinical signs is recurrent external bilateral otitis externa. CAD is the most common cause of external otitis externa (Figure 24-2). Therefore it is important to look for other diagnostic criteria of CAD when a dog is presented for otitis externa

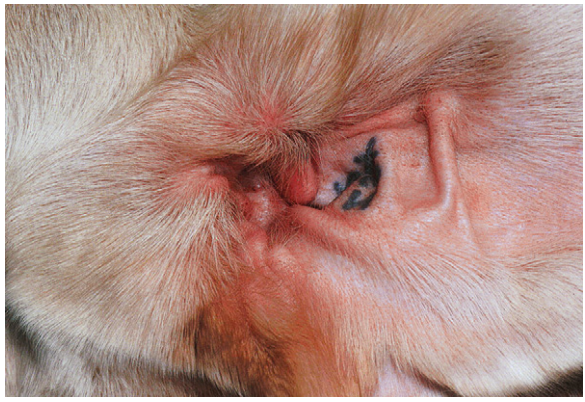

Figure 24-2 Otitis externa is an important clinical sign of CAD; it is common to overlook the diagnosis of CAD when dogs present with a chief complaint of otitis externa.

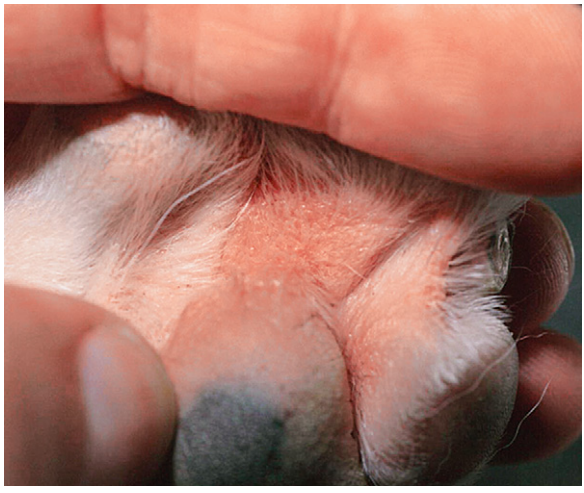

Figure 24-3 Bilateral erythematous pododermatitis of the front feet, even when lesions are very mild, is a major diagnostic criterion of CAD.

(for examples, see Table 24-2; Figures 24-3 and 24-4). Most veterinary dermatologists agree that in some cases otitis externa is the only clinical sign of CAD. Recurrent bacterial folliculitis, localized deep pyoderma, and *Malassezia* dermatitis are other common chief complaints for which the clinician must consider CAD as a possible underlying cause.

7. I am not used to interdermal testing (IDT). How can I begin?

IDT is a very simple technique. Beginners are often overwhelmed by the choice of allergenic extracts and the price of these products. Most companies provide IDT kits adapted to each country or state. Such regionalized IDT test kits are typically complete enough to identify more than 95% of aeroallergen allergies.

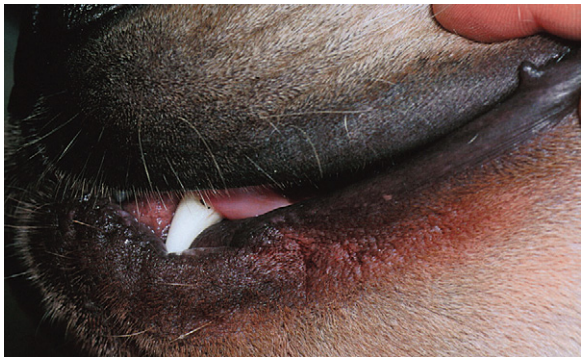

Figure 24-4 Cheilitis is a major diagnostic criterion of CAD. Be sure to look for these lesions even if the owner does not report facial pruritus because the lesions help support the diagnosis of CAD.

There is a very simple and cheap way to prepare a personal IDT kit. Human allergists frequently use prick test solutions that contain 50% glycerine, 0.4% phenol, and highly concentrated (100-fold more than for most canine IDT) allergenic extracts. These solutions can be kept 3 years in refrigeration. Because these solutions are often provided free for allergists, it is easy for veterinarians to ask them for free samples! These extracts can be prepared for use in dogs by making a 1:100 dilution using 4.5-mL vials containing saline with 0.4% phenol (can be obtained from most allergy companies). Glycerine at 0.5% is not an irritant; we have used these modified human kit preparations for more than 15 years to test dogs in France and find them to be as effective as classic IDT solutions.[5]

8. What are the indications for in vitro allergy testing?

Allergen-specific IgE serology in vitro testing is very practical for practitioners. Commercials tend to propose these tests as a tool to diagnose an allergic skin disease. This is erroneous and can lead to misdiagnosis, since positive tests can be observed in any non-atopic dog. In vitro testing, just like IDT, are only indicated after the diagnosis of CAD has been made and is used primarily to choose allergens for immunotherapy. Positive in vitro test results do not mean the dog is atopic and likewise a negative test result does not mean it is not. There are a lot of different techniques and companies offering in vitro allergy testing. The specifics of the type of test being used is not as important as some companies advertise. Commercials often present the analytical specificity of the method being used as a guarantee of the diagnostic specificity of the technique. In fact, the diagnostic specificity also depends on the controls used and the way the threshold of positivity is determined.[5]

9. What are the most common mistakes made in the diagnosis of CAD?

The main mistake in the diagnosis of CAD is failure to diagnose demodicosis and sarcoptic mange because lesions can be very similar (it is especially common to overlook the diagnosis of demodicosis in breeds predisposed to CAD—such as Bulldogs, West Highland White Terriers, etc.). Sarcoptic mange must be ruled out by a treatment trial if there is a diagnostic doubt.

Another pitfall in the diagnosis of CAD is the failure to consider and diagnose and then treat the very frequent complications of staphylococcal and *Malassezia* infections and external otitis. This is why clinical examinations must include all the skin with a thorough examination of the ears and the use of skin scrapings and cytology at each clinical visit.

10. Is it possible to cure an atopic dog?

It is important to explain to the owner of an atopic dog that a cure is very rare. CAD has a genetic basis that cannot be controlled. These dogs will frequently re-present with dermatitis during their whole life, with or without important crises. This is why even if CAD is well controlled, hygienic procedures must be scrupulously followed.

11. What is essential advice to give to an atopic dog's owner?

There is no good treatment of CAD without good understanding and compliance from the owner. At least the two main domains the owner must learn are hygienic measures and early detection of an impending CAD crisis. Hygienic measures include constant flea control; premium food (or "hypoallergenic" or hydrolyzed diets if adverse food reaction was demonstrated), ideally with essential fatty acid supplementation; plus regular brushing and regular bathing using emollient shampoos in a manner that does not interact with flea control (e.g., do not bathe for 3 days before or after applying a residual flea product). It is also important to have good and frequent interactions between owner and dog to minimize risk of anxiety. The owner must be able to identify the first element of an AD crisis in his dog and begin an appropriate treatment. CAD crises may include otitis externa, bacterial folliculitis, and *Malassezia* pododermatitis (Table 24-3).

Table 24-3 ***Therapeutic Options for Treatment of Pruritus Adapted to Each Etiologic Factor***

CAUSE	THERAPEUTIC OPTIONS
Aeroallergens allergy	Hyposensitization, emollient shampoos
Adverse food reaction	Hypoallergenic diet
Flea allergy or enhancement by flea bites	Flea control
Keratinization defect	Emollient and/or keratomodulator shampoos, EFA, retinoids
Malassezia infection	Chlorhexidine shampoo, ketoconazole
Staphylococcal infection	Antiseptic shampoos, antibiotics

12. Is steroid therapy necessary for all cases of CAD?

Steroid therapy is not necessary in all cases of CAD. Most dogs can be controlled with hygienic and antimicrobial treatments. Steroid therapy can be used to treat otherwise uncontrollable pruritus and to prevent dogs from experiencing recurrent pruritic crises. The treatment of an uncontrollably pruritic CAD crisis is with prednisone or prednisolone or methylprednisolone for 3 to 10 days (at a dosage of 0.5-1 mg/kg orally every 24 hours). The treatment can then be stopped in most cases. No weaning is necessary with such a short treatment. If relapses are frequent and the intervals severely pruritic crisis are very short, maintenance steroid therapy can be prescribed, using the lowest effective dosage. In such a case, cyclosporine is a safer option for long-term treatment of the patient.

13. Is flea control inescapable?

Excepted in geographic areas where there are no fleas, one must say yes. Flea control is inescapable for three reasons: control of a potent pruritic stimulus, preventing flea allergy dermatitis (FAD) development, and preventing an AD crisis induced by flea bites (probable role of flea saliva super-antigens). If these reasons are simply explained, owners accept such constraint even if they never see any fleas. If this is not done, there always will be a doubt concerning the involvement of fleas when the patient is presented for an AD crisis.

14. Is there any relationship between behavioral disorders and CAD?

In human medicine, the link between AD crisis and behavioral disorders, like anxiety, is very clear and widely recognized. Psychotherapy can be one of the tools used in the treatment of AD in human beings. In the dog, such a link is more difficult to demonstrate. There are anecdotal reports of high frequency of behavioral disorders or acral lick dermatitis in atopic dogs or of the efficacy of fluoxetine in the treatment of CAD. Sometimes, owners observe a link between CAD crisis and behavior modifications. However, it is often impossible to know if behavior alterations are due to pruritus, or if pruritus or licking are manifestations of substitution activity, or if a CAD crisis is induced by a behavioral alteration.

In practice, it is important in such a chronic disease to identify any behavioral disease (anxiety, depression) in which substitutive activities can be observed (chewing, licking, scratching) and treat them using behavior modification and appropriate medications.

15. What is the best way to treat atopic dogs?

There is no universal recipe for the treatment of CAD. Each treatment must be adapted to each case and to the owner's motivation.

The first step is identification of the causes of pruritus in the atopic dog: bacterial and/or fungal (*Malassezia*) infection, possible flea infestation, other ectoparasites, allergy to aeroallergens, adverse food reactions, and keratinization defects (see Table 24-2).

Then the goal of treatment must be defined and explained to the owner. In some cases, the aim can be a definitive control of pruritus and lesions, but in severe cases, it can be first a decrease of lesions and pruritus severity and decrease of frequency of crises through symptomatic treatments.

Each element of the treatment must be clearly explained, especially long term treatments such as immunotherapy, cyclosporine and steroid prescriptions, and the need for regular hygienic measures.

Regular visits between the veterinarian, client, and pet must be done to adapt treatment to the owner's compliance and motivation and the pet's clinical response.

16. Why are antibiotics so often used in the treatment of CAD?

Antibiotics are the drug of choice in the treatment of any CAD crisis. These are of course used to treat associated skin infections (bacterial folliculitis, BOG), but also to prevent the role of bacterial infection because *Staphylococcus intermedius* can enhance CAD lesions or initiate a CAD crisis. This can be due to protein A or superantigens produced by staphylococci and to the IgE response directed against *Staphylococcus intermedius* in atopic dogs.[6]

17. Is it necessary to treat very minor forms of CAD?

It depends on the owner's complaint. If mild symptoms of otitis externa or interdigital erythema do not generate too much discomfort, treatment may not necessary. Hygienic and preventive prescriptions may also be sufficient treatments for many cases. These treatments may simply include the use of essential fatty acids, emollient shampoos, and flea control.

18. Is it possible to use only topical treatments?

In minor forms of atopic dermatitis, topical treatment can be used alone. These may include emollient shampoos for cases with cutaneous xerosis, steroid shampoos to control a minor AD crisis, or topical steroids used on limited erythematous areas such as the ear pinnae or feet.

19. Is immunotherapy effective in treating CAD?

Yes, however, one must explain what effectiveness is. It is important to explain to the owner that effectiveness is not cure, even after 2 to 3 years of immunotherapy. Cures may only be seen in 10-20% of cases. For most dogs, the goals of immunotherapy are to reduce AD crisis severity or frequency and the need for other drug administration. If a beneficial response is not observed

after one year of treatment, immunotherapy can be discontinued. During the first year of treatment, it is important to make control visits regularly so the veterinarian can alter adjunctive treatments and monitor the severity of the disease. Monitoring may include assignment of a monthly drug administration score. Drug administration scoring can be made using 2 points for each day of steroid or cyclosporine therapy, 1 point for antibiotics or antifungal treatments, ½ point for antihistamines or essential fatty acids treatments, and so on. A progressive decrease in drug administration scores over several months indicates a beneficial response to the immunotherapy.

20. When can I use cyclosporine A (CSA) in the treatment of CAD?

Cyclosporine A is a new treatment option for CAD at an initial dosage of 5 mg/kg per day orally. It is as effective as steroids and in most dogs has fewer side effects. However it takes longer (7-10 days) to achieve control of pruritus than with steroids (1-3 days). CSA can be used for long-term treatment of CAD when the use of a potent anti-inflammatory medication is necessary for long periods. It can be used continuously on an alternate-day basis or can be stopped after a few months of treatment. Relapses are significantly less frequent when AD crises are treated with CSA compared to treating AD crises with steroids.[6]

21. What are the main causes of treatment failure?

The main causes are lack of owner motivation and lack of control of one or more contributing causes of pruritus.

During immunotherapy, owners may stop treatment after a few months because they do not observe any improvement. The owner must understand that immunotherapy should be continued for a full year before assessing how effective it has been. Lack of compliance with restrictive diets is also a very frequent cause of failure, as is the lack of systematic control of secondary infections (staphylococcal folliculitis, *Malassezia* dermatitis, otitis externa, etc.). This is why it is very important to use cytology at each consultation to identify staphylococcal or *Malassezia* infections. Flea infestation can also provoke an AD crisis, and motivating the owner to maintain regular flea control is necessary at each visit.

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25. DIETARY HYPERSENSITIVITY

Stephanie R. Bruner, DVM, DACVD

1. What is dietary hypersensitivity?

"Dietary hypersensitivity" is a phrase associated with great confusion in veterinary medicine today. As the third most common hypersensitivity in both dogs and cats, this is a disorder veterinarians may see with some frequency, yet have difficulty defining. Dietary hypersensitivity and food allergy are terms often applied indiscriminately, when in fact "allergy" refers to a physiologic response to an allergen and hypersensitivity is an abnormal immunologic reaction to an allergen. In practical usage, however, the terms "allergy" and "hypersensitivity" are used interchangeably. Regardless, an immunologic reaction is responsible for the clinical outcome.

Much of what is diagnosed as dietary hypersensitivity or food allergy should probably be more accurately referred to as "adverse reaction to food," which encompasses both immunologic and non-immunologic responses to foods. The phrase "food intolerance" suggests a non-immunologic response such as an idiosyncratic reaction, pharmacologic reaction, food poisoning, or a metabolic reaction. For the purposes of this discussion, "food allergy" will be used to describe all of the above because this is the terminology most frequently used by the veterinary community when explaining this disorder to a client.

2. What are the causes and pathogenesis of food allergy?

Proteins are by far the most widely diagnosed causative agents, although carbohydrates, food additives, and preservatives are anecdotally reported as allergens. Client education must emphasize that food allergies involve reactions to dietary ingredients, not food brands or manufacturers. Adult dogs may eat a specific brand of food for several months or years before developing a food allergy. Alternatively, dogs may change food brands frequently and still develop a food allergy. The latter circumstance is largely due to the fact that many brands contain similar ingredients, regardless of manufacturer. While the quality of the protein varies widely in commercially prepared diets, the sources of the proteins frequently overlap.

Various mechanisms of food allergy in the dog are proposed. While most food allergies are thought to be type I hypersensitivity reactions, type III and IV hypersensitivity reactions have been proposed. Type II hypersensitivity reactions have also been hypothesized but are even less well supported. Even less discussion on the topic exists for cats. An exact immunologic mechanism for food allergy in small animals has not been convincingly elucidated to date. Hence, it is safe to say that no veterinarian has ever definitively diagnosed food allergy or food hypersensitivity in the dog or cat. Fortunately, whether food allergy, food hypersensitivity, or simply adverse reactions to food is being investigated, the approach to the diagnosis and management is the same.

3. What is the history and clinical presentation of food allergy in dogs?

Nonseasonal pruritus is perhaps the most common chief complaint for dogs with food allergies. Pruritus may be recurrent or intermittent if the dog's diet is varied by season or work expectations, e.g., hunting dogs. Response of the pruritus to glucocorticoids is variable. The pruritus is often perceived by the owner as generalized in distribution but may be focused on the ear canals/pinnae, face, feet, axillae, inguinal areas, and/or the perineum. When discussing food allergies with owners, the author refers to these clinical signs as "The Big Five"—head shaking, face rubbing, foot licking, belly scratching, and bottom scooting. Chronic recurrent otitis externa by itself is a common chief complaint. Infrequently, dogs demonstrate dermatologic lesions

without pruritus. Upon further questioning, pet owners may report concurrent changes in fecal consistency, increased frequency of defecation, lethargy, claw loss, and seizures. The incidence of concurrent gastrointestinal signs (other than subtle changes in defecation) is a source of controversy in the veterinary literature.

There is no known gender predilection for food allergies in dogs. The age of onset for clinical signs is widely variable, ranging from less than 4 months to greater than 12 years of age. An estimated one third to one half of all cases, however, are reported to begin before 1 year of age. While some studies report no breed predilection, other studies report American Cocker Spaniels, Boxers, Chinese Shar-Pei, Collies, Dachshunds, Dalmatians, Labrador Retrievers, Lhasa Apsos, Miniature Schnauzers, Soft-Coated Wheaten Terriers, Springer Spaniels, West Highland White Terriers, and terrier breeds in general as being associated with an increased incidence of food allergies.

4. What are the physical examination findings in dogs with food allergy?

Physical examination may reveal porphyrin staining of the haircoat due to excessive licking behavior, papular eruptions, erythroderma, post-inflammatory hyperpigmentation, hyperkeratosis, lichenification, and/or self-induced alopecia. Evidence of secondary pyoderma (follicular oriented papules, a patchy "moth-eaten" alopecia, epidermal collarettes), secondary *Malassezia* dermatitis, bacterial or yeast otitis externa, pyotraumatic dermatitis ("hot spots"), secondary seborrhea, and seborrheic dermatitis may also be present. Skin lesion severity may range from non-existent to marked, and in my opinion relates to chronicity and the presence of secondary dermatoses as much as to the actual severity of the food allergy itself. Less common clinical findings include lymphadenomegaly and onychodystrophy (Figures 25-1 to 25-3).

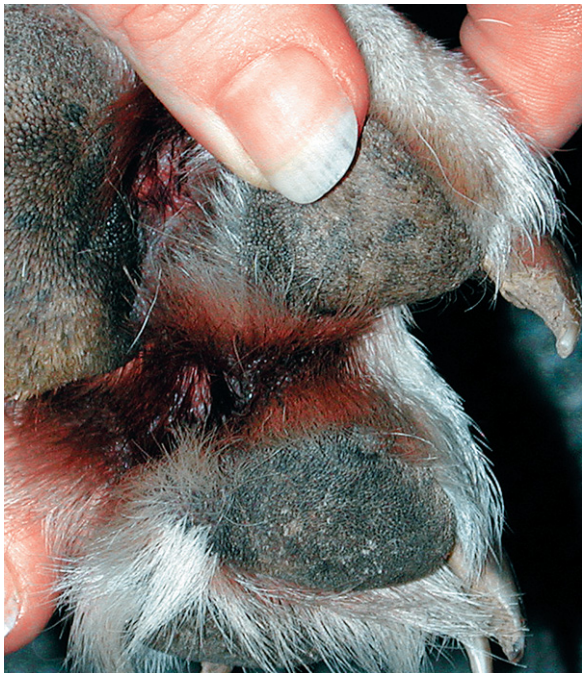

Figure 25-1 Palmar interdigital fur staining secondary to *Malassezia* pododermatitis in a dog with food allergies.

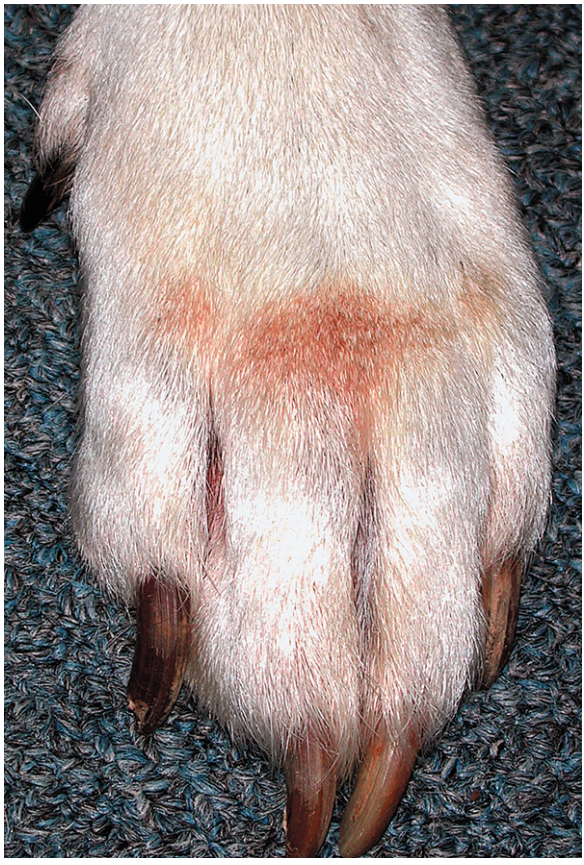

Figure 25-2 Staining of the dorsal forefoot in a dog with food allergies.

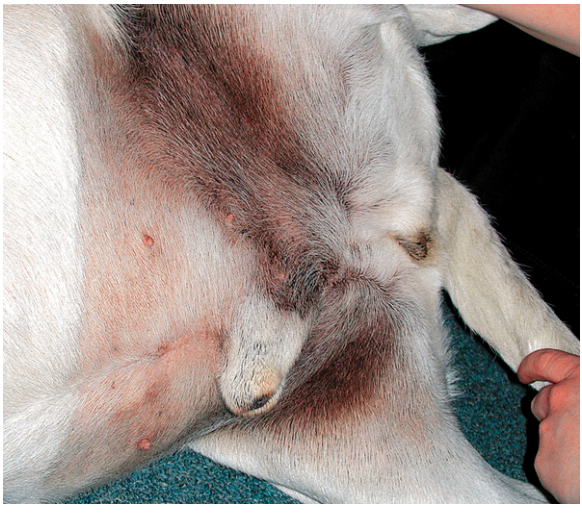

Figure 25-3 Postinflammatory hyperpigmentation of the ventral abdomen in a dog with food allergies.

5. What are the differential diagnoses for food allergies in dogs?

The primary differential diagnoses for food allergies in dogs include atopy, flea allergy dermatitis, scabies and other ectoparasites, and primary seborrhea. To further add to the confusion, concurrent environmental hypersensitivity disorders are frequently diagnosed. Dietary hypersensitivity with concurrent atopy is hypothesized to vary from 13% to as much as 80% in the affected dog population. This wide variance probably reflects the prevalence of atopy in various geographic regions of the United States as well as proposed "regional pockets" of food-allergic dogs of specific breeds across the country.

6. What are the history and clinical signs of food allergy in cats?

There is no known age or gender predilection for food allergy in cats. Siamese cats are predisposed over other breeds. Food-allergic cats demonstrate great variation in their clinical signs. True to their nature, cat skin is unpredictable, but cats do exhibit a group of clinical signs that should alert the veterinarian to consider a food allergy. These clinical signs typically involve marked nonseasonal pruritus and include miliary dermatitis, face/neck pruritus, self-induced symmetric alopecia, and eosinophilic granuloma complex. Angioedema, urticaria, lymphadenomegaly, and conjunctivitis as well as gastrointestinal signs are infrequently reported. The face/neck pruritus typically focuses on the preauricular, periorbital, pinnal, and neck regions; self-trauma is a common and potentially severe sequela.

7. What are the differential diagnoses for food allergy in cats?

The primary differential diagnoses for food allergy in the cat include flea allergy dermatitis, atopy, dermatophytosis, and *Malassezia* dermatitis. Once the veterinarian suspects food allergy or nonseasonal atopy as the primary cause of the dermatologic disease, and eliminates other differential diagnoses such as ectoparasitism and dermatophytosis, the testing process for food allergy begins.

8. What tests are commercially available for food allergy diagnosis?

In vitro serum testing (enzyme-linked immunosorbent assay or radioimmunoassay testing), intradermal testing, and the basophil degranulation test (available in Europe) are not recommended for food allergy evaluation at this time. Serology focuses on IgE-mediated reactions, and thus will not detect other hypersensitivity reactions or non-immunologically mediated responses. Likewise, intradermal testing has poor positive and negative predictive values for food allergies in dogs and cats.

9. What is the best way to diagnose food allergy in dogs and cats?

The test of choice for diagnosing food allergy in veterinary patients is an elimination diet trial. The elimination diet involves feeding the dog or cat a home-cooked novel protein and carbohydrate source food for a minimum of 10-12 weeks. Various periods of test duration are recommended. The author recommends using an extended 10-12 week duration to allow for a brief period of transition from the current diet to the test diet, and to ensure compliance for at least the minimum recommended duration (8-10 weeks).

10. How is an elimination test diet chosen?

The choice of dietary components is highly individualized to the patient and requires a careful dietary history. There is no such thing as a single "hypoallergenic diet." A hypoallergenic diet for a given patient is simply any food that the pet has never eaten previously.

Obtaining a complete dietary history can be quite challenging if the owner is not particularly observant or if the pet eats table food. Likewise, a complete dietary history may be impossible to obtain if pets are given treats by the neighbors, are coprophagic, eat another pet's food, or are outdoor predators. It is important to raise all these possibilities when interviewing the client before test diet selection. It is also helpful to ask the client to present labels from the pet's foods,

medications and treats or to maintain an inter-office binder that contains ingredient labels from popular dog and cat food products. After a dietary history has been obtained, an appropriate trial diet is selected.

11. What test diets are available for diagnosing food allergy?

A home-cooked diet composed of a single protein source and a single carbohydrate source is considered to be the "gold standard." Home cooking reduces the potential for food antigen changes associated with commercial processing procedures, the use of additives, or contamination with other proteins at the factory. Unfortunately, home cooking requires considerable effort on the part of the owner. Not only are some novel protein sources (duck, rabbit, venison, elk, horse) more difficult to purchase in large quantities on a reliable basis, some of these foods tend to be expensive. Lamb is typically more accessible than other "specialty" meats, but as a rule, lamb is avoided because it is likely to have been fed, often unwittingly, as part of a dog's (and with increasing frequency, cat's) growth or adult maintenance diet. Concern is also often raised regarding the feeding of an unbalanced diet for the test period. In a healthy adult animal, this is unlikely to be a problem. In a young, growing animal, however, 10-12 weeks of dietary imbalance may be inappropriate. Dogs and cats on an elimination diet trial, particularly with a home-cooked diet, are weighed at regular intervals to ensure that their caloric requirements are being met.

When home cooking is impractical or inappropriate, a balanced commercial diet is selected. Several diets are currently marketed specifically as test diets. The author prefers to use novel whole protein and whole carbohydrate diets when possible. Several hydrolysate diets are currently being marketed for use in the dog and cat. These diet formulations are based on data in humans that suggest food molecules less than 8,000-12,000 Daltons are hypoallergenic. As this information is extrapolated from human to veterinary patients, we await the publication of data specific to the dog and cat before recommending these foods on a broad basis. Currently, dietary selection remains a case-by-case assessment.

The premise for selecting any one of these diets is the same—find a food with a few, simple ingredients that are novel to the pet in question. Next, ensure that the pet will eat the diet. Owners should be warned about the perils of inappetence, particularly in the cat, and instructed to notify the veterinary office immediately if any animal will not eat the test diet.

12. What is the most difficult part of an elimination diet trial?

Clearly the most difficult aspect of conducting a diet trial is obtaining and maintaining client compliance for the entire test duration. Clients may be reluctant to begin a diet trial because previous changes in food brands have resulted in little or no improvement. In these cases, the difference between changing brands and changing protein sources must be carefully explained. Many commercial diets look, smell, and probably taste substantially different, yet on careful inspection of the ingredient label, these diets share common protein and carbohydrate sources. Changing manufacturers does not necessarily mean changing antigens. Many clients are deceived by label claims of "lamb and rice" diets with lamb as the first ingredient, but these diets may also contain fish meal and other protein sources. These are not diets that are suitable for food trials.

Excellent client compliance can usually be obtained by explaining the purpose and importance of the restrictive food trial. Clients should be informed that their pets cannot eat any other foods, treats, chew toys or flavored medications for the duration of the test. Unflavored, injectable or topical heartworm prophylaxis is used. Routine contact is maintained with the patient and client during the test period. This can be in the form of telephone follow-ups with a veterinary technician or assistant, regular weigh-ins, and/or re-evaluations for the treatment of any concurrent or secondary dermatoses.

13. How is food allergy definitively diagnosed?

The elimination diet trial is strongly suggestive of food allergy when the patient's clinical

signs resolve or improve by 50-75% without other ongoing medical support. A return of clinical signs upon dietary challenge is necessary to confirm a food allergy. This is accomplished by adding the original diet, and eventually any routine table foods or treats, to the test diet followed by careful observation for up to 14 days. If the clinical signs do not recur, food allergy has not been confirmed. If the clinical signs do recur, food allergy is confirmed. Upon provocation, the original diet is immediately removed, and the test diet alone is fed until the clinical signs resolve (usually within a few days to weeks). Time to recurrence of clinical signs is controversial. Many dermatologists report that a short time to recurrence (15 minutes to 4 days) is suggestive of a true immunologically based mechanism. Later responses are more likely to reflect a non-immunologically based reaction. Regardless, the dog's clinical response is the same.

14. What happens after a food allergy is diagnosed?

After food allergy is confirmed, the owner has three feeding options: 1) continue feeding a balanced but severely restricted diet, 2) trial and error with commercially available diets, or 3) feeding "basic" foods individually. Trial and error involves selecting commercially available maintenance diets that have relatively few label ingredients. Feeding basic foods involves feeding one new protein or carbohydrate source every 2 weeks, mixed gradually into the test diet. The basic foods selected will depend on the pet's previous diet, but common offending allergens should be considered. Some of the most frequent allergens in the dog are beef, soy, chicken, milk/dairy, corn, wheat, and egg. The three most commonly implicated food allergens in the cat are cow's milk, beef, and fish. The list of provocative foods is likely to vary somewhat in the future as some products lose and others gain popularity on the pet food market. The average number of dietary allergens for dogs and cats remains controversial, with some sources citing only one food while others suggest an average of two to three and in some individuals, up to five. Hence, clients are encouraged to test numerous basic foods before electing to transfer to a commercially available diet and practice antigen avoidance.

15. What is the prognosis for food allergy in the dog and cat?

The prognosis is good, provided that constant vigilance is maintained and the offending food allergens are avoided. Clients must understand that dietary avoidance is a means of control and not cure. Re-introduction of an allergen results in recurrence of the clinical signs. The likelihood of developing an allergy to a new food is unknown at this time, although many veterinary dermatologists agree that it is a possible but uncommon occurrence.

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26. CONTACT HYPERSENSITIVITY

Rosanna Marsella, DVM, DACVD

1. What is a hypersensitivity?

Hypersensitivity is an altered state of immune reactivity. The normal function of the immune system is the discrimination between self and non-self and the protection of the organism from noxious substances. Hypersensitivity occurs when the immune system starts attacking inoffensive materials, such as pollen or itself. There are many different types of hypersensitivities. Allergies are one manifestation of hypersensitivity.

2. What is a contact hypersensitivity?

Contact hypersensitivity is a type of delayed reaction, mediated by cells called T lymphocytes. T lymphocytes are very important in the cell-mediated immune response. There are several subpopulations of T lymphocytes. They include helper cells, suppressor cells, and memory cells. In contact hypersensitivity, T helper cells are exposed to the antigen (e.g., plant material) through professional antigen-presenting cells called Langerhans cells. These cells are able to capture the offending substance that has come in contact with the skin and digest it in a way that can be processed by T cells. The information is then processed and memorized by T cells. At this stage of the disease, no clinical signs are evident (incubation period or sensitization phase). Repeated exposure to the same substance is necessary for sensitization to occur. After sensitization has been completed, the next time that the same substance is encountered, an immune reaction is triggered and T cells release mediators called cytokines, which cause the development of an inflammatory reaction against the offending substance.

3. What is an antigen?

An antigen is a substance capable of inducing a detectable immune response.

4. What is an allergen?

Allergens are antigens able to induce an allergic reaction.

5. What is a hapten?

A hapten is a substance that is not immunogenic by itself but needs to bind to a larger carrier molecule to become antigenic and trigger an immune response. Haptens are often called incomplete antigens due to their low molecular weight. In cases of contact hypersensitivity, most of the molecules responsible for clinical signs are haptens.

6. How long does sensitization last?

The length of sensitization is variable and, in animals, this period can range from a couple of months to several years.

7. After the sensitization period is completed, how quickly do clinical signs develop upon re-exposure to the offending substance?

Clinical signs have a delayed onset. It takes an average of 24-48 hours before the symptoms become evident. This latent period can be as short as a few hours in highly sensitized individuals, and as long as 5 days in very mild cases.

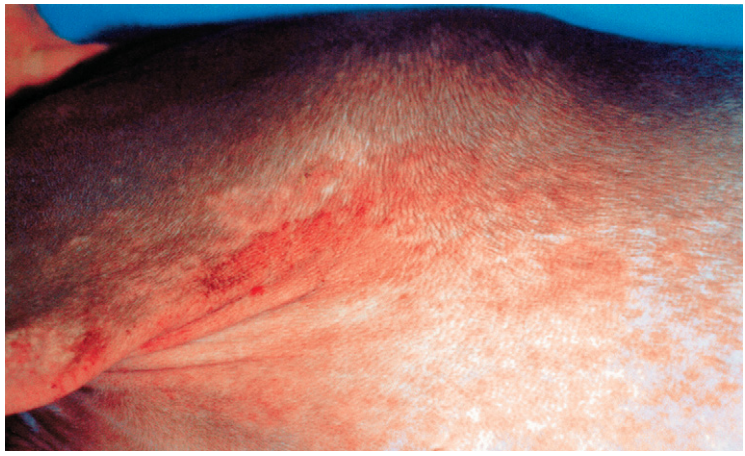

Figure 26-1 Papular and macular lesions on the ventrum of a dog with contact hypersensitivity.

8. How does contact hypersensitivity manifest in animals?

Intense pruritus and a papular eruption are the initial manifestation of the disease (Figures 26-1 to 26-3). As trauma of the skin occurs (due to scratching), secondary infections, lichenification (increased thickness of the skin), and hyperpigmentation (increased pigmentation) develop.

9. What is a papular eruption?

Papules are red firm lesions, resembling little insect bites. They develop into pustules when they become filled with opaque liquid (pus).

10. What are the differences between contact allergy and atopic dermatitis?

Contact allergy is a type IV hypersensitivity (cell-mediated, delayed hypersensitivity at 24-48 hours after exposure), while atopic dermatitis is thought to be a type I hypersensitivity (IgE-mediated, immediate reaction at 15 minutes and late phase reaction at 4-6 hours following exposure). From the clinical standpoint, the two diseases may look very similar, manifesting with pruritus, and erythema primarily affecting face, feet, and ears. One clinical difference is that contact allergy manifests with a primary papular/pustular eruption, whereas in atopic dermatitis the presence of papules usually is related to the presence of a secondary bacterial folliculitis.

11. What are the common causes of contact hypersensitivity in people?

Virtually any chemical can cause contact hypersensitivity. In humans, topical medications, such as neomycin and benzocaine, are common sensitizers. Plants can also cause disease—poison ivy is the most common plant responsible for contact hypersensitivity in people. Finally, metals, such as nickel and gold, are often responsible for contact hypersensitivity.

12. What are the common causes of contact hypersensitivity in dogs?

In dogs, shampoos, insecticides, topical medications, and plants have been reported to cause contact allergy. The plants most commonly responsible are plants belonging to the family of the Commelinaciae (Figure 26-4) and jasmine. These plants are quite common in the Southeastern United States. Other reported contact allergens in the dog include plastic, detergents, wool, synthetic rugs, and fertilizers.

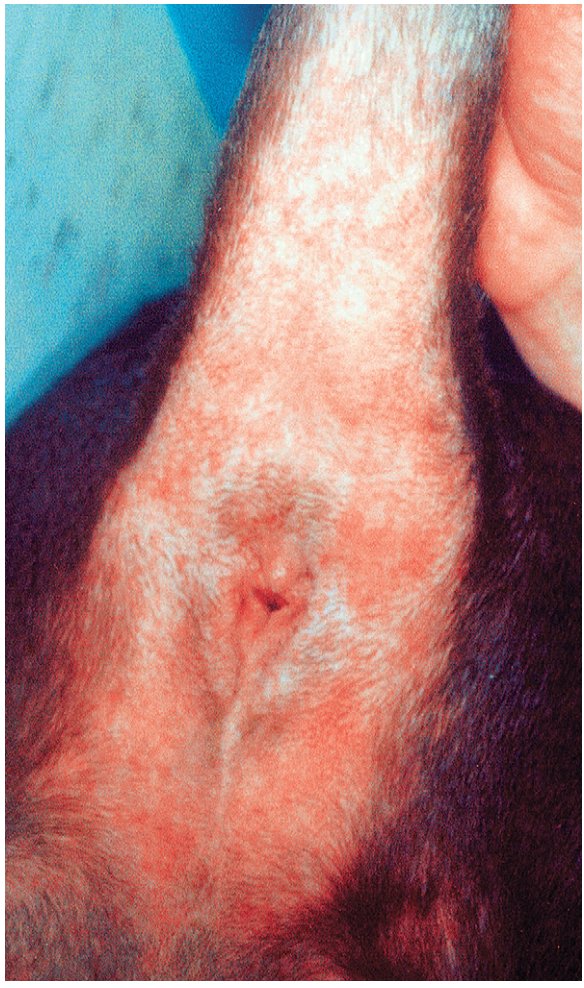

Figure 26-2 Papular rash in the perineal region resulting from contact hypersensitivity.

13. How common is this disease in small animals?

It is not very common. It is estimated to affect from 1% to 10% of companion animals. It seems to be more common in humid tropical climates, possibly because of the increased exposure to plants that have the potential of causing this disease or because of the concomitant occurrence of other forms of allergies (e.g., flea allergy and atopic dermatitis).

14. Do animals develop reactions to poison ivy?

Animals are allergic to other plants but are rarely allergic to poison ivy, which is a common cause of problems for humans.

15. How can I differentiate between an irritant reaction and an allergic reaction?

Irritant reactions do not require prior sensitization; therefore, symptoms rapidly develop at the first exposure to the offending substance. Furthermore, when multiple animals are exposed to

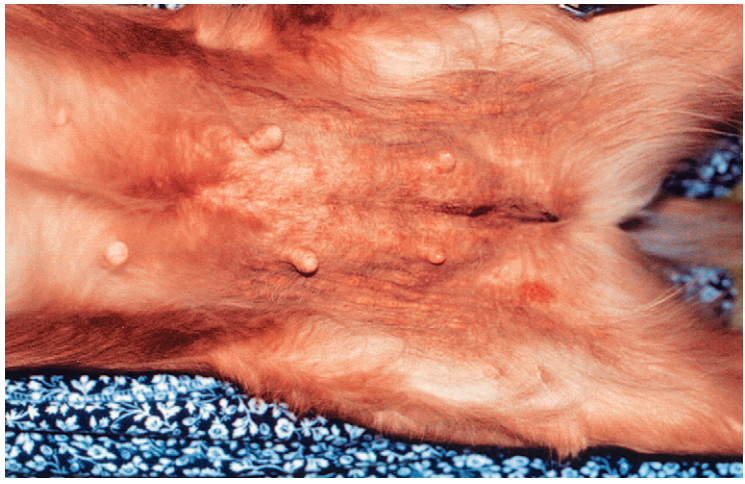

Figure 26-3 Papules, lichenification, and hyperpigmentation of the ventrum from chronic exposure to a contact allergen.

Figure 26-4 Leaves of the *Commelina* plant, a common cause of contact hypersensitivity reactions in dogs.

irritant substances, reactions develop in all individuals as opposed to allergic reactions, which only develop in the sensitized ones.

16. How long do symptoms persist after the last contact?

Resolution, after avoidance of the offending substance, may take 7-10 days.

17. Can the reaction be transferred from one part of the body to another?

Yes. The offending material can be transferred from the area of initial exposure to other parts by scratching, thereby triggering an inflammatory response in various body locations.

18. Is it contagious?

No. Contact hypersensitivity is an individual reaction that occurs only in previously sensitized patients.

19. Can contact hypersensitivity be prevented?

No. Unfortunately, there is no prevention for the development of sensitization. In humans, contact hypersensitivity is more common in patients with chronic skin diseases; therefore it is believed that abrasions and repeated minor trauma may facilitate the development of contact allergy. Development of clinical signs (elicitation), however, may be prevented by pre-medication with oral pentoxifylline 48 hours before exposure to the offending substance in individuals that are already sensitized. The efficacy of pentoxifylline has been tested in both dogs and people and the response was found to be satisfactory.

20. What are possible risk factors for this disease?

Very little is known about risk factors of contact hypersensitivity in companion animals. It appears that dogs with concurrent allergies, such as atopic dermatitis, may develop contact hypersensitivity more frequently, possibly because of the impaired barrier function of the skin. To date, there are not sufficient data to suggest a genetic component for contact hypersensitivity in dogs. No breed or gender predilection has been identified in companion animals.

In humans, males are at increased risk for contact hypersensitivity. Application of the agent to extensive parts of the body, at high concentrations, when the skin is inflamed or otherwise damaged, in a repetitive fashion, and under occlusion, facilitate the development of this hypersensitivity.

21. Is there any blood test that can be done to identify individuals at risk?

No. This disease is limited to the skin and it is not detectable in the blood.

22. How is contact hypersensitivity diagnosed?

It is diagnosed by complete resolution of clinical signs with avoidance and recurrence of signs with re-challenge. Once contact allergy is suspected, patch testing with individual substances can be done to identify the offending allergen. In a patch test, a small amount of the substance is applied directly onto the skin and contact is allowed for 24 hours. After that time, the skin is examined for the presence of pruritic papules (positive reaction).

23. Does it help to take a biopsy to make a diagnosis?

Biopsies may help to support a clinical suspicion but they are rarely of diagnostic significance by themselves.

24. Can contact hypersensitivity be "cured"?

No. There is no cure for this disease. Avoidance is the best long-term solution for contact hypersensitivity. All the treatments available on the market target the suppression of the symptoms but do not represent a cure for the disease.

25. Which drugs can be used to improve the symptoms of contact hypersensitivity?

Steroids are highly effective to decrease pruritus and papules. They can be used orally and topically. Adverse effects of systemic steroids include increased thirst (polydipsia) and increased urination (polyuria). Chronic use of steroids will also predispose to the development of secondary skin and urinary tract infections. Topical steroids may also induce decreased thickness of the skin (cutaneous atrophy). Besides steroids, other drugs are useful in decreasing the signs of contact allergy. In 2001, a strong immunomodulator, similar to cyclosporine, was introduced in the United States. It is called tacrolimus and is formulated as an ointment (Protopic). It has the advantage of not causing skin atrophy after topical application and is highly effective in decreasing the signs of contact dermatitis.

26. Do antihistamines work for this type of allergy?

Unfortunately, because this disease is not histamine-mediated, antihistamines do not provide

relief. Antihistamines are mainly used for allergies that have an immediate reaction (e.g., pollen allergies).

27. Does allergy vaccine work for this type of allergy?

Individuals with atopic dermatitis (e.g., pollen allergies) often benefit from an allergy vaccine (hyposensitization). Unfortunately, hyposensitization does not provide relief for contact hypersensitivity (Table 26-1).

Table 26-1 ***Differentiation of Contact Hypersensitivity and Atopic Dermatitis***

VARIABLE	CONTACT HYPERSENSITIVITY	ATOPIC DERMATITIS
Route of allergen access	Percutaneous	Percutaneous Inhalation?
Type of hypersensitivity	Type IV (mediated by lymphocytes, delayed reaction at 24-48 hr)	Type I (mediated by IgE, immediate reaction at 15 min, late phase reaction at 4-6 hr)
Incidence	Uncommon	Common (up to 10% of canine population)
Clinical signs	Pruritus Primary papular/pustular eruption Erythema	Pruritus Primary erythema Papules are secondary to development of pyoderma
Distribution of lesions	It depends on the offending substance	Face, feet, ears, axillae, groin
Diagnosis	Resolution of signs with avoidance and relapse with re-challenge Patch test	Clinical signs, history, exclusion of other pruritic skin diseases Positive serology or intradermal skin testing is considered a secondary criterion
Therapy	Glucocorticoids Pentoxifylline Tacrolimus No response to antihistamines, essential fatty acids, and hyposensitization	Glucocorticoids Pentoxifylline Tacrolimus Cyclosporine Moderate response to antihistamines, essential fatty acids, 70-80% success with hyposensitization

28. Does contact allergy improve with age?

No. Unfortunately, this allergy tends to get worse with age and with repetitive exposure.

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27. FLEA ALLERGY DERMATITIS

Diane E. Bevier, DVM, DACVD

1. What is flea allergy dermatitis?

Flea allergy dermatitis (FAD) is the development of pruritic skin disease in the dog or cat associated with allergic hypersensitivity to the saliva injected by the bite of the flea.

2. Does dermatitis develop in all dogs and cats exposed to fleas?

No, but dermatitis rarely occurs in the absence of an allergic hypersensitivity reaction.

3. How important a problem is flea allergy dermatitis?

In many areas of the United States, fleas and flea-related diseases account for greater than 50% of dermatologic cases presented to veterinarians.

4. What is the most common flea species to parasitize dogs and cats?

Ctenocephalides felis is the most common flea species to parasitize dogs and cats.

5. What other species of fleas parasitize dogs and cats and how common are they?

- *Ctenocephalides canis* is rarely isolated from dogs and cats in the United States.
- *Pulex irritans* is found frequently on dogs, but seldom on cats.
- *Echidnophaga gallinacea* parasitizes both dogs and cats.

6. Are fleas host-species specific?

No. *C. felis* is the least host-specific flea.

7. What is the immunopathogenesis of flea allergy dermatitis? (i.e., Why do some dogs and cats become flea allergic?)

Numerous studies on the immunopathogenesis of FAD in guinea pigs, humans, and dogs have been published, with lesser research available on the disease in cats. Saliva from the flea *Ctenocephalides felis* contains numerous allergenic proteins. Cfe11 is a high-molecular-weight protein in flea saliva and may be the major allergen in dogs. In the dog, FAD is due to an

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6. Are fleas host-species specific?

No. *C. felis* is the least host-specific flea.

7. What is the immunopathogenesis of flea allergy dermatitis? (i.e., Why do some dogs and cats become flea allergic?)

Numerous studies on the immunopathogenesis of FAD in guinea pigs, humans, and dogs have been published, with lesser research available on the disease in cats. Saliva from the flea *Ctenocephalides felis* contains numerous allergenic proteins. Cfe11 is a high-molecular-weight protein in flea saliva and may be the major allergen in dogs. In the dog, FAD is due to an

immediate type I hypersensitivity reaction with both a late-phase reaction and a delayed cutaneous basophil hypersensitivity reaction. In the cat, some authors report only immediate intradermal reaction to the flea, whereas others also mention delayed reactions.

Intermittent exposure to flea bites can cause the development of positive skin test reactions within 12 weeks and flea-specific IgE and IgG antibody development. Delayed and intermediate hypersensitivity reactions develop in a random sequence. Continual exposure of dogs to flea bites results in failure to develop hypersensitivity or delayed development of a lesser degree of hypersensitivity.

8. What are the important allergens that cause flea allergy dermatitis?

The allergens are contained in the flea saliva and include a low-molecular-weight hapten, and at least two additional allergens of greater than 20,000-dalton molecular weight.

9. Do dogs and cats that have other allergic disease show a greater incidence of flea allergy dermatitis?

Yes, a greater percentage of dogs and cats with atopy are also allergic to fleas.

10. Do certain environmental conditions favor fleas and the development of flea allergy dermatitis?

Yes, a moist, warm environment with a relative humidity of 75% to 85% and a temperature of 65 to 80° F is most favorable for the rapid completion of the life cycle of the flea.

11. When considering the life cycle of fleas, what factors are critical to achieve effective control of the fleas?

The entire flea life cycle may be as short as 16 to 21 days under optimal conditions or as long as a year when unfavorable conditions prevail. After hatching, the adult flea immediately searches for a host. The flea is attracted to the host by the increase in carbon dioxide levels from the breath of the host and changes in light intensity caused by the host. The entire life span of the flea ranges from 6 to 12 months. Adult fleas in humid environments can live from 4 to 12 months without nutrition.

12. What determines the severity of the clinical signs associated with flea allergy?

The dermatologic and other clinical signs related to flea allergy depend on the degree of immunologic sensitivity and the level of flea exposure.

13. At what age does flea allergy dermatitis develop?

Flea allergy dermatitis may develop at any age in the dog or cat, but it is rare to see an affected animal younger than 6 months old. The most common age of onset is 3 to 6 years.

14. Are there gender or breed predilections associated with flea allergy dermatitis?

No gender or breed predilections have been reported in FAD. There may be an increased incidence of FAD in long-haired dogs.

15. Is flea allergy dermatitis a seasonal disorder?

FAD is a seasonal disorder in areas with cold winters, with the most severe infestation and clinical signs seen in summer and fall. In warm climates, or where household infestation persists, flea infestation and FAD may be non-seasonal problems.

16. What are clinical signs of FAD in the cat?

Clinical signs in the cat include:

Flea-infested cats without hypersensitivity may appear asymptomatic.

Flea-bite dermatitis may cause mild-to-moderate pruritus and lesions associated with

scratching. Small crusts (miliary dermatitis: see Chapter 28) are located primarily on the head, neck, and dorsum of the body; papules may be located on the abdomen.

The primary lesion in cats with FAD is an erythematous papule covered by a small reddish-brown crust (Figure 27-1). Lesions are usually most severe on the neck, head, and dorsal lumbosacral regions but have a tendency to generalize. The degree of alopecia is highly variable.

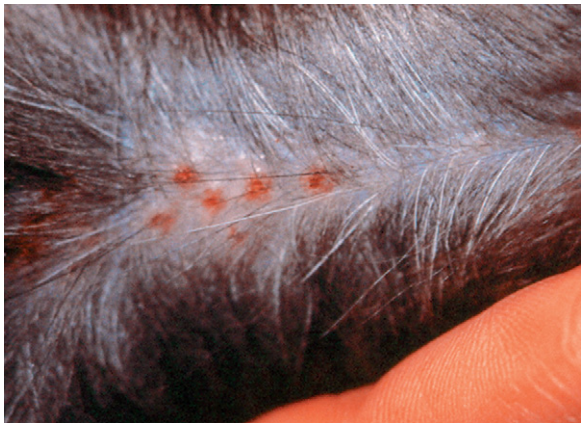

Figure 27-1 Miliary dermatitis lesions in a cat with flea allergy dermatitis.

Localized or generalized patchy or confluent alopecia with associated mild-to-severe underlying dermatitis may also be seen in cats with FAD.

17. How do cats demonstrate that they are pruritic?

Cats manifest moderate-to-severe pruritus by licking, scratching, chewing, shaking of the head, ripping hairs out, rippling of the skin on stimulation, or turning and violently attacking areas of the skin without visible provocation.

18. What are additional non-dermatologic signs of feline flea infestation/allergy?

Additional clinical signs seen in the cat with flea bite dermatitis or FAD may include the finding of segments of *Dipylidium caninum* in the stool, the presence of gastric trichobezoars (e.g., hairballs), peripheral eosinophilia, anemia, and loss of weight or general condition due to pruritus and scratching combined with the anemia and intestinal parasitism.

19. What are clinical signs of FAD in the dog?

Clinical signs in the dog include:

Asymptomatic carriers of small to large numbers of fleas.

In non-sensitized individuals, response to bites is minimal and results in mild pruritus, seborrheic changes, and excoriations. Some individuals may have a staphylococcal folliculitis secondary to flea dermatitis.

In the dog with flea-bite hypersensitivity, the severity of the dermatitis is determined by the animal's immunologic status, flea burden, extent of self-trauma, other secondary lesions, duration of disorder, and previous therapy.

When the flea bites a hypersensitive dog, a small wheal develops at the site of the bite that either resolves, or if the animal has a delayed hypersensitivity response, develops into a papule that later crusts over.

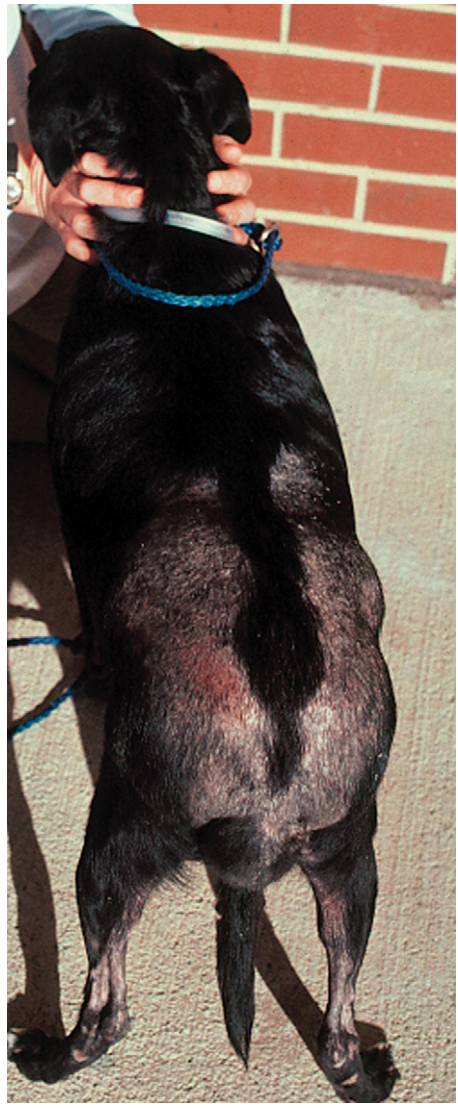

Figure 27-2 Flea allergy dermatitis in the dorsal lumbosacral area and caudal thighs in a dog.

The highly pruritic papulocrustous dermatitis is typically confined to the dorsal lumbosacral area, caudomedial thighs, ventral abdomen, flank, and neck (Figures 27-2 and 27-3).

In severely hypersensitive animals, generalized cutaneous signs may be seen.

Affected dogs show varying degrees of erythema, excoriation, and alopecia with stubbled hairs due to chewing and licking. Secondary seborrhea may be mild to severe and an offensive odor may be present.

Some animals experience recurrent episodes of acute moist dermatitis ("hot spots").

Long-standing pruritus and self-trauma may lead to marked secondary changes of acanthosis, hyperkeratosis, lichenification, and hyperpigmentation. Severely affected animals may develop redundant folds of skin over the caudal back and caudomedial thighs.

Figure 27-3 Close-up view of the skin of a dog with flea allergy dermatitis.

Staphylococcal folliculitis may accompany FAD.
Fibropruritic nodules are sometimes associated with FAD; these are most commonly found in the lumbosacral region of flea-allergic German Shepherd Dogs.

20. What are additional non-dermatologic signs of canine flea infestation/allergy?

Additional systemic signs may include findings of *Dipylidium caninum* segments in the stool, peripheral eosinophilia (observed in 13 to 20% of dogs and cats with FAD), anemia, and loss of weight or general condition due to the pruritus and scratching.

21. How is the diagnosis of FAD made?

History and clinical findings.
Do not abandon the diagnosis if fleas are not present at the time of examination (especially in cats due to arduous grooming!).
It may be difficult to locate fleas or excreta on a flea-allergic cat because of fastidious grooming habits.
Examine the animal carefully for fleas, especially on the ventrum and the perineal region. Use a fine-toothed metal comb (flea comb, 32 teeth/inch) to help pick fleas or flea excreta out of the coat.
Intradermal skin testing with flea antigen (whole-body flea) at 1:1000 and 1:4000 dilutions, with reactions evaluated immediately and for delayed reactivity (48-72 hours).

22. Is there a blood test available for the diagnosis of FAD in the dog or cat?

There is an excellent new enzyme-linked immunosorbent assay (ELISA) test offered by the HESKA Corporation (Ft. Collins, CO) that measures IgE directed against flea saliva. All other available tests measure IgE against whole flea extracts, which contain less than 0.5% flea saliva.

23. Can skin biopsy and dermatohistopathology help in the diagnosis of FAD?

Skin biopsy is non-diagnostic and reveals perivascular dermatitis with eosinophils seen as the predominant cell type. Other findings include intraepidermal eosinophilic microabscesses and pathology consistent with secondary pyoderma and seborrhea.

24. What differential diagnoses must be considered in evaluating a case of FAD?

Differential diagnoses include atopy, food hypersensitivity, drug hypersensitivity, intestinal parasite hypersensitivity, and folliculitis in the dog. In the cat, differential diagnoses include

cheyletiellosis, dermatophytosis, food hypersensitivity, trombiculiasis, parasite hypersensitivity, drug hypersensitivity, bacterial folliculitis, atopy, and idiopathic miliary dermatitis.

25. How can FAD be differentiated conclusively from atopy?

Atopy can only be conclusively differentiated from FAD with ELISA and/or complete intradermal skin testing. Many animals have both conditions.

26. What are the treatments available for FAD?

Treatment for FAD involves controlling the fleas on the animal and in the environment and treatment for the inflammatory dermatitis, secondary seborrhea, and pyoderma. Parasiticides and symptomatic management of pruritus are covered in the chapters on dermatologic therapy.

27. Are there ways in which the therapy for FAD differs from other allergic dermatitides?

In general, FAD is non-responsive to antihistamine and fatty acid therapy. If the fleas are not controlled, response to corticosteroids may also be poor.

28. What about immunotherapy for FAD?

The most recent advance in therapy is an excellent double-blind placebo-controlled study evaluating the use of flea saliva immunotherapy in flea-allergic dogs at Ohio State University (Kwochka et al.). In a population of 21 dogs with FAD, this study showed that rush immunotherapy using a proprietary mixture of flea salivary antigens controlled clinical lesions and pruritus significantly better than a placebo. This response was verified during controlled experimental flea challenge. At the current time, therapy using native flea salivary antigens is cost-prohibitive and should be considered experimental, but, to my knowledge, this is the first study to show efficacy, using immunotherapy, in naturally occurring canine FAD.

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28. MILIARY DERMATITIS

Diane E. Bevier, DVM, DACVD

1. What is miliary dermatitis?

Miliary dermatitis (MD) is a cutaneous reaction pattern seen in the cat characterized by variable degrees of a pruritic, papulocrustous dermatitis (Figures 28-1 and 28-2). Feline MD is not a single disease, but rather a disease complex. There are a number of specific diseases that can cause this characteristic eruption (Table 28-1).

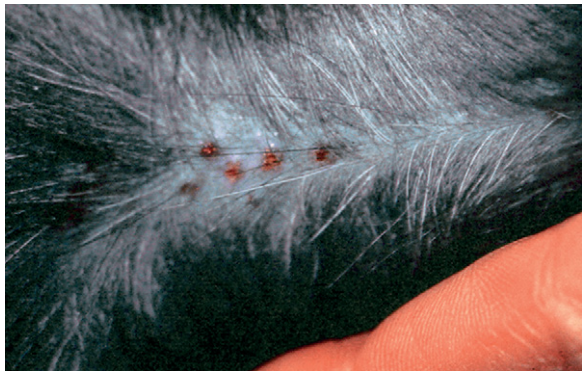

Figure 28-1 Lesions of miliary dermatitis on the back of a cat with flea allergy dermatitis.

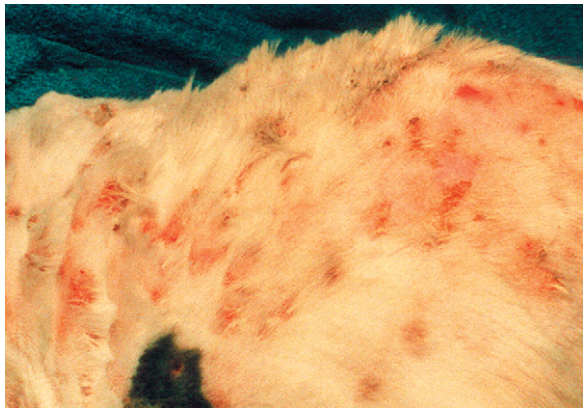

Figure 28-2 Generalized miliary dermatitis on the back of a cat with cheyletiellosis.

Table 28-1 ***Miliary Dermatitis (Papulocrustous Dermatitis) in the Cat: Differential Diagnosis***

Ectoparasitism	Fleas
	Cheyletiellosis
	Otodectic mange
	Pediculosis
	Demodicosis
	Notoedric mange
	Trombiculiasis
	Cat fur mite
Hypersensitivity reactions	Flea allergy dermatitis
	Atopy
	Food hypersensitivity
	Mosquito bite hypersensitivity
	Intestinal parasite hypersensitivity
	Pemphigus foliaceus
	Pemphigus erythematosus
	Feline hypereosinophilic syndrome
	Cutaneous drug reaction
Infectious	Dermatophytosis
	Staphylococcal folliculitis
	Viral dermatitis: herpes/calicivirus
Dietary imbalance	Biotin deficiency
	Fatty acid deficiency
Neoplastic	Mast cell tumors
Idiopathic	

2. Why is the dermatitis called miliary?

The dermatitis is called miliary because the small crusted lesions are thought to resemble millet seeds.

3. Which species get miliary dermatitis?

The cat is the primary species that develops miliary dermatitis.

4. What is the incidence of miliary dermatitis in the cat?

- To get an idea of the incidence of varying types of dermatitis and underlying causes in the cat, the best statistics are those resulting from an American Academy of Veterinary Dermatology joint study that included eight institutions and private practices in the United States, England, and the Netherlands and looked at the absolute and relative incidence of skin diseases in 800 cats. The percentage incidence of the various causes of dermatitis in these cats was as follows: parasitic 22.1%, miliary dermatitis 10.5%, eosinophilic granuloma complex 9.9%, endocrine 9.5%, fungal 7.3%, allergic 6.4%, bacterial 6.1%, neurodermatitis 4.5%, seborrhea 4.4%, idiopathic pruritic dermatitis 4.3%, neoplastic 3.3%, contact dermatitis 2.3%, autoimmune 1.4%, and other 8.0%. With the exception of endocrine disorders, all these diseases have the potential to be pruritic.
- Note that many of the other diagnoses can show dermatitis characterized as a miliary dermatitis.
- In another study at the New York State College of Veterinary Medicine (NYSCVM), MD was the most common cutaneous reaction pattern. In a 2-year study conducted at the NYSCVM, miliary dermatitis counted for 38.1% of the feline dermatologic cases examined.

The most common causes of feline MD in this study were fleabite hypersensitivity (54.9% of the total), atopy (12.1% of the total), food hypersensitivity (10.6%), bacterial folliculitis (3.9%), and otodectic mange (3.1%).

5. **Is there any age, breed, or gender predilection for the development of miliary dermatitis?**
MD occurs in any breed, age, or gender of cat, irrespective of neutering.

6. **Are there certain areas of the body that are more likely to be affected with miliary dermatitis?**
The primary area(s) of the body affected by MD depends on the underlying cause (Table 28-2). Skin lesions often begin over the dorsum of the cat (tailhead, head, and neck) but can become generalized.

Table 28-2 ***Areas of the Body Affected by Miliary Dermatitis: Regional Diagnosis***

REGION	DISEASE
Head and ears	Otodectic mange
	Demodicosis
	Food hypersensitivity
	Dermatophytosis
	Mosquito bite hypersensitivity
	Notoedric mange
	Trombiculiasis
	Pemphigus foliaceus
	Pemphigus erythematosus
	Mast cell tumors
	Viral dermatitis: herpes/calicivirus
	Biotin deficiency
Oral cavity and mucocutaneous junctions	Cutaneous drug reaction
	Viral dermatitis: herpes/calicivirus
Chin and neck	Flea allergy dermatitis
	Biotin deficiency
Trunk	Flea allergy dermatitis
	Feline hypereosinophilic syndrome
	Fatty acid deficiency
	Intestinal parasite hypersensitivity
	Biotin deficiency
Dorsum	Cheyletiellosis
	Pediculosis
	Flea allergy dermatitis
	Trombiculiasis
	Cat fur mite
	Staphylococcal folliculitis
Ventrum	Atopy
	Trombiculiasis
Legs and paws	Mosquito bite hypersensitivity
	Biotin deficiency

7. **Is miliary dermatitis pruritic?**
MD is variably pruritic. The degree of pruritus is not necessarily related to the number and type of lesions. Also, the underlying cause may influence the degree of pruritus.

8. Is miliary dermatitis seasonal?

MD may be seasonal if the underlying cause is atopy, flea allergy, pediculosis, or mosquito bite hypersensitivity; or non-seasonal if due to food allergy, dermatophytosis, bacterial folliculitis, or endoparasitism.

9. What other historical aspects of the cat's miliary dermatitis may help discover the underlying cause?

If other animals and/or human contacts are affected, it suggests a contagious cause such as fleas, cheyletiellosis, lice, and dermatophytosis.

A history of poor response to glucocorticoids may suggest idiopathic MD, dermatophytosis, bacterial folliculitis, food allergy, or drug eruption.

10. What diagnostic tests should be done to diagnose the underlying cause of miliary dermatitis?

Because of the myriad of potential causes for MD, diagnostics would include those as listed below (Table 28-3). History and physical examination findings may suggest other underlying causes that should be investigated.

Table 28-3 ***Diagnostic Tests Recommended in MD Cases***

REACTION PATTERN	ALL PRURITIC CATS	PRIMARY HEAD AND FACE MD AND PRURITUS	MILIARY DERMATITIS	CRUSTING/ SCALING
Diagnostic test				
Physical examination	X	X	X	X
CBC count and profile	X	X	X	X
Skin scraping	X	X	X	X
Fecal examination	X	X	X	X
Dermatophyte culture	X	X	X	X
Tape preparation			X	X
KOH digestion			X	X
Flea I.D. test/Flea saliva ELISA		X	X	X
Trial flea control	X		X	X
Hypoallergenic diet		X	X	X
I.D. skin test		X	X	X
Antibiotic trial		X	X	
Skin biopsy		X	X	X
Histopathology		X	X	X
Immunofluorescence		X		
Antinuclear antibody		X		X
Urinalysis		X	X	X
Ear swab: mites		X	X	
Ear swab: Gram stain		X	X	
Ear swab: culture and sensitivity		X	X	
Ear mite Rx trial		X	X	
Cytology under crust		X	X	
Culture and sensitivity		X	X	

CBC, Complete blood cell; *ELISA,* enzyme-linked immunosorbent assay; *I.D.,* identification; *KOH,* potassium hydroxide.

11. Can dermatohistopathologic studies help distinguish the various causes of miliary dermatitis?

The histopathologic findings in MD of idiopathic, food allergy, drug eruption, or *Cheyletiella* spp. origins are very similar and are characterized by subacute to chronic, nonsuppurative dermatitis, with variable numbers of neutrophils, mast cells, and mononuclear cells. Histopathologic findings in MD of flea, louse, or intestinal parasite origins are similar to the above, except that eosinophils are a major, if not the major, inflammatory cell component.

12. What is the treatment for miliary dermatitis?

- Treatment for MD involves identifying and treating the underlying cause(s) and management of the pruritus.
- Parasiticides and symptomatic management of pruritus are covered in the chapters on Dermatologic Therapy (Chapters 5 and 7).

13. How about adjunctive therapy and therapy for idiopathic miliary dermatitis?

- When entertaining the idea that a case of MD is idiopathic, it is imperative to rule out all the possibilities of underlying disorders in Table 28-1. Most important are a trial with flea control for a 2-month period and an antibiotic trial for a period of 3 weeks.
- If a case of MD is determined to be idiopathic, corticosteroids can be tried, although may be disappointing in some cases.
- Prednisone, prednisolone, and methylprednisolone given orally are ideal choices for long-term corticosteroid use in cats. Unfortunately, they are not as routinely effective in cats as in dogs. The recommended initial dose is 1.1 to 2.2 mg/kg every 12 hours until remission of clinical signs occurs. At that time, the dosage should be gradually tapered until a dosage of 0.5 to 1.0 mg/kg every 48 hours is reached. For cats in which prednisone or prednisolone is ineffective, oral methylprednisolone may be effective. Occasional refractory cases of pruritus in cats will require the use of a more potent, longer acting oral glucocorticoid such as oral dexamethasone or triamcinolone. Dexamethasone is given orally at a dosage of 0.05 to 0.1 mg/kg every 24 hours for 7 days followed by maintenance therapy twice weekly. Triamcinolone is given at 0.25 to 0.5 mg/kg every 24 hours for 7 days then two to three times weekly.
- Injectable corticosteroids are used frequently in cats. It is imperative to dose the cat using its correct body weight, rather than some of the recommended dosage-per-cat guidelines that are in the literature. Adult cats may vary from 3 to 10 kg in body weight; keeping this in mind is critical if one is to achieve expected therapeutic results. Methylprednisolone acetate is the most effective injectable corticosteroid for use in cats. It is dosed at 5 mg/kg subcutaneously. If a favorable response is noted, the injection should be repeated twice more at 2- to 3-week intervals. For long-term maintenance of miliary dermatitis cases, it is recommended that this drug not be given more frequently than every 8 weeks and preferably every 12 weeks. Alternatively, if methylprednisolone acetate injections have become ineffective, injectable triamcinolone at a dose of 0.25 to 0.5 mg/kg may be used. An excellent, short-lived anti-inflammatory response can be obtained with injectable dexamethasone given at 0.25 to 0.5 mg/kg subcutaneously.
- Antihistamines are also effective in some cats. Cats are not as predictable as dogs in response to these drugs and have shown greater problems with adverse behavioral reactions. One study demonstrated an excellent response in 73% of atopic cats to chlorpheniramine dosed at 2 mg/cat every 12 hours. Many other investigators have reported favorable response to this antihistamine, but not in as high a percentage of cases. Cats weighing more than 6 kg may be dosed at 4 mg every 12 hours. Hydroxyzine at 2.2 mg/kg every 12 hours also has been used, but will make an occasional cat aggressive and hyperactive. Clemastine, at the dose of 0.67 mg/cat orally every 12 hours, was shown to control pruritus adequately

in 50% of the cases treated. Side effects reported in cats with the use of antihistamines have included anorexia, vomiting, diarrhea, and excitement.

- Fatty acid supplements such as Derm Caps (DVM Pharmaceuticals) are helpful for some cats. Although fewer studies have been reported in cats than in dogs, non-placebo–controlled studies would suggest that 50% to 75% of treated cats have a good response to products containing omega-3/omega-6 fatty acids. The dosage is generally 1 capsule per cat per day. Nutritional supplements always should be given a minimum 6-week trial before being declared ineffective. Some cats may benefit from the possibly synergistic effects of combining fatty acids with chlorpheniramine or glucocorticoids. In general, the quantity of fatty acid should be increased gradually over a 2-week period to avoid the cat's tendency to reject dietary changes. Certainly, fatty acid supplements are an extremely safe way to help control pruritus and should be tried as an initial treatment with or without antihistamines.
- Although pyoderma is a less common cause of MD, an occasional cat will respond well to a 2- to 4-week course of appropriate anti-staphylococcal antibiotic therapy (such as Clavamox, Lincocin, cephalexin, or Tribrissen). An antibiotic treatment trial should be done especially in cats that start to require increasing dosages of corticosteroids to control their dermatitis or worsen after corticosteroid administration. Another indication that antibiotics are required is the finding of neutrophils and coccal bacteria on cutaneus cytologic evaluation.
- The progestational compound megestrol acetate can be a highly effective antipruritic and anti-inflammatory medication in cats. Remission of clinical signs is achieved with an oral dose of 2.5 to 5.0 mg/cat every 48 hours for 1 to 3 weeks followed by weekly maintenance doses. Megestrol acetate is not licensed for use in cats and has the potential to cause alarming side effects. These include polyphagia/weight gain, polyuria/polydipsia, personality and behavioral changes, pyometra or stump pyometra, mammary hyperplasia, mammary neoplasia, diabetes mellitus, and adrenal suppression. This drug should be reserved for cases that have become refractory to glucocorticoids, have had a trial of antibiotic therapy, and have owners who have been informed of the life-threatening risks these drugs may cause.

Topical therapy is not practical for the majority of cats but can be soothing and help to dry the lesions of MD. Some cats are helped by the use of 10% hydrogen peroxide on a cotton ball two to three times weekly. Although many cats resist bathing, for those that tolerate it, medicated baths may be very helpful. Products containing sulfur, benzoyl peroxide, or salicylic acid are acceptable for use in cats. Tar-containing products are potentially toxic to cats and should not be used. Use of a soothing, antipruritic shampoo and spray containing colloidal oatmeal, combined with the anesthetic agent pramoxine hydrochloride, may be beneficial.

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29. FELINE EOSINOPHILIC GRANULOMA COMPLEX

Christine A. Rees, DVM, DACVD

1. What is feline eosinophilic granuloma complex (EGC)?

This is a dermatologic term used to describe a skin problem in cats that involves several different syndromes. These syndromes consist of the indolent ulcer (eosinophilic ulcer, rodent ulcer), the eosinophilic plaque, and the eosinophilic granuloma (linear granuloma).

2. What is an indolent ulcer?

An indolent ulcer is a raised ulcerated lesion on a cat that occurs most commonly on the upper lip (Figure 29-1) but may also occur in the oral cavity. Although not as common, indolent ulcers have occasionally been reported to occur on other areas of the body.

Figure 29-1 Feline indolent ulcer on the upper lip of a cat's mouth.

3. What is an eosinophilic plaque?

A feline eosinophilic plaque is an erythematous, raised, flat, firm lesion on the skin. The plaques can be either single or multiple. These lesions most commonly occur on the abdomen (Figure 29-2) and medial thighs. Other affected areas may include the cornea and conjunctiva.

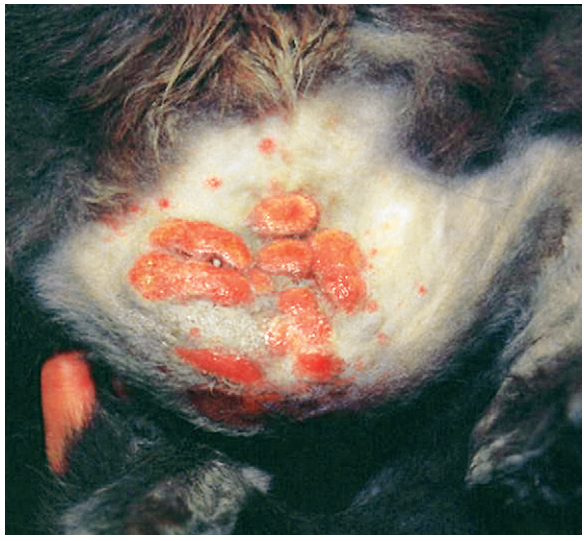

Figure 29-2 Eosinophilic plaque on a cat's ventrum.

4. What is an eosinophilic granuloma (linear granuloma)?

A eosinophilic granuloma consists of raised plaques that occur in a linear configuration. These lesions can sometimes become eroded or ulcerated. Eosinophilic granulomas most commonly develop on the caudal aspects of the cat's thighs (Figure 29-3) but may occur on the face and in the oral cavity.

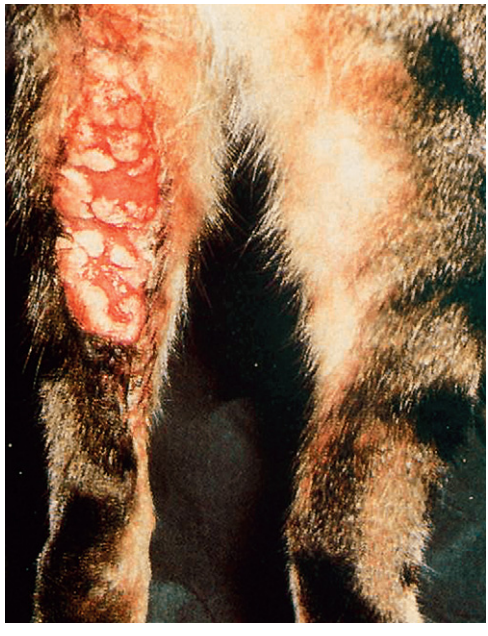

Figure 29-3 Linear granuloma down the back of a cat's leg.

5. What is the etiology of feline EGC?

Feline EGC has been associated with underlying allergies in cats. The types of allergies that have been associated with EGC are insect hypersensitivity (especially flea allergy), food allergy, and atopy. The term *idiopathic* is used if an underlying allergy cannot be found. This basically means that the cause for the cat having the EGC is not known.

6. Are there any other clinical signs other than skin lesions with feline EGC?

See Table 29-1.

Table 29-1 *Clinical Signs of Eosinophilic Granuloma Complex*

CLINICAL SIGNS	INDOLENT ULCER	EOSINOPHILIC PLAQUE	EOSINOPHILIC GRANULOMA
Pain	+/–	–	–
Pruritus	+/–	+++	–
Peripheral lymphadenopathy	–	+/–	+

+, Mild; ++, moderate; +++, severe; –, not present; +/–, may or may not be present.

7. What are the differential diagnoses for EGC?

The differential diagnoses for EGC are infectious ulcers (feline leukemia virus, feline immunodeficiency virus, bacterial, fungal), trauma, and neoplasia (squamous cell carcinoma, mast cell tumor, cutaneous lymphoma).

8. What is the most useful diagnostic test for diagnosing feline EGC?

The most useful diagnostic test for diagnosing ECG is a skin biopsy. The types of histologic lesions vary with the type of complex that is present and chronicity of the lesions.

- Indolent ulcer: For the indolent ulcer, the histologic findings include hyperplastic, ulcerated, superficial perivascular to interstitial dermatitis with eosinophils and mononuclear cells. Fibrosis usually occurs when the lesions become more prominent. Tissue eosinophilia is rare.
- Eosinophilic plaque: Tissue eosinophilia is common with eosinophilic plaques. A hyperplastic superficial to deep perivascular dermatitis with eosinophils is usually seen. An interstitial to diffuse eosinophilic dermatitis will also be present. Flame figures may be seen. Some cases of eosinophilic plaque will also have microvesicles or microabscesses, which contain eosinophils.
- Eosinophilic granuloma: A nodular to diffuse granulomatous dermatitis with multifocal areas of collagen degeneration is usually seen with eosinophilic granulomas. Eosinophils and multinucleated histiocytic giant cells are common. Flame figures are possible. Mucinosis of the epidermis and hair follicle of the outer root sheath is also common. Focal eosinophilic folliculitis or furunculosis and panniculitis can occur. The eosinophils appear to be less prominent in chronic lesions.

9. What are flame figures?

A flame figure consists of a bundle of altered collagen that is surrounded by eosinophils and eosinophilic granules. These lesions often resemble the shape of a starburst or have a flame shape. The eosinophilic material can be either granular or amorphous. The canine and feline dermatologic conditions that most commonly have flame figures as a histopathologic finding are eosinophilic granulomas, insect and arthropod reactions, eosinophilic panniculitis, and eosinophilic pustulosis.

10. How do you diagnose a flea allergy in a cat?

Flea allergy in a cat can be diagnosed several ways. If the cat is pruritic and has either fleas or flea dirt present, then these findings would be supportive of a diagnosis of flea allergy. The easiest way to collect fleas and/or flea dirt on a cat is to use a flea comb. The material from the flea comb is put on a white paper towel. The contents in the towel are then wetted with tap water. If, when you press the wet dirt against the towel and you get a reddish color, then you are dealing with flea dirt.

However, cats are excellent groomers and oftentimes fleas or flea dirt are not found on cats. The location of lesions on the body does not help you with the diagnosis. Unlike flea allergies in the dog, which tend to occur on the caudal one third of the body, fleas and flea-associated lesions can be found anywhere on a cat. Even oral lesions have been associated with a flea allergy. Because anatomic location is not going to help you much, you need some other options in order to make your diagnosis of flea allergy. Your options for diagnosing are either a serum allergy test for fleas or an intradermal allergy test for fleas. I prefer an intradermal allergy test because this test seems to be more sensitive. However, it is important to remember that feline mast cells appear to degranulate more quickly than in dogs. Therefore, it is recommended to watch the reactions closely and take readings every 5 minutes for a total of 15 minutes. A wheal that is at least half the size of the positive histamine control and the same firmness as the histamine control is considered a positive reaction.

11. How do you diagnose a food allergy in a cat?

Food allergy in cats is diagnosed by giving the cat a hypoallergenic (restrictive) diet for 8 to 12 weeks. This hypoallergenic diet can be either a diet that consists of novel protein and carbohydrate sources (commercially prepared or home-cooked) or a hydrolyzed diet (ZD, Hill's Science Diet, Topeka, KS). It is important that the cat gets no treats or flavored medications while the cat is on the hypoallergenic diet. At the end of the food trial, the cat is rechallenged to the old diet and within 7 to 14 days, the skin condition recurs if the cat is food allergic.

12. How do you diagnose atopy in a cat?

The two diagnostic options for diagnosing atopy in a cat are serum allergy testing and intradermal allergy testing (IDT). A lot of controversy exists as to whether feline IgE has been isolated. For this reason and because I find the IDT to be more sensitive, IDT is recommended. Due to the difficulty in interpreting feline IDT reactions, refer cats for testing to a board-certified veterinary dermatologist.

13. What is the treatment for EGC?

The treatment for EGC varies according to which allergy is present.

Treatment for flea allergy consists of flea control for the pet, any pets in the household, and the environment. If the cat is extremely pruritic then oral or injectable steroids may be used.

After a cat is diagnosed with food allergy, it can either be left on the hypoallergenic (restrictive) diet or individually rechallenged to individual food ingredients. Most cat owners do not want to rechallenge their cat to individual food ingredients. They usually stay on the special diet for life. Because the hydrolyzed diets are new, it is not known what the long-term effects, if any, are of keeping cats on these diet for life.

If the cat has atopy then the treatment options are either to use steroids, antihistamines, fatty acids, and/or hyposensitization vaccines (immunotherapy). The recommended dose for cats being administered prednisolone or prednisone is 4 to 5 mg/kg every 24 hours orally until resolution of the skin lesions, then a maintenance dose of 2 mg/kg every 48 hours orally. Methylprednisolone may also be used in the cat. The initial dosage is 0.8 to 1.5 mg/kg every 24 hours orally with a maintenance dose of this same dose or the lowest possible dose that the cat will tolerate at an every-other-day dosage schedule. Injectable steroids have also been used. Methylprednisolone

(DepoMedrol, Pharmacia and Upjohn, Kalamazoo, MI) has been used at a dosage of 4 mg/kg intramuscularly with a maximum dosage of 20 mg per cat.

Several antihistamine treatment options exist for cats with atopy. The most commonly used antihistamine is chlorpheniramine maleate at a dosage of 2 to 4 mg/cat orally every 12 hours. Sedation is the most common side effect of antihistamines. Another antihistamine that has been used in cats is clemastine at a dosage of 0.15 mg/kg every 12 hours orally. The only reported side effect in cats with clemastine is diarrhea. Diphenhydramine has also been used in cats. The dosage for diphenhydramine is 2.2 mg/kg every 8 hours. Sedation is a side effect commonly reported with diphenhydramine administration.

Fatty acids supplementation alone has been reported to help up to 50% of pruritic cats. However, in the case of atopic cats, I usually use the fatty acids in conjunction with an anti-istamine. Previous studies have suggested that these two medications have a synergistic activity.

If a serum allergy or an intradermal allergy test were performed, then hyposensitization vaccines (immunotherapy) may be administered to the cat to help control the cat's allergies. The dosage and frequency of vaccine administration varies. You should consult the serum allergy company or a veterinary dermatology specialist with any questions concerning the vaccine schedule that is provided to you.

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30. CANINE EOSINOPHILIC FURUNCULOSIS

Dennis W. Crow, DVM, DACVD

1. What is furunculosis?

Furunculosis is simply defined as a deep necrotizing form of folliculitis with pus accumulation. The pus accumulation associated with eosinophilic furunculosis is, as the name implies, characterized by eosinophils. This is a histologic classification.

2. How is the diagnosis of eosinophilic furunculosis made?

Eosinophilic furunculosis should be suspected when a peracute to acute onset of papules or nodules progresses to hemorrhage and ulceration. These lesions are typically located on the face (Figures 30-1 and 30-2), and may also be found around the eyes or on the trunk. The furunculosis lesions may be painful. Diagnosis is supported by compatible impression cytology and cutaneous biopsy results and by excluding other differentials.

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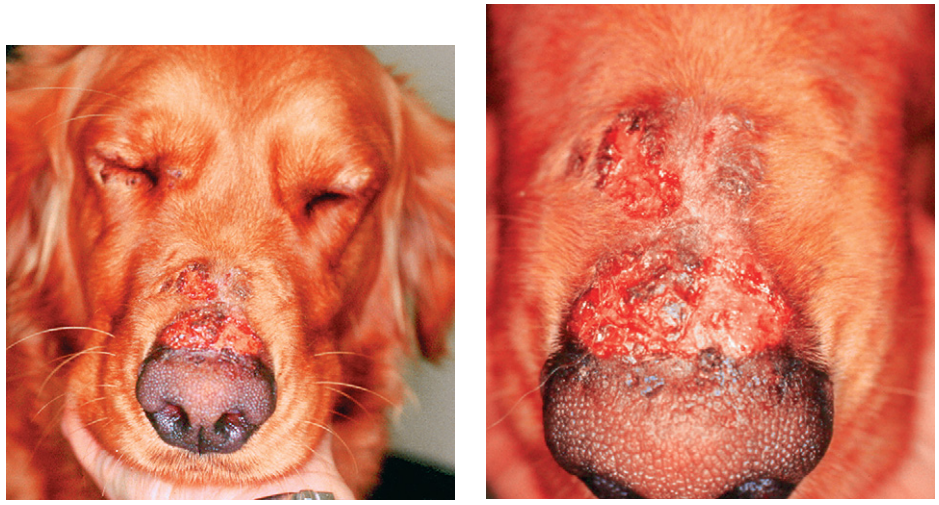

Figure 30-1 **A,** Crusted, erosive nodules on dorsal aspect of nasal bridge and periocular in a 2-year-old female spayed Golden Retriever with eosinophilic furunculosis. **B,** Close-up view of nasal bridge lesions.

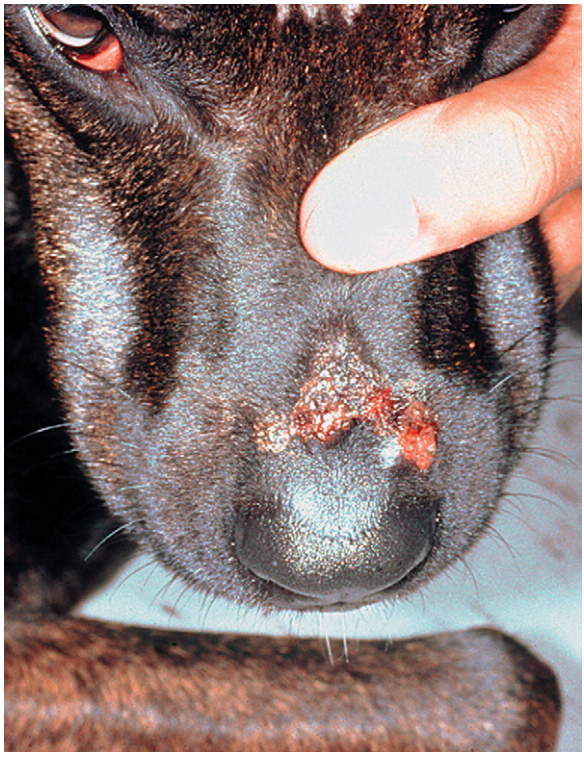

Figure 30-2 Patches of erosion and adherent crust on dorsal aspect of nasal bridge in a 3-year-old female spayed mixed-breed dog with eosinophilic furunculosis. (Courtesy Dr. Randall C. Thomas.)

3. **What are differential diagnoses for eosinophilic furunculosis? How are these differential diagnoses ruled out?**
   - Dermatophytosis can be ruled out by dermatophyte culture, trichography, and special stains for fungal organisms on biopsy specimens.
   - Localized bacterial pyoderma can be ruled out by cutaneous cytology and biopsy supportive of bacterial infection. Superficial bacterial infections, as a general rule, spare the head and face.
   - Drug eruption can be ruled in or out by a thorough history, in combination with histologic findings.
   - Pemphigus foliaceus or pemphigus erythematosus could be mistaken for this disorder; however, clinical lesions associated with eosinophilic furunculosis are papular to nodular and typically spare mucocutaneous junctions such as the palpebral margins and the nasal planum. Biopsy is helpful in differentiating these immune-mediated dermatoses from eosinophilic furunculosis in most cases.

4. **What can be done to increase the chances of a histologic diagnosis?**

Whatever you do, don't scrub the biopsy area before the procedure! Select multiple clinical stages of the lesions and obtain a biopsy specimen from each site. In general, a new lesion, a middle stage lesion, and an older lesion should be sampled to maximize chances at a diagnosis. Punch biopsy specimens 6 mm or greater will yield much greater information than smaller specimens. Immediately place the specimens into buffered formalin. Write a good clinical description for the pathologist, including time frame of lesion development, what regions of the body are affected, and the specific locations from which the biopsy specimens were taken. Don't forget to include your clinical differential diagnosis. A thorough history and lesion description is one of the most important tools a pathologist will use in helping you arrive at a diagnosis. Do not leave the history section blank on the pathology submittal form or expect a receptionist or technician to fill out this section for you if you want the best chance at supporting your diagnosis histologically.

5. **Are certain breeds or ages of dogs over-represented?**

Canine eosinophilic furunculosis is a syndrome noted primarily in young, large breed dogs with access to the outdoors.

6. **What are suspected inciting factors?**

This is a good question and the reality is, we do not really know for sure. Arthropod stings are commonly suspected to be a factor. To date, a direct link between an arthropod sting and the development of this syndrome is lacking; however, one study has reported known exposure to arthropods within 24 to 72 hours of onset of clinical signs in most patients. Eosinophils are commonly associated with allergic inflammation, especially in response to arthropod and parasitic insults. Thus, the presence of eosinophils in these lesions would support an arthropod sting as an etiologic factor.

7. **Describe the typical histopathologic findings in biopsy specimens of these lesions.**

Eosinophils are the predominant inflammatory infiltrate and typically fill and surround hair follicles (folliculitis). Many follicles are ruptured (furunculosis) and free keratin (hair) may be seen in the dermis near a furuncle. Dermal edema is usually present and often severe. Mixed superficial perivascular to diffuse infiltration of neutrophils, lymphocytes, and macrophages is usually present, but far outshadowed by the intense eosinophilic folliculitis and furunculosis (Figure 30-3). Bacteria and dermatophytes are not observed within the lesions.

8. **What is the prognosis?**

The prognosis is very good for full recovery. Most patients respond rapidly and completely

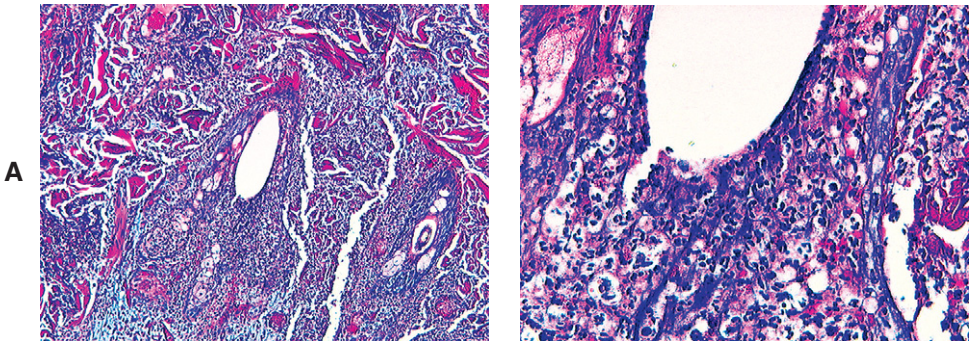

Figure 30-3 **A,** Biopsy of an eosinophilic furuncle (H&E ×100). **B,** Higher magnification (H&E, ×400) of biopsy in **A**.

to anti-inflammatory doses of corticosteroids. Patients have been reported to experience relapse (presumably if re-exposed to arthropod stings).

9. What are some treatment options?

Current recommendations are systemic anti-inflammatory doses of corticosteroids. If a strong historical link to arthropods is identified, reduction or elimination of exposure would make a relapse less likely. Some patients will spontaneously resolve within days to weeks without therapy.

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31. IDIOPATHIC STERILE GRANULOMA AND PYOGRANULOMA SYNDROME

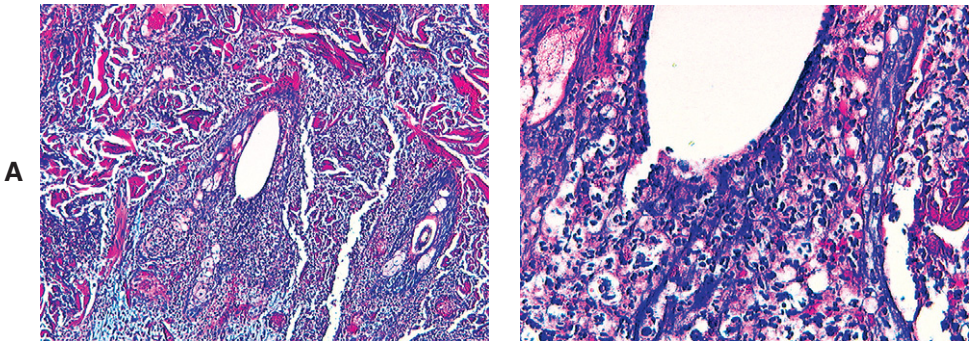
Dennis W. *Crow,* DVM, DACVD

1. What is idiopathic sterile granuloma and pyogranuloma syndrome?

Based on the name alone, it is quite obvious that we know very little about this entity. The disease is named based on histopathologic findings with appropriate clinical presentation and the exclusion of other causes of granulomas and pyogranulomas.

2. When should I suspect this disorder?

Clinically, patients with this disorder present with firm, non-painful intradermal nodules or plaques that typically affect the head. Pinnal flaps, third eyelids (Figure 31-1), and paws may also



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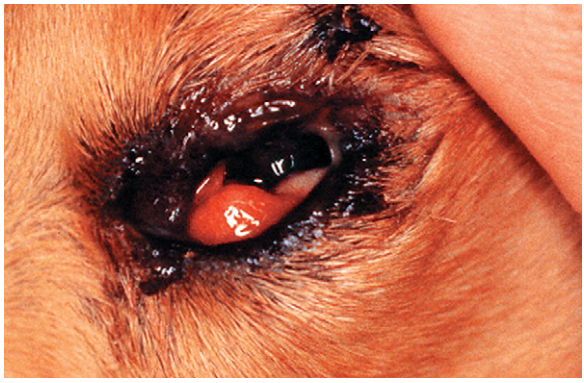

Figure 31-1 Haired intradermal nodule with hemorrhagic crust and nodular episcleritis in a 3-year-old male castrated Collie with sterile pyogranuloma syndrome. (Courtesy Dr. Reid A. Garfield.)

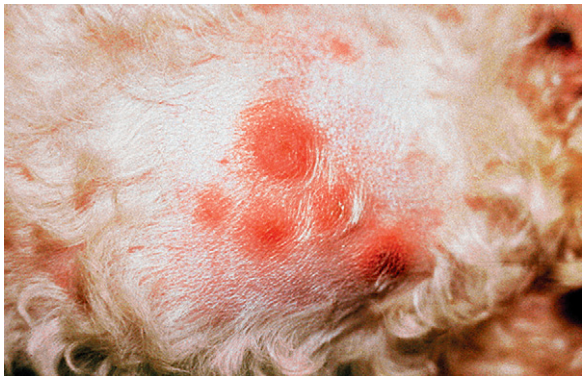

Figure 31-2 Erythematous, alopecic nodules on the lateral thorax of a female spayed 4-year-old Cocker Spaniel with sterile pyogranuloma syndrome. (Courtesy Dr. Reid A. Garfield.)

be affected and occasionally nodules are noted on the trunk (Figure 31-2). Initial haired masses may progress to alopecic and ulcerated lesions as the disease develops.

3. What species are affected?

Dogs and cats have been reported with this condition. A similar "sterile" granulomatous condition called sarcoidosis has been documented in human beings. Recent polymerase chain reaction testing has identified several species of mycobacterial deoxyribonucleic acid from the lesions of sarcoidosis in human beings.

4. What is the differential diagnosis list?

- Cutaneous and systemic histiocytic proliferative disorders
- Infectious causes of nodular pyogranulomas and granulomas:
  - *Nocardia* spp.
  - *Actinomyces* spp.
  - *Blastomyces* spp.
  - *Coccoides immitis*
  - *Histoplasma* spp.

  - *Cryptococcus* spp.
  - *Sporothrix* spp.
  - *Basidiobolus* and *Conidiobolus* spp.
  - *Pythium* and *Lagenidium* spp.
  - Fast- and slow-growing mycobacterial organisms
  - Canine leproid granuloma syndrome
- Penetrating foreign bodies

5. Describe how the diagnosis is made and supported.

The diagnosis is problematic. One must rule out all potential infectious causes of granulomas and pyogranulomas with appropriate tissue cultures and special stains on histopathologic specimens, and have compatible clinical and routine histologic changes (Figure 31-3) to arrive at a firm

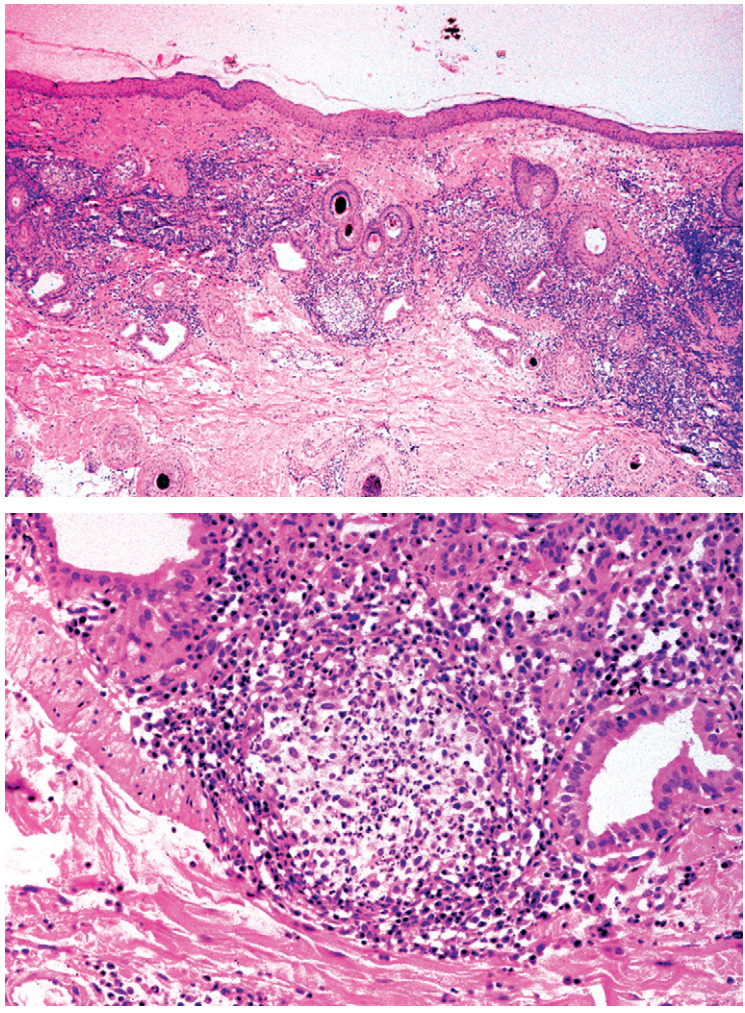

Figure 31-3 **A,** Intradermal pyogranulomatous foci from patient in Figure 31-1, consistent with sterile pyogranuloma syndrome (H&E, ×100). **B,** A closer view of the pyogranulomatous nodule between two dilated apocrine glands (H&E, ×500).

diagnosis of this syndrome. Histiocytic proliferative disorders can easily be confused with this disorder histologically, and immunohistochemical markers may be of benefit.

6. What is the prognosis for idiopathic sterile granuloma and pyogranuloma syndrome (ISGPS)?

Typically, these patients are expected to respond well to immunomodulatory (tetracycline and niacinamide) or immunosuppressive (steroids +/- azathioprine or chlorambucil) therapy. Most patients required prolonged therapy to maintain remission.

7. Are there breed or age predilections?

Any age, breed, or gender of dog may be affected; however, Boxers, Collies, Golden Retrievers, Great Danes, and Weimaraners may be predisposed.

8. Compare and contrast idiopathic sterile granuloma and pyogranuloma syndrome with sarcoidosis in human beings.

See Table 31-1.

Table 31-1 ***Sarcoidosis vs. Idiopathic Sterile Granuloma and Pyogranuloma Syndrome***

FEATURE	SARCOIDOSIS IN HUMANS	ISGPS IN DOGS AND CATS
Nonspecific constitutional signs (fever, fatigue, weight loss)	Possible	Possible but uncommon
Respiratory symptoms	Possible	Not reported
Peripheral lymph nodes affected	Possible	Not reported
Spleen	Possible	Not reported
Gastrointestinal tract	Possible	Not reported
Heart	Possible	Not reported
Musculoskeletal	Possible	Not reported
Kidneys	Possible	Not reported
Salivary glands	Possible	Not reported
Upper respiratory tract	Possible	Not reported
Endocrine glands	Possible	Not reported
Nervous system	Possible	Not reported
Hypercalcemia	Possible	One documented case (dog)
Mycobacteria spp. present in tissue lesions*	Yes	Yet to be investigated

*As by polymerase chain reaction technique.
ISGPS, Idiopathic sterile granuloma and pyogranuloma syndrome.

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32. IMMUNE-MEDIATED SKIN DISEASES

Sheila Torres, DVM, MS, PhD, DACVD

1. What are the immune-mediated skin diseases?

The immune-mediated skin disorders are a large group of inflammatory diseases that have in common the central participation of the immune system in their development. Most conditions in this broad disease category are well recognized, but uncommon in dogs and cats.

2. How are the immune-mediated skin diseases classified?

They are classified into primary or autoimmune, and secondary or immune-mediated. This chapter will cover only the primary or autoimmune skin diseases (Table 32-1).

Table 32-1 ***Autoimmune (Primary) and Immune-Mediated (Secondary) Skin Diseases***

AUTOIMMUNE	IMMUNE-MEDIATED
Pemphigus complex	Cutaneous adverse drug reaction
Pemphigus foliaceus	Erythema multiforme
Pemphigus erythematosus	Toxic epidermal necrolysis
Pemphigus vulgaris	Vasculitis
Pemphigus vegetans	Auricular chondritis
Paraneoplastic pemphigus	Alopecia areata
Subepidermal bullous diseases	Sterile nodular panniculitis
Bullous pemphigoid	
Epidermolysis bullosa acquisita	
Linear IgA bullous dermatosis	
Mucous membrane pemphigoid	
Cutaneous lupus erythematosus	
Discoid lupus erythematosus	
Vesicular cutaneous lupus erythematosus	
Exfoliative cutaneous lupus erythematosus	

3. How do the autoimmune skin diseases develop?

They develop as a result of deregulation of the individual's immune system that for not well known reasons fails to recognize his or her own tissue as self. Some of the abnormal mechanisms speculated to participate in disease development are: (1) suppressor T-cell dysfunction or bypass; (2) modification of self-antigen; (3) presence of exogenous antigens cross-reacting with self-antigens; (4) abnormal expression or abnormal interaction of the major histocompatibility complex II; (5) disclosure of non-tolerant T-cells to previously hidden self-antigens; and (6) genetic predisposition or acquired genetic defects.

4. What is the pemphigus complex?

The pemphigus complex or pemphigus diseases comprises four clinical presentations of cutaneous autoimmune disorders; these include pemphigus foliaceus, pemphigus erythematosus, pemphigus vulgaris, and pemphigus vegetans.

5. How common are the pemphigus diseases?

They are rare to uncommon skin disorders. Pemphigus foliaceus is the most common of the pemphigus diseases and the most common autoimmune skin disorder of dogs and cats. Pemphigus erythematosus is the second most common, followed by pemphigus vulgaris and pemphigus vegetans, which is very rare.

6. What do the pemphigus diseases have in common?

They have in common the formation of autoantibodies against keratinocytes and surface attachment molecules (desmosomes). This results in destruction of the attachment molecules, a process called acantholysis that gives rise to detached keratinocytes, called acantholytic cells. This separation of keratinocytes results in the formation of spaces in the epidermis called vesicles (when their content is predominantly clear fluid) or pustules (when their content is rich in neutrophils). The vesicles and pustules will also contain the acantholytic cells, which are the hallmark diagnostic finding for these diseases.

7. Do the skin lesions differ among the types of pemphigus?

Yes. The differences are highly associated with the depth of the epidermis where the acantholytic process occurs and, therefore, where the pustules or vesicles are formed (Figure 32-1). In pemphigus foliaceus and pemphigus erythematosus, pustules form superficially in the skin right beneath or within the stratum corneum, the outermost layer of the skin. In pemphigus vulgaris, vesicles form directly above the basal cell layer, the deepest layer of the epidermis. Based on the location of lesion formation within the epidermis; pemphigus diseases have been further classified into superficial pemphigus (pemphigus foliaceus and pemphigus erythematosus) and deep pemphigus (pemphigus vulgaris). In pemphigus vegetans, lesions form in the middle of the epidermis this disease has not been placed in the depth classification.

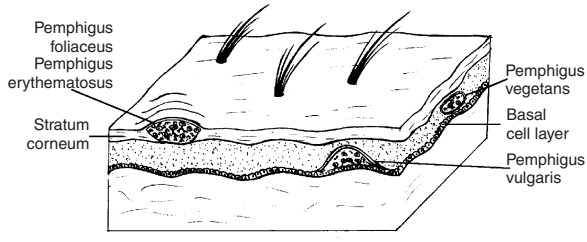

Figure 32-1 Pemphigus diseases. Location of lesions within the epidermis.

8. Describe the skin lesions associated with pemphigus foliaceus and pemphigus erythematosus.

In pemphigus foliaceus and pemphigus erythematosus, the initial lesion is an intracorneal or subcorneal pustule. This superficial pustule ruptures very easily, resulting in the formation of a honey-colored to brown crust that is the most common lesion observed clinically (Figure 32-2). The skin underneath the crust is often eroded and moist.

9. Are pemphigus foliaceus and pemphigus erythematosus the same disease?

No. Pemphigus erythematosus is considered a benign form of pemphigus foliaceus with the skin lesions limited to the face. In people, pemphigus erythematosus has immunodiagnostic features that cross over with lupus erythematosus (linear immunofluorescence staining of the basement membrane and positive antinuclear antibody test). However, this has not been consistently documented in the canine and feline cases, possibly because immunodiagnostic tests are not performed routinely.

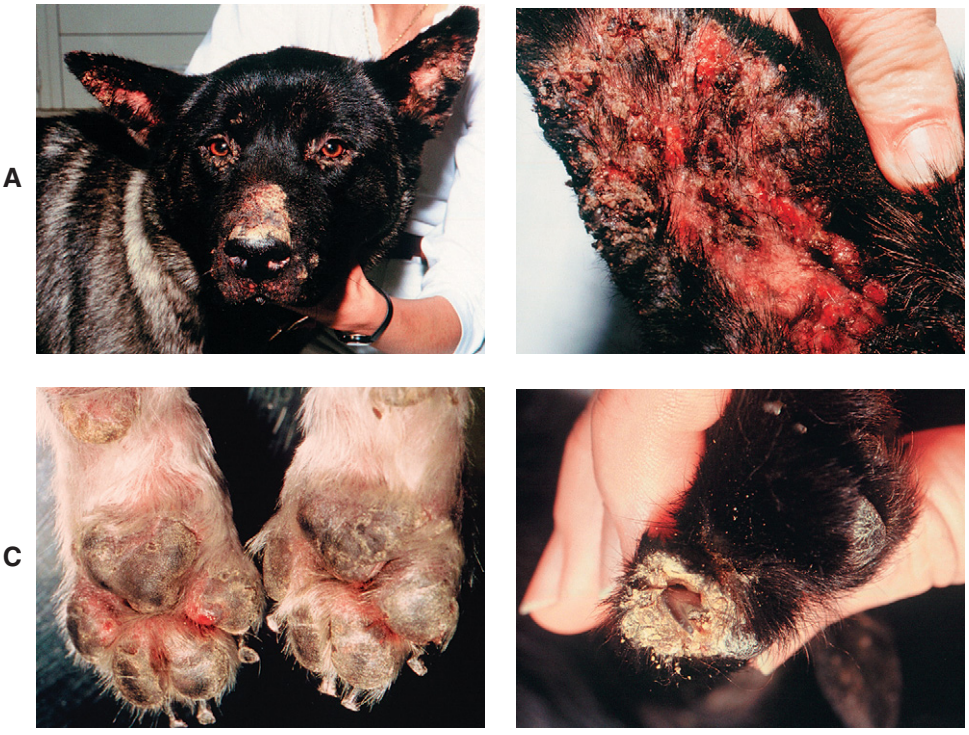

Figure 32-2 **A,** Pemphigus foliaceus. Yellowish-brown crusts localized predominantly on the bridge of the nose and inner aspects of the pinnae. **B,** Pemphigus foliaceus. Eroded skin areas are present underneath the yellowish-brown crusts on the pinna of the dog shown in **A**. **C,** Pemphigus foliaceus. Hyperkeratosis of the footpads and metacarpal pads. The skin adjacent to the pads is very inflamed. **D,** Thick yellowish-brown crust present on the nail bed of a cat (paronychia).

10. Describe the skin lesions associated with pemphigus vulgaris.

In pemphigus vulgaris the initial lesion is a suprabasilar vesicle. The vesicle ruptures very easily, leaving behind deep erosions or ulcerations that constitute the most common lesions observed clinically (Figure 32-3).

11. Do the lesions of pemphigus diseases occur in characteristic distributions?

Yes. Location of the lesions is helpful in differentiating these disorders (see Table 32-1, Figures 32-2 and 32-3).

12. Is there a gender, age, or breed predilection for any of the pemphigus disorders?

No age, gender, or breed predilection has been reported. However, most cases have been diagnosed in middle-aged animals (mean age: 4 years). In addition, pemphigus foliaceus has been reported more frequently in Akitas, Chow Chows, Dachshunds, Bearded Collies, Newfoundlands, Doberman Pinchers, Finnish Spitz, and Schipperkes.

13. Are the pemphigus diseases pruritic or painful?

Pruritus and pain are variable. Pemphigus foliaceus usually causes lesions on the footpads, which can be painful. Most dogs and cats are nonpruritic; however, some animals with pemphigus foliaceus can present with moderate-to-severe pruritus.

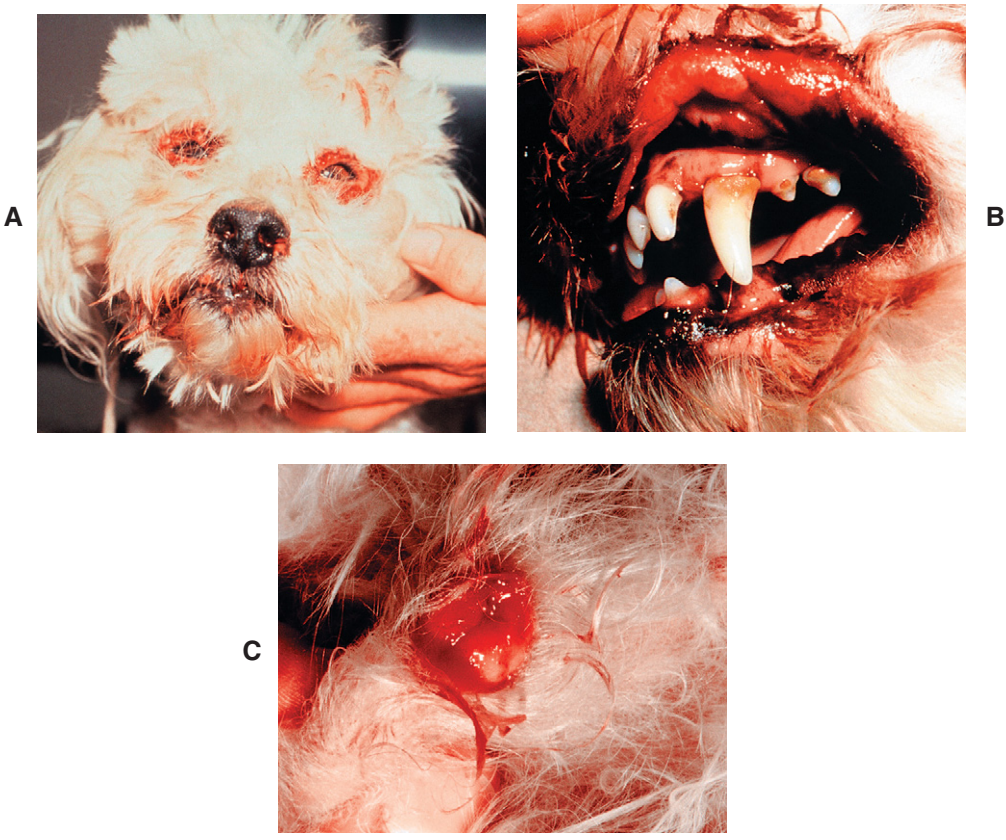

Figure 32-3 **A,** Pemphigus vulgaris. Eroded to ulcerative lesions localized to the mucocutaneous junctions of the eyes, lips, and nasal planum. **B,** Pemphigus vulgaris. Eroded to ulcerative lesions localized to the oral mucosa. **C,** Pemphigus vulgaris. Eroded to ulcerative lesions at the mucocutaneous junctions of the vulva covered with serosanguineous exudate.

14. Are secondary bacterial skin infections commonly seen with pemphigus disorders?

Secondary bacterial skin infections may be present but they are not as common as one would expect. Nevertheless, always look for their presence.

15. Are systemic signs present with the pemphigus diseases?

Severe and generalized cases of pemphigus foliaceus and pemphigus vulgaris may present with fever, anorexia, depression, and lymphadenopathy.

16. Can the clinical signs of the pemphigus diseases wax and wane?

Yes. A waxing and waning course is characteristic of pemphigus foliaceus and pemphigus erythematosus.

17. Describe the first treatment choice for the pemphigus complex.

Oral Glucocorticoids

- Most commonly used drugs: prednisone, prednisolone, methylprednisolone.
- Oral glucocorticoids work as the sole therapy in about 50% of cases.

- Induction dosage:
  - Dogs: 2.2 to 6.6 mg/kg every 24 hours.
  - Cats: 4.4 to 6.6 mg/kg every 24 hours.
- Re-evaluate response to treatment in 2 weeks. When remission is achieved, the ultimate goal is to find the lowest dosage that maintains the disease under control and causes minimal side effects. This maintenance dosage should be given every other day or less frequently.
- If no significant improvement or intolerable side effects are seen after 2 weeks of therapy, add another immunosuppressive drug to the treatment regimen.
- Side effects: cushingoid changes.

18. Describe the other immunosuppressive drugs commonly added to the glucocorticoid treatment regimen.

Azathioprine

- It is the first choice for dogs.
- Dose: 2.2 mg/kg every 24 to 48 hours, orally (PO).
- Remember that it has a lag phase of 4 to 6 weeks; therefore, do not expect a rapid response and do not reduce the glucocorticoid dosage too quickly.
- Do not use azathioprine in cats because they are very susceptible to the bone marrow suppression induced by this drug.
- Side effects: bone marrow suppression, vomiting, and diarrhea.

Chlorambucil

- It is the first choice for cats.
- Dose: 0.2 mg/kg every 24 to 48 hours, PO.
- Remember that it has a lag phase of about 4 to 6 weeks; therefore, do not reduce the glucocorticoid dosage too fast.
- Side effects: bone marrow suppression, vomiting, and diarrhea.

Gold Salts

- These can be used in dogs and cats in combination with glucocorticoids.
- Use the parenteral forms: aurothioglucose (Solganol) or aurothiomalate (Myochrysine).
- Induction dosage: 1 mg/kg per week given intramuscularly (IM) until clinical response is noted.
- Maintenance dosage: 1 mg/kg IM once per month or as needed.
- Remember that gold salts have a lag phase of 6 to 12 weeks; therefore do not reduce the glucocorticoid dosage too fast.
- Side effects: hepatic necrosis, thrombocytopenia, stomatitis, and proteinuria.

19. Can any of the previously mentioned immunosuppressive drugs be initially used in combination with glucocorticoid therapy to manage the pemphigus diseases?

Yes, some people will start treatment with glucocorticoids combined with another immunosuppressive drug. However, this protocol will increase therapy cost, add risk for development of side effects, and it may not be necessary considering that approximately 50% of the cases respond solely to glucocorticoids.

20. Describe the test protocol recommended to monitor for potential side effects associated with the immunosuppressive drugs.

- Glucocorticoids: Complete blood cell (CBC) count, chemistry profile, urinalysis, and urine culture every 6 to 12 months to monitor for cushingoid changes.
- Azathioprine and Chlorambucil: CBC and platelet count weekly to every other week for the first 3 months to monitor for bone marrow suppression. Thereafter, every 2 to 4 months.

Table 32-2 ***Characteristic Distribution of Lesions of the Pemphigus Diseases***

DISEASE	CHARACTERISTIC DISTRIBUTION*
Pemphigus foliaceus	Ear pinnae, bridge of the nose, nasal planum, footpads, nail beds (cats).
Pemphigus erythematosus	Ear pinnae, bridge of the nose, nasal planum
Pemphigus vulgaris	Mucocutaneous junctions, oral cavity, groin, axillae

*One or more of these sites may be affected on any single animal. In addition, other body regions may be involved, with the exception of pemphigus erythematosus, where lesions are limited to the face.

A chemistry profile should be performed monthly or more frequently to monitor for hepatotoxicity that can result from azathioprine therapy.

- Gold salts: CBC count, platelet count, and urinalysis every 2 weeks for the first 16 weeks. Thereafter, every 2 to 4 months.

21. Are antibiotics routinely used in combination with the immunosuppressive drugs?

No. Antibiotics are used when secondary bacterial skin infection is documented.

22. Can topical therapy be used to manage the pemphigus complex?

Yes. Topical glucocorticoids can be used to treat small, localized lesions. However, prescribe them judiciously because most preparations contain very potent glucocorticoids and their frequent application can cause skin atrophy and eventually cushingoid signs.

23. Can the pemphigus diseases be cured?

No. These diseases need lifelong therapy. The ultimate therapeutic goal is to find the lowest dosage of the immunosuppressive agent(s) that controls the disease with minimal side effects. Ideally, these medications should be administered every 48 hours or less frequently. Occasionally, a case will undergo complete remission and therapy can be discontinued.

24. What is paraneoplastic pemphigus?

Paraneoplastic pemphigus is a well-recognized skin disorder in humans only recently described in dogs. As the name indicates, this autoimmune skin disease occurs in association with neoplastic conditions, and there is evidence that the neoplasia is responsible for development of the skin lesions.

25. How does paraneoplastic pemphigus develop?

The disease pathogenesis is not completely understood. However, it is hypothesized that anti-tumor antibodies cross-react with epidermal antigens (e.g., desmosome molecules) and cause the initial skin damage. As the disease progresses, the damaged keratinocyte membrane allows for exposure of hidden (intracellular) antigens to the immune system which broadens the autoimmune attack. This immunologic phenomenon is known as "epitope spreading."

26. What neoplasms have been reported in association with paraneoplastic pemphigus in dogs?

One case each of thymic lymphoma, Sertoli cell tumor, and mammary carcinoma.

27. What is the prognosis for this disorder?

Very poor unless the associated neoplasia is cured.

28. List the autoimmune subepidermal vesiculobullous diseases.

- Bullous pemphigoid
- Epidermolysis bullosa acquisita
- Linear IgA bullous dermatosis
- Mucous membrane pemphigoid

29. Describe the similarities and differences among these diseases.

- They are all very rare autoimmune skin diseases.
- The skin lesions are very similar in all of them and are characterized by vesicles or bullae that easily rupture and result in the formation of ulcers. The ulcers are the most common lesions found on physical examination.
- Oral cavity involvement has been reported to occur with all forms of subepidermal vesiculobullous diseases.
- Mucocutaneous junctions are affected in cases of mucous membrane pemphigoid and bullous pemphigoid. In addition, axillae and groin areas are frequently affected in bullous pemphigoid (bullous pemphigoid and pemphigus vulgaris cannot be clinically differentiated). A recent report states that mucosal and mucocutaneous involvement occur more often with mucous membrane pemphigoid than with bullous pemphigoid.
- The very few cases reported of epidermolysis bullosa acquisita and linear IgA bullous dermatosis have shown a more varied distribution of skin lesions.
- According to a recent report, most cases of mucous membrane pemphigoid appear to occur in German Shepherds and most cases of epidermolysis bullosa acquisita appear in Great Danes.
- The target antigens are localized in the skin basement membrane in all four disorders. However, the specific component of the basement membrane targeted by the immune system is different for each disorder.
- Because the autoimmune attack occurs at the basement membrane, the routine histopathologic findings are very similar among the four disorders and are mainly characterized by a subepidermal cleft and vesicle formations.
- Similarly, the immunohistochemistry and immunofluorescence results are characterized by linear or reticulated staining of the basement membrane in all four diseases.

30. How are the autoimmune subepidermal bullous diseases managed?

The same treatment protocol listed for the management of the pemphigus diseases (see questions 17-19) can be applied for the management of the subepidermal bullous diseases.

31. How easy is it to manage the subepidermal bullous diseases?

Few reported cases of these diseases indicate that they are more difficult to manage than the pemphigus diseases. Most cases will not respond solely to glucocorticoids and will need another immunosuppressive drug. Therefore, the prognosis for these diseases should be considered guarded to poor.

32. List the cutaneous forms of lupus erythematosus.

- Discoid lupus erythematosus
- Vesicular cutaneous lupus erythematosus, also known as "idiopathic ulcerative dermatosis of Collies and Shetland Sheepdogs"
- Exfoliative cutaneous lupus erythematosus, also known as "hereditary lupoid dermatosis of German Shorthaired Pointers"

It is important to mention that vesicular cutaneous lupus erythematosus and exfoliative cutaneous lupus erythematosus were only recently suggested as subtypes of cutaneous lupus. Future studies may support this classification or may place these disorders under a different category.

Table 32-3 ***Clinical Signs of the Three Forms of Cutaneous Lupus Erythematosus***

DISEASE	LESIONS	DITRIBUTIONS
Discoid LE	Depigmentation, erythema, scales, erosion, ulceration, crust	Nasal planum (initially/common), bridge of the nose, other sites (rare)
Vesicular cutaneous LE*	Vesicles/bulla (initially/transient), serpiginous ulcers (common)	Groin/axillae (common), other sites (rare)
Exfoliative cutaneous LE†	Scale, crust, erythema	Face, ears and back initially, then generalized

*Also known as "idiopathic ulcerative dermatosis of Collies and Shetland Sheepdogs.
†Also known as "hereditary lupoid dermatosis of German Shorthaired Pointers."
LE, Lupus erythematosus.

33. Describe the clinical signs of the three forms of cutaneous lupus erythematosus.
See Table 32-3 and Figure 32-4.

34. Are the cutaneous forms of lupus erythematosus common disorders?
Discoid lupus erythematosus is the second most common autoimmune skin disorder of the dog after pemphigus foliaceus. However, it is still uncommon.
Vesicular and exfoliative cutaneous lupus erythematosus are rare disorders.

35. Is there any gender, age, or breed predilection for the development of these diseases?
Gender
- No gender predilection has been reported.

Age
- In discoid lupus erythematosus and vesicular cutaneous lupus erythematosus, the lesions usually first appear at middle to old age.
- In exfoliative cutaneous lupus erythematosus, the lesions typically first appear before 1 year of age.

Breed
- Discoid lupus erythematosus has been reported more frequently in German Shepherds, Collies, Shetland Sheepdogs, Siberian Huskies, and Brittany Spaniels.
- Vesicular cutaneous lupus erythematosus has been reported only in Collies and Shetland Sheepdogs.
- Exfoliative cutaneous lupus erythematosus has been reported only in German Shorthaired Pointers.

36. Can sun exposure aggravate the skin lesions of the cutaneous lupus erythematosus diseases?
Yes, in cases of discoid lupus erythematosus; however, not documented in the other two forms of cutaneous lupus erythematosus. However, recrudescence of skin lesions has been reported to occur more often during the summer months in cases of vesicular cutaneous lupus erythematosus, indicating that sun exposure aggravates the skin lesions.

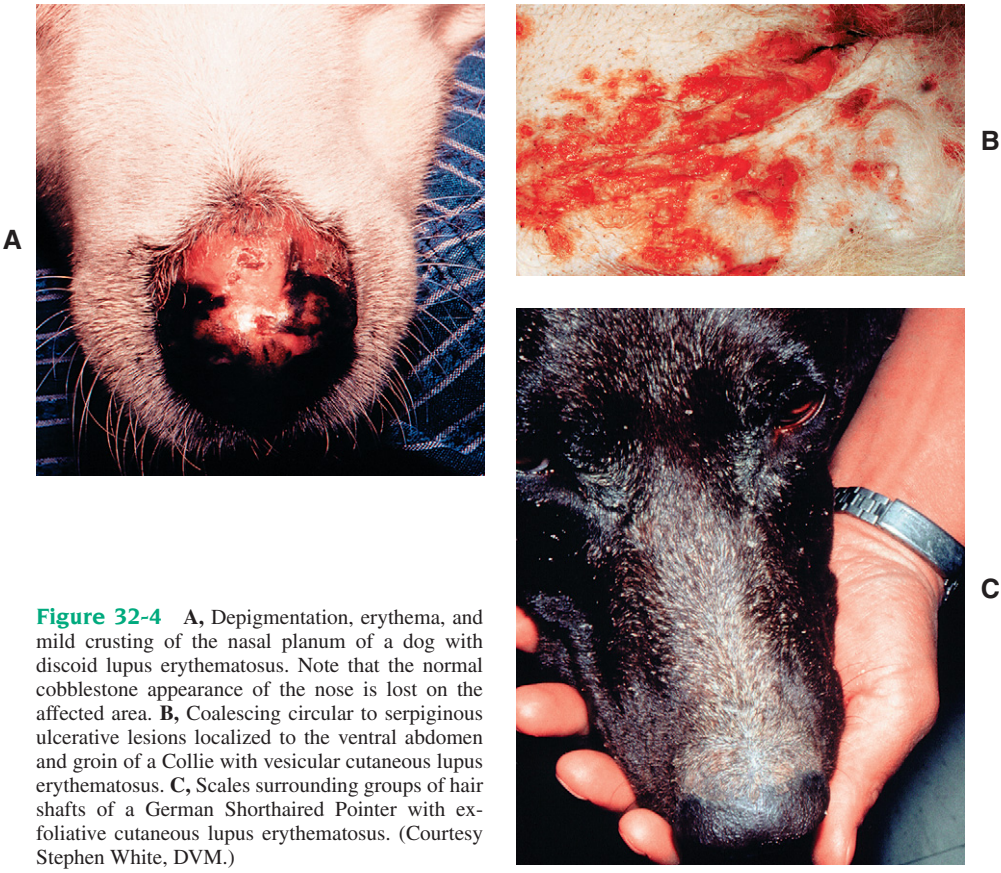

Figure 32-4 **A,** Depigmentation, erythema, and mild crusting of the nasal planum of a dog with discoid lupus erythematosus. Note that the normal cobblestone appearance of the nose is lost on the affected area. **B,** Coalescing circular to serpiginous ulcerative lesions localized to the ventral abdomen and groin of a Collie with vesicular cutaneous lupus erythematosus. **C,** Scales surrounding groups of hair shafts of a German Shorthaired Pointer with exfoliative cutaneous lupus erythematosus. (Courtesy Stephen White, DVM.)

37. List treatment protocols used to manage discoid lupus erythematosus.

Mild Cases

- Sun avoidance from 10:00 AM to 5:00 PM. If the dog is outside be sure to provide a shaded area and to apply a sunscreen with a SPF of at least 15.
- Aqueous vitamin E at the dosage of 400 to 800 IU every 12 hours orally can be used as adjunctive therapy but it will not work as the sole therapy.
- Topical glucocorticoids:
  - Initially stronger products (betamethasone, triamcinolone, fluocinolone acetonide, clobestone propionate) should be applied once to twice daily until remission is reached, usually in 10 to 14 days.
  - Once remission is achieved, reduce the frequency to once every 48 to 72 hours and/or switch to a milder topical product such as hydrocortisone 0.5% to 2.5%.
  - Remember that nonjudicious use of topical glucocorticoids can result in skin atrophy and cushingoid changes.
- Topical tacrolimus (Protopic):
  - It is an immunomodulating drug with the mechanism of action similar to that of cyclosporine.

  - It has recently shown to work very well for cases of discoid lupus.
  - Apply the formulation containing 0.1% or 0.03% to the affected areas at least twice daily until remission is achieved and then reduce to the lowest frequency that keeps the disease under control.
  - It has the advantage of minimal to no side effects. However, the cost can be a limiting factor.
- Tetracycline and niacinamide:
  - They have an anti-inflammatory effect.
  - Dosage: 250 mg of each PO three times daily in dogs <10 kg;
  - 500 mg of each PO three times daily in dogs >10 kg.
  - If no significant improvement is noticed after 2 months of therapy, consider another treatment option.
  - Side effects are rare and include vomiting and/or diarrhea. (Editorial comment: niacinamide has anecdotally been associated with an increased frequency of seizures and should be used with caution in dogs with a history of seizures.)

Severe Cases or Cases Refractory to the Therapy Listed Above:
- Systemic glucocorticoids:
  - Oral prednisone, prednisolone, or methylprednisolone.
  - Induction dosage: 2.2 mg/kg for dogs or 4.4 mg/kg for cats until the disease achieves remission, usually 10 to 14 days. Then reduce the dosage to the lowest dosage that keeps the disease under control.
  - A common practice is to combine the oral glucocorticoid with one or more of the medications listed above with the ultimate goal of stopping the oral glucocorticoid once the disease achieves remission.
- Sun avoidance as described above.

38. List treatment protocols for vesicular cutaneous lupus erythematosus.
- Immunosuppressive dosages of oral glucocorticoids as single therapy or in combination with azathioprine.
- Pentoxifylline (Trental):
  - It improves tissue oxygenation in addition to having an anti-inflammatory effect.
  - Dosage: 10 to 15 mg/kg orally two to three times daily.
  - If no response is observed after 2 months of therapy consider other treatment modalities.
- Tetracycline and niacinamide in combination can be tried in mild cases. However, the author's experience with this combination therapy to manage vesicular cutaneous lupus erythematosus is disappointing.
- Topical tacrolimus (Protopic 0.1% or 0.03%) can be applied to treat more severe focal lesions with good results.
- Sun avoidance.
- Lesions are often complicated with secondary infections. Identify and treat the secondary infections appropriately.
- According to the author's experience, this condition can be challenging to manage.

39. List the treatment options for exfoliative cutaneous lupus erythematosus.
- Most cases do not respond well to traditionally recommended therapies.
- The following medications have been tried with variable results:
  - Immunosuppressive dosages of oral glucocorticoids.
  - High dosages of omega-3 and/or omega-6 fatty acids.
  - Vitamin A (retinol) or retinoic acids.
- Frequent baths with keratolytic and/or keratoplastic shampoos.
- Identify and treat appropriately secondary skin infections.

40. What are the prognoses for the three forms of cutaneous lupus erythematosus?

Good for discoid lupus erythematosus. However, vesicular and exfoliative cutaneous lupus erythematosus are more difficult to manage with the currently available therapies, and the prognosis for disease control should be considered guarded. Therapy is lifelong for all three forms of cutaneous lupus erythematosus. Exfoliative cutaneous lupus erythematosus can wax and wane spontaneously.

41. List the diagnostic tests used for the autoimmune skin diseases.

- Cytology
- Skin biopsy
- Immunofluorescence or immunohistochemistry
- Indirect immunofluorescence
- Advanced immunologic tests:
  - Immunoblotting
  - Immunoprecipitation
  - Enzyme-linked immunoassay

42. How beneficial is it to perform cytology in the diagnosis of autoimmune skin diseases?

It is very beneficial. The presence of sheets of acantholytic keratinocytes (Figure 32-5) with neutrophils and with or without eosinophils strongly supports a diagnosis of pemphigus diseases if the history and clinical signs are suggestive of these disorders. In addition, the cytology can provide information regarding the presence of secondary infections.

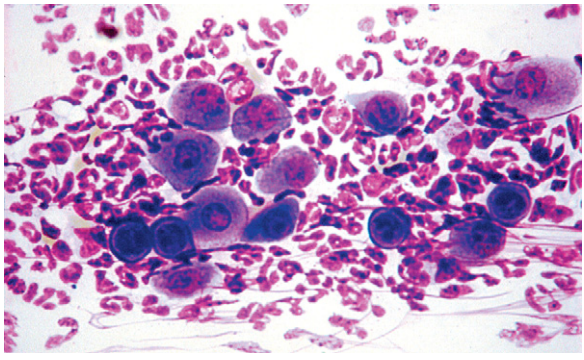

Figure 32-5 Groups of acantholytic keratinocytes associated with neutrophils (high-power field).

43. Is the presence of acantholytic keratinocytes pathognomonic for the diagnosis of pemphigus diseases?

No. Small numbers of acantholytic keratinocytes can be rarely seen in cases of severe *Staphylococcus* pyoderma. In addition, their presence has been reported in cases of dermatophytosis caused by *Trichophyton mentagrophytes*.

44. How beneficial is it to perform a skin biopsy in the diagnosis of autoimmune skin diseases?

It is very beneficial. Skin biopsy for routine dermatohistopathology is the most common test used in the diagnosis of the autoimmune skin diseases. Skin biopsies are sporadically used for direct immunofluorescence or immunohistochemistry.

45. How should a skin biopsy be performed to diagnose the autoimmune skin diseases?

- Use a 4-mm or 6-mm punch biopsy instrument. In some occasions, wedge biopsy may be required to preserve primary lesions (e.g., vesicles, pustules).

- Ideally, biopsy samples should be taken when the animals are not being treated with immunosuppressive therapy and after secondary skin infections have resolved.
- Administer the local anesthetic subcutaneously and not intradermally.
- Do not surgically prepare the skin because it removes or destroys diagnostic lesions.
- When performing a biopsy of a crusty lesion do not remove the crust but rather include it as part of your sample. Crusts often contain diagnostic elements.
- Take multiple skin samples that represent the different stages of lesion development.
- Biopsy lesional skin and not normal skin. The only exception applies to samples taken for immunohistochemistry or immunofluorescence, when perilesional skin biopsy specimens should be obtained in addition to lesions (vesicles, pustules) if they are present.
- For routine histopathology preserve samples in 10% neutral formalin.
- For immunofluorescence, preserve samples in Michel's fixative.
- For immunohistochemistry, preserve samples in 10% neutral formalin.
- Ideally, samples should be sent to a dermatohistopathologist with a complete history, physical examination findings, and list of differential diagnoses.

46. How beneficial are direct immunofluorescence and immunohistochemistry in the diagnosis of the autoimmune skin diseases?

They can be beneficial to distinguish the pemphigus complex diseases (intercellular staining) from the subepidermal vesiculobullous diseases (linear staining of the skin basement membrane). However, results have to be interpreted cautiously due to the significant numbers of false-positive and false-negative results. Currently, these tests are seldom used in the diagnosis of the autoimmune skin diseases in veterinary medicine.

47. What sample should be collected for indirect immunofluorescence and how useful is this test in the diagnosis of autoimmune skin diseases?

Indirect immunofluorescence investigates the presence of circulating autoantibodies; therefore, a serum sample should be collected. This test is not routinely used in the diagnosis of autoimmune skin diseases in animals due to poor sensitivity. However, a recent study demonstrated good results with the use of canine lip as substrate. This immunologic method is beneficial to distinguish some forms of subepidermal vesiculobullous diseases if the salt-split technique is applied. Nevertheless, the routine use of indirect immunofluorescence in the diagnosis of autoimmune skin diseases in animals awaits further investigation and easy accessibility to this test.

48. How beneficial are the advanced immunologic methods in the diagnosis of autoimmune skin diseases?

These tests are beneficial in the identification of the specific antigens targeted by circulating autoantibodies and more importantly are applied to distinguish the forms of subepidermal vesiculobullous disorders. Unfortunately, at present, they are only available at a few veterinary research laboratories.

49. Is the antinuclear antibody test useful in the diagnosis of the autoimmune skin disorders discussed here?

No. If this test is performed, the results should be negative or have very low titers in all the autoimmune skin disorders discussed here. Therefore, a positive test result should be considered false or nonspecific.

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33. ERYTHEMA MULTIFORME AND TOXIC EPIDERMAL NECROLYSIS

Jan A. Hall, BVM&S, MS, MRCVS, DACVD

1. What is erythema multiforme?

Erythema multiforme (EM) is an uncommon, acute, self-limiting eruption of the skin and mucous membranes and is characterized by distinctive, erythematous macules and characteristic histopathology. Confirmatory diagnosis is usually made by histopathology. Drug administration, systemic diseases, neoplasia, and idiopathic factors have been suggested as underlying causes. Identification and removal of the offending trigger factor normally leads to recovery.

2. What is the pathogenesis of EM?

The pathogenesis is not fully understood but likely involves an immunologic process. The condition is believed to represent a host-specific cell-mediated reaction toward an unknown antigen. Drugs, systemic disease, neoplasia, infections, and stress have all been implicated as sources of the offending antigen. Generally there is a precipitating cause although it may be hard to identify. Many cases end up being classified as idiopathic. This condition may well be multifactorial. Age, gender, and breed predilections have not been identified.

3. What is known about the possible immunologic basis for this disease?

EM is believed to represent a host-specific cell-mediated reaction toward an unknown antigen. Recent immunohistochemical studies have suggested that the immunological reaction in EM is similar to that noted in graft versus host disease (GVHD). GVHD results from the transfer of immunologically competent donor cells into an immunologically incompetent host. The graft cells recognize the host cells as antigenically different and respond by triggering an immunological reaction resulting in GVHD and leading to the development of skin, gastrointestinal, and liver pathology. Although the pathogenesis of EM is unknown, antigenic stimulation associated

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33. ERYTHEMA MULTIFORME AND TOXIC EPIDERMAL NECROLYSIS

Jan A. Hall, BVM&S, MS, MRCVS, DACVD

1. What is erythema multiforme?

Erythema multiforme (EM) is an uncommon, acute, self-limiting eruption of the skin and mucous membranes and is characterized by distinctive, erythematous macules and characteristic histopathology. Confirmatory diagnosis is usually made by histopathology. Drug administration, systemic diseases, neoplasia, and idiopathic factors have been suggested as underlying causes. Identification and removal of the offending trigger factor normally leads to recovery.

2. What is the pathogenesis of EM?

The pathogenesis is not fully understood but likely involves an immunologic process. The condition is believed to represent a host-specific cell-mediated reaction toward an unknown antigen. Drugs, systemic disease, neoplasia, infections, and stress have all been implicated as sources of the offending antigen. Generally there is a precipitating cause although it may be hard to identify. Many cases end up being classified as idiopathic. This condition may well be multifactorial. Age, gender, and breed predilections have not been identified.

3. What is known about the possible immunologic basis for this disease?

EM is believed to represent a host-specific cell-mediated reaction toward an unknown antigen. Recent immunohistochemical studies have suggested that the immunological reaction in EM is similar to that noted in graft versus host disease (GVHD). GVHD results from the transfer of immunologically competent donor cells into an immunologically incompetent host. The graft cells recognize the host cells as antigenically different and respond by triggering an immunological reaction resulting in GVHD and leading to the development of skin, gastrointestinal, and liver pathology. Although the pathogenesis of EM is unknown, antigenic stimulation associated

with drug administration, viral infections, systemic disease, neoplasia, or idiopathic causes is believed to trigger the immunological reaction.

The involvement of cytotoxic T-lymphocytes has been suggested in both GVHD and EM. It has been shown that epidermal and follicular keratinocytes express the adhesion molecules, ICAM-1 and MHC II. Upregulation of these molecules is believed to occur during the early stages of the disease process in response to antigenic stimulation. The upregulation may occur through production of IFN-α and TNF-β from CD8+ (cytotoxic) and CD4+ T lymphocytes. It is believed that the upregulated adhesion molecules trap cytotoxic lymphocytes attracted into the epithelium, where they trigger apoptosis (programmed cell death) of the keratinocytes, leading to epidermal damage and the progressive development of clinical disease.

4. How do the forms of EM described in humans compare with those in dogs?

Erythema multiforme was first described in humans in 1814, although reports of an EM-like disease date back to antiquity. In humans, EM is divided into two subsets: a milder form, known as *erythema multiforme minor*, that is most often associated with viral infections, and a more severe form, *erythema multiforme major,* more often associated with drug reactions. An additional severe form, Stevens-Johnson syndrome, has also been described; however, recent histopathologic and immunohistochemical studies suggest that this is more likely a form of toxic epidermal necrolysis (TEN).

The human classification of EM has been adopted for use in dogs. It has been suggested that EM cases have flat or raised target or polycyclic erythematous macules, with less than 50% of the body surface affected and less than 10% showing evidence of epidermal detachment. EM cases are classified as *minor* if one or no mucosal surfaces is affected and *major* if more than one mucosal surface is involved. Stevens-Johnson syndrome/TEN cases refer to those in which greater than 50% of the body surface is affected, with extensive mucosal involvement but no target or polycyclic lesions. Using this system it has been shown that the vast majority of cases associated with drug exposure have produced Stevens-Johnson syndrome/TEN lesions rather than EM. However, there is quite clearly an overlap between these disease conditions.

As most cases of EM are usually diagnosed by the results of histopathology, it is probably not critical to be concerned about the exact classification of a particular case. From a clinical point of view both EM and TEN will be included as differential diagnoses for individuals with compatible skin lesions.

5. How common is EM in dogs and cats?

EM is an uncommon disease in dogs and cats. It has been recognised in dogs in association with a wide variety of drugs, infections, and systemic diseases, including neoplasia although idiopathic cases, where no causal agent can be identified, are common. EM has also been reported in association with an adverse reaction to food. In cats, EM has been associated with drug therapy and herpes virus infection. Reported causes of EM in dogs and cats are included in Table 33-1.

6. What are the clinical features of EM?

The skin lesions in EM are usually characterized as bilaterally symmetrical erythematous macules and papules, which often spread peripherally. Vesiculobullous lesions, ulcerations, and epidermal collarettes may also be noted. Lesions may affect the skin and mucous membranes at any location, but often the face, oral mucous membranes, and ventral abdomen are more severely involved (Figure 33-1). Epidermal necrosis may occur with the development of eroded and ulcerated lesions. Sloughing of skin may be noted. Secondary infections may occur because of the destructive nature of the condition. The skin lesions may be painful although rarely pruritic. Target lesions, Nikolsky's sign (the outer layer of the skin is rubbed off when pressure is applied to the lesion), and pitting edema may occasionally be noted. If prodromal or systemic signs are noted they usually reflect the underlying cause. In cats, the lesions are most often

Table 33-1 ***Reported Trigger Factors for EM and TEN in Dogs and Cats***

TRIGGER FACTORS	SPECIES (D = DOG/C = CAT)
ANTIBIOTICS	
Amoxicillin	D
Clavulanic acid–potentiated amoxicillin	D
Cephalexin	D
Chloramphenicol	D
Enrofloxacin	D
Erythromycin	D
Gentamicin	D
Lincomycin	D
Ormetoprim-sulfadimethoxine	D
Penicillin	D/C
Tetracycline	D
Trimethoprim-sulfadiazine	D/C
Trimethoprim-sulfamethoxazole	D/C
MISCELLANEOUS DRUGS	
Aurothioglucose	D
Chlorpyrifos	D
Heartworm preventative (beef)	D
D-limonene	D
Griseofulvin	C
Ivermectin	D
Levamisole	D
L-Thyroxine	D
Ear drops	D
Phenobarbital	D
Propylthiouracil	C
OTHER	
Adverse food reaction	D
Anal sacculitis	D
Disseminated intravascular coagulation	D
Herpes virus	C
Idiopathic	D/C
Internal neoplasia	D/C
Pseudomonas otitis externa	D/C
Staphylococcal dermatitis	D

vesiculobullous and/or ulcerative. The trunk and mucocutaneous junctions are most commonly affected.

7. How do you diagnose EM?

The diagnosis of EM is normally made by histopathology. Historical features may include acute onset, drug administration, infectious disease, stress, or systemic disease. Routine hematologic studies, chemistry profile, and urinalysis may indicate changes associated with the severe inflammatory nature of the condition or secondary illness. ANA titers are negative. Histopathology may be diagnostic and reveal interface dermatitis, reflecting a cell-mediated immune

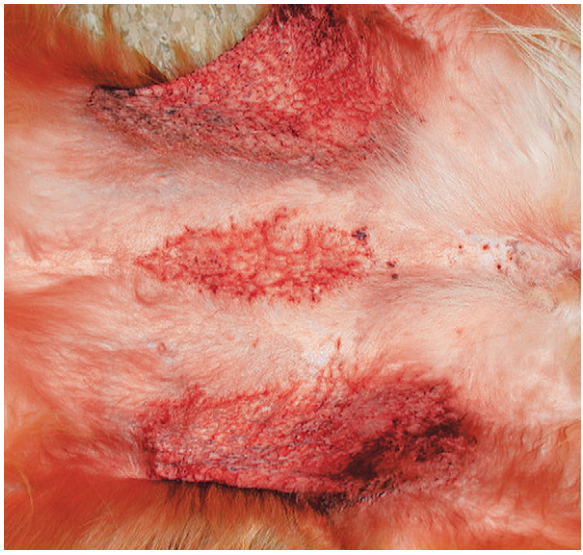

Figure 33-1 Erythematous maculopapular eruption of erythema multiforme on the ventral abdomen of a Golden Retriever dog.

attack upon the epidermis (apoptosis of keratinocytes, which can be so severe that the epidermis ulcerates, plus lymphocyte infiltration of the epidermis).

The differential diagnosis for EM includes bacterial folliculitis, demodicosis, dermatophytosis, urticaria, and other vesiculobullous diseases including pemphigus foliaceus, systemic lupus erythematosus, and TEN.

8. What are histopathologic changes noted in EM?

The typical histopathologic changes noted in EM include hydropic interface dermatitis with single cell necrosis (apoptosis) that may be noted at all levels of the epidermis with satellitosis of lymphocytes and macrophages. A superficial interstitial or lichenoid band of inflammation may be noted within the superficial dermis. The histopathologic findings may not be able to distinguish between mild and severe forms of the disease and may vary dramatically with the gross morphology of the lesions.

9. How does the histopathology of EM differ from that of TEN?

Both EM and TEN are diagnosed by the microscopic features identified on histopathology. In dogs with EM, the cellular infiltrate is of high density with large numbers of T-lymphocytes, whereas in TEN a minimal infiltrate is noted. Apoptosis of keratinocytes is commonly noted in cases of EM but not in TEN. In humans, the infiltrate in TEN has been shown to include mainly macrophages and dermal dendritic cells, whereas in EM T lymphocytes are the prominent cell.

10. How do you treat erythema multiforme?

A thorough search for an underlying cause is crucial to a successful outcome. Unfortunately, it is not unusual for this search to be fruitless, as many cases end up being classified as idiopathic. Potential triggering drug therapy should be discontinued. Symptomatic and supportive care is recommended. Although the use of systemic glucocorticoids is controversial in human medicine, immunosuppressive therapy has gained wide acceptance in veterinary dermatology because of the presumed immunological etiology of the disease. Doses of prednisone starting from 2 mg/kg

per day have been recommended, with the addition of azathioprine in severe cases. The prednisone dose is gradually weaned down based on response. Clinical improvement should be noticed in a few days. Mild problems may be self-limiting, lasting up to 4 weeks. Severe problems may be life-threatening. I routinely treat with prednisone at 2 to 4 mg/kg per day and azathioprine at 2.2 mg/kg every 48 hours, with excellent results. Other treatment options that have been suggested include the use of cyclosporine and pentoxifylline. Pentoxifylline may be used as an alternative to prednisone in mild cases. A strict exclusion diet trial has been suggested in idiopathic cases to rule out an adverse reaction to food as the underlying cause. It is possible that "idiopathic" EM may resolve spontaneously after a few weeks, suggesting that the unidentified antigenic trigger has been eliminated.

11. What is toxic epidermal necrolysis?

Toxic epidermal necrolysis (TEN) is rare, severe, vesiculobullous or ulcerative disease affecting the skin and/or the oral mucosa, characterized by necrosis of the epidermis. The affected skin may appear scalded. The condition has been reported in dogs, cats, and humans. TEN shares many clinical features with EM, although whether they are truly related conditions is controversial. It has been suggested that the severe form of EM, the Stevens-Johnson syndrome, may represent a milder form of TEN. An immunologic mechanism has been suggested, although only a minimal inflammatory response is noted on histopathology. A recent multicenter study suggested that many cases of TEN are drug-induced, although some are still classified as idiopathic. In humans, 80-95% of cases have a temporal association to drug use. Drugs incriminated in the development of TEN are similar to those associated with EM (see Table 33-1).

12. What is the pathogenesis of TEN?

The pathogenesis of TEN is unknown; however, an immunologic mechanism has been suggested. Because TEN shares some historical and clinical features with EM, a similar mechanism involving apoptosis (programmed cell death) has been proposed, although this is very controversial. It has been suggested that both EM and TEN represent a cutaneous toxicity reaction to drug therapy metabolites. It has been proposed that the epidermal apoptosis noted in TEN is so severe as to lead to the devitalisation of the affected epidermis, epidermal necrosis, and the characteristic vesiculobullous and ulcerated lesions.

13. What are the clinical features of TEN?

The clinical signs of TEN are generally acute in onset. In humans, prodromal signs include fever, inappetence, a burning sensation, or sensitive skin or joint pain. In animals, an erythematous rash may develop over hours to days, although this may only be noted in the sparse areas of the axilla and groin because of the extensive hair coat (Figure 33-2).

Affected individuals normally present to the clinic with well-demarcated areas of erythroderma that may have progressed to ulcerations, scaling, and crusting of the affected areas. Ulcerations may involve the oral mucosal and mucocutaneous junctions. A truncal distribution is common although some authors have reported that the face may be the first area affected. Increased epidermal fragility associated with a positive Nikolsky sign is often noted. Lesions often progress over a few days to sloughing lesions (Figures 33-3 through 33-5). Secondary pyoderma or yeast infection may occur. Systemic signs may be noted, including depression, anorexia, and pyrexia. Pain may be moderate to intense depending on the extent of the skin involvement.

14. How do you diagnose TEN?

Like EM, TEN is a disease that is definitively diagnosed by the results of histopathology. Historical features usually include an acute onset, drug administration, infectious disease, stress, or systemic disease. Routine hematology, chemistry profile and urinalysis may indicate changes associated with systemic illness, severe nature of the condition (protein loss), or secondary illness. ANA titers are negative.

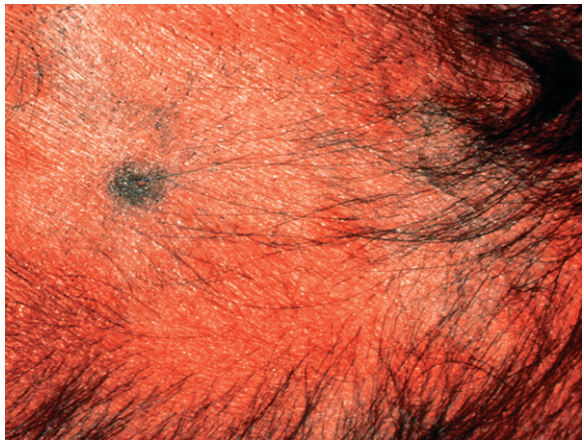

Figure 33-2 Erythematous rash in early stage of toxic epidermal necrolysis.

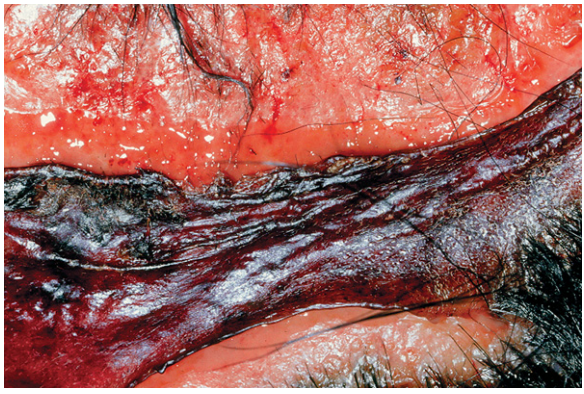

Figure 33-3 Full-thickness epidermal necrosis in advanced toxic epidermal necrolysis.

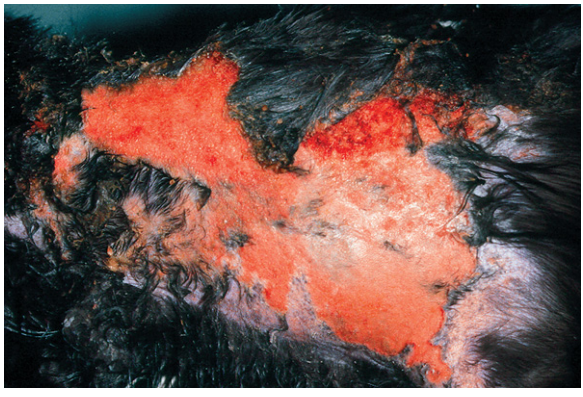

Figure 33-4 Toxic epidermal necrolysis involving the back of a cat following a flea dip.

Figure 33-5 Extensive ulceration in toxic epidermal necrolysis after two injections of cephalothin given to this cat in treatment of upper respiratory disease.

The histopathologic changes of TEN are pathognomonic for the disease, and characteristic regardless of the underlying cause. Histopathology reveals full thickness eosinophilic coagulation necrosis of the epidermis. Epidermal cleavage and cleft formation at the dermal-epidermal junction may be noted. The most characteristic lesion is a minimal dermal inflammatory infiltrate. Skin biopsies taken at a later stage of lesion development may only reveal ulceration. The upper third of the follicular epithelium may also be affected.

Differential diagnosis includes chemical/thermal burns, contact allergic and irritant reactions, pemphigus vulgaris, subepidermal bullous diseases, SLE, candidiasis, thallotoxicosis, cutaneous lymphomas and drug eruption.

15. How do you treat TEN?

The prognosis for TEN is guarded to poor. In humans the mortality rate may be as high as 50%. All cases of TEN should be regarded as potentially life-threatening. Any possible triggering drug therapy should be discontinued and any underlying disease controlled. Treatment is geared to a thorough search for an underlying cause while at the same time providing supportive care (fluid therapy, antibiotics, topical therapy). Systemic steroids may be critical to survival although their use is controversial. Recommended treatment is prednisone starting from 2 mg/kg per day, weaning down based on response. Clinical improvement should be noticed in a few days. The use of whirlpool baths in the healing phase may be beneficial.

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34. PANNICULITIS

Adam P. Patterson, DVM

1. What is panniculitis?

Panniculitis, a localized form of steatitis, is an uncommon inflammatory condition of the subcutaneous fat tissue (panniculus adiposus) seen in dogs and cats. It is characterized by cutaneous nodules that ulcerate and/or fistulate.

2. Is panniculitis a specific disease entity?

No. Panniculitis is a clinically descriptive term referring to lesions that have several possible etiologies. It has been associated with numerous causes, including infectious organisms (bacteria, mycobacteria, fungi), pancreatic disorders (inflammation, hyperplasia, necrosis, and neoplasia), vasculitis, immunologic conditions (lupus erythematosus and rheumatoid arthritis), drug reactions, neoplasia, nutritional disorders (vitamin E deficiency), and physiochemical factors (trauma, foreign bodies, injections). The majority of cases are attributed to idiopathy and are referred to as *sterile nodular panniculitis*. A hereditary deficiency of α_1-antitrypsin is a cause of panniculitis in humans but has not been documented in dogs or cats.

3. Describe what happens to the surrounding tissue when an adipocyte is damaged.

Adipocytes are very susceptible to trauma, ischemia, and inflammation. When damaged, these cells release intracellular lipid that hydrolyzes into fatty acids and glycerol. Fatty acids themselves can initiate or perpetuate regional inflammation because they are highly inflammatory agents. As more and more adipocytes are damaged, an unrelenting granulomatous response may ensue.

4. What cutaneous signs are suggestive of panniculitis?

Lesions consist of single or multiple deep-seated subcutaneous nodules that vary in size (Figure 34-1, *A*). Early lesions tend to be well circumscribed and firm with older lesions becoming soft and poorly defined as the nodule liquefies. Nodules that fistulate discharge an oily clear to straw-colored material (Figure 34-1, *B*). When secondarily infected, the discharge is purulent. The overlying skin may appear normal, or be alopecic, erythematous, scaly, crusty, hyperpigmented, ulcerated, and/or scarred. Occasionally, nodules may spontaneously regress. In dogs and cats, nodules are commonly seen along the ventrolateral thorax, neck, and abdomen.

5. Can patients with panniculitis present with systemic signs?

Yes. Noncutaneous clinical signs may be attributed to underlying diseases (e.g., systemic infections, immune-mediated diseases, pancreatitis, etc.). Signs could include vomiting, abdominal pain, polydipsia, polyuria, arthralgia, and/or lameness. Many times constitutional signs such as fever, anorexia, depression, and lethargy are noted.

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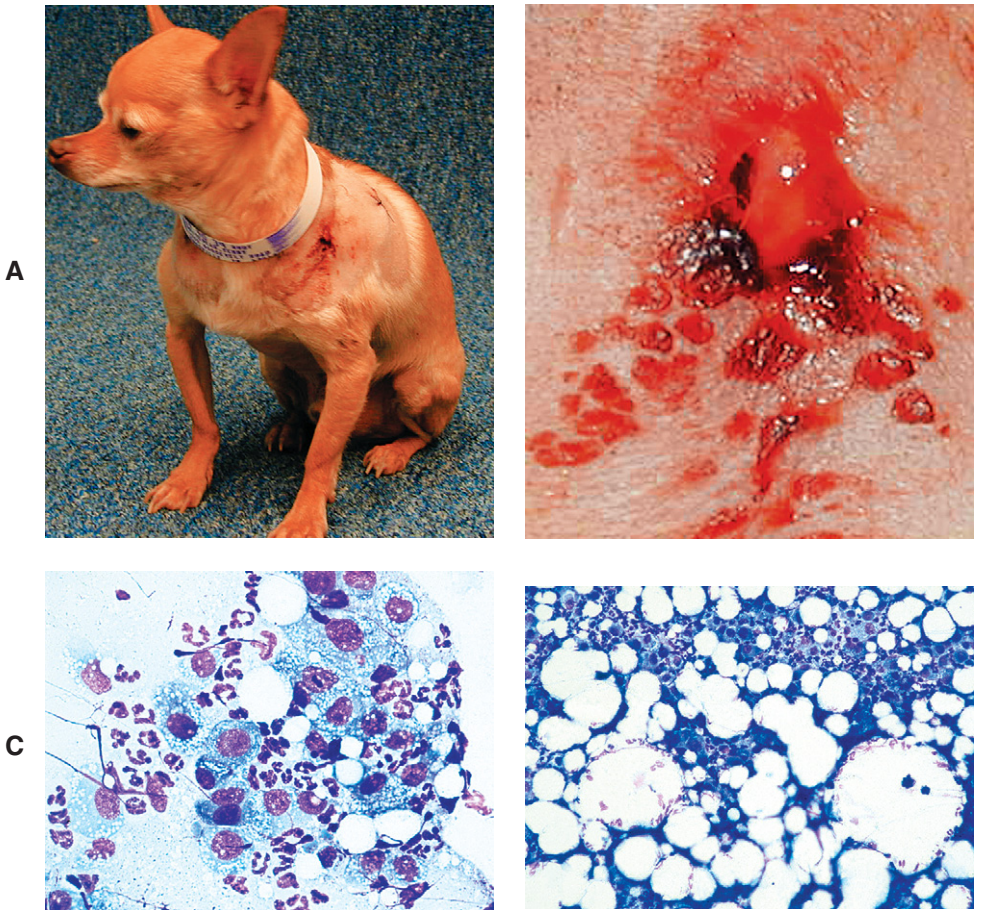

Figure 34-1 **A,** Chihuahua with panniculitis involving the left shoulder. **B,** A close-up of one of the lesions on the shoulder of the dog in **A**. Note the "liquefied" fat appearance of the exudate. **C,** Cytology of the exudate from the lesion in **B**. Note the foamy macrophages and non-degenerate neutrophils. **D,** Biopsy from one of the early lesions of dog in **A**. Note the subcutaneous fat is infiltrated with neutrophils and macrophages (H&E, ×100).

6. **Discuss any breed, age, or gender predilections associated with panniculitis.**
   Poodles and Dachshunds may be predisposed; however, any pure- or mixed-breed dog may be affected. Otherwise, there are no predilections seen in dogs or cats.

7. **List a few differential diagnoses for nodular dermatitis.**
   See Table 34-1.

8. **A thorough diagnostic approach is warranted to identify etiologies associated with panniculitis. Provide mandatory and ancillary diagnostic tests that could be used to support the diagnosis.**
   See Table 34-2.

Table 34-1 ***Differential Diagnosis of Nodular Dermatitis***

Bacterial	Bacterial folliculitis/furunculosis, abscess, mycobacteriosis, nocardiosis, actinomycosis
Fungal	Dermatophytosis, eumycotic mycetoma, phaeohyphomycosis, pythiosis, lagenidiosis, zygomycosis, sporotrichosis, blastomycosis, cryptococcosis, histoplasmosis, protothecosis
Parasitic	Demodicosis, *Cuterebra*, arthropod bite/sting
Neoplastic	Lipoma, histiocytosis, fibrosarcoma, mastocytoma, cutaneous lymphoma, melanoma, hair follicle tumors, internal neoplasia
Sterile	Sterile nodular panniculitis, sterile granuloma, calcinosis cutis, drug eruption, xanthoma, cysts

Table 34-2 ***Testing to Support Diagnosis of Panniculitis***

MANDATORY TESTS	ANCILLARY TESTS
Impression cytology	Complete blood cell count
Fine needle aspirates including acid-fast staining	Serum chemistry with amylase and lipase
Bacterial (aerobic and anaerobic), mycobacterial, and fungal culture of nodular tissue	Urinalysis
Excisional biopsy for histopathology	Serology (FeLV/FIV, ANA, rickettsial) titers
	Direct immunofluorescence of biopsy
	Diagnostic imaging
	Ocular examination
	Lymph node aspirates

9. Describe fine needle aspirate cytologic findings of panniculitis.

Suppurative, eosinophilic, granulomatous, pyogranulomatous, or mixed inflammation may be seen on cytology depending on the etiology of the disease. Classically, cytology of sterile nodular panniculitis reveals nondegenerate neutrophils, foamy macrophages, and no microorganisms (Figure 34-1, *C*). However, if the nodule is open to the surface then it may be secondarily infected. In this case, degenerate neutrophils with bacteria would be seen. It is important to perform acid-fast staining on aspirate samples to rule out mycobacteriosis and nocardiosis.

10. Biopsy is the only way to definitively diagnose panniculitis. What is the pathologist looking for to make a diagnosis of panniculitis?

Again, depending on the etiology the biopsy may show varying types and degrees of inflammation and necrosis. Regardless, the inflammation is in the panniculus and may extend in any direction. In addition, vasculitis and/or interface dermatitis may be present when lupus erythematosus is responsible for lesion development. Panniculitis may be septal, lobular, diffuse, or a mixture of these patterns. Initially with sterile nodular panniculitis, the infiltrate is predominantly neutrophils and macrophages (Figure 34-1, *D*). Lymphocytes, plasma cells, and macrophages tend to dominate in more chronic lesions. With time the panniculus is gradually replaced with fibrous tissue. Special stains are used to evaluate for microorganisms. Polarized light examination is used to evaluate for foreign bodies. Injection remnants, specifically rabies vaccine, may appear as shiny amorphous-to-globular gray-brown material within macrophages or necrotic tissue.

11. When can a diagnosis of sterile nodular panniculitis be given?

Sterile nodular panniculitis is a diagnosis of exclusion. Supporting history, clinical signs, histopathology, and negative culture and special staining results are needed to make the diagnosis.

12. List treatments for sterile nodular panniculitis.

- Surgical excision of solitary nodules may be curative.
- Prednisone orally at 2 mg/kg every 24 hours (dogs) or 4 mg/kg every 24 hours (cats) for multiple nodules; give until lesions resolve (4-8 weeks) then gradually taper (2-3 months) to the lowest alternate-day dose that maintains remission.
- Vitamin E orally at 400 IU every 12 hours given 2 hours before or after a meal.
- Tetracycline/niacinamide orally for dogs >10 kg 500 mg of each every 8 hours or dogs <10 kg 250 mg of each every 8 hours; give until lesions resolve (2-3 months) then gradually taper to once-daily administration of each drug for maintenance.
- Pentoxifylline orally in dogs at 10-15 mg/kg every 12 hours; used as adjunctive therapy initially then possibly alone for maintenance.
- Antibiotics for secondary infection.
- Antimicrobial topical agents for secondary infection.
- Discontinue any drugs that may have been associated with lesion development.

13. Is therapy lifelong?

Not necessarily. Many young patients experience permanent remission, thereby allowing cessation of therapy. Some patients may experience long-term remission with disease recurrence. These patients will require therapy again and will probably need life-long maintenance therapy thereafter. Unfortunately, there are individuals that will have to stay on maintenance therapy lifelong to prevent sudden recurrence. In all cases, timely re-examinations are warranted to evaluate disease status, medication dosages, and medication side effects.

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35. VASCULITIS AND VASCULOPATHY

Daniel O. Morris, DVM, DACVD

1. What is vasculitis?

Vasculitis simply means "inflammation of vessels," but there is often misuse of terminology that may lead to confusion. Perivasculitis is an example: this is a very common inflammatory pattern seen in allergic dermatitis, where inflammatory cells are concentrated near small blood vessels in the dermis, but there is no disruption of the vessels themselves. A true vasculitis results in destruction of vessel walls by inflammatory cells, which disrupts blood flow and causes hypoxia of the recipient tissues. Histologically, a pathologist should be describing changes such as vessel wall necrosis, intramural inflammation (i.e., inflammatory cells within the vessel walls), endothelial cell swelling, leukocytoclasia ("nuclear dust," which results from the breakdown of inflammatory cell nuclei), and hemorrhage into the surrounding dermis or subcutis. However, not all of these criteria will be present in every case of vasculitis. It is the responsibility of the clinician to interpret the skin biopsy report and correlate this with the clinical signs to make a diagnosis of vasculitis.

2. What is vasculopathy?

Vasculopathy would technically mean any pathologic process that involves blood vessels. Clinically, we use this term when there are gross or histologic changes suggestive of tissue hypoxia, but an active vasculitis cannot be appreciated histologically. The pathologist may use terms such as dermal edema, "smudging" of collagen, atrophy of hair follicles (or "fading follicles"), perivascular cuffing by inflammatory cells, degenerative changes of the vessel walls without intramural inflammation, and hydropic degeneration of the basal cell layer of the epidermis and/or hair follicles. The term vasculopathy is also used to refer to thromboembolic accidents, such as occlusion of vessel walls by fibrin thrombi.

3. So, is a vasculopathy the same thing as a vasculitis, and we just can't prove it?

Possibly, although this will be highly variable depending upon the individual case and the etiology of the problem. For example, dermatomyositis and rabies vaccine-associated vasculitis with alopecia often meet only the histological criteria for "vasculopathy," but in the rare case of each, we find a very convincing vasculitis. I should also mention that in human beings, true vasculitis is a fleeting lesion. When biopsy specimens of the skin lesion are obtained sequentially, the inflammatory infiltrate shifts and eventually only "burned out" changes (that we as veterinarians would refer to as vasculopathy) remain.

4. Are there any pathognomonic clinical signs? What does the lesion actually look like?

Unfortunately, vasculitis/vasculopathy can present many faces. Lesions range from well-demarcated crateriform ulcers to nondescript scaling and crusting. Punctate ulcers of the foot pads and ischemic necrosis of pinnal margins are probably the most common lesions that I see (Figures 35-1 and 35-2), after dermatomyositis and rabies vaccine–associated vasculopathy. However, lesions may occur anywhere on the body, including mucocutaneous junctions and within the oral cavity.

A rare presentation of vasculitis is hemorrhagic urticaria, which may involve any area of the body. These are literally urticaria (welts) that are purpuric (deep red due to hemorrhage into the dermis; see Ghersetich et al.'s article for more complete information).

Figure 35-1 Punctate ulcers and hyperkeratosis on the footpads of a Yorkshire Terrier with idiopathic leukocytoclastic vasculitis.

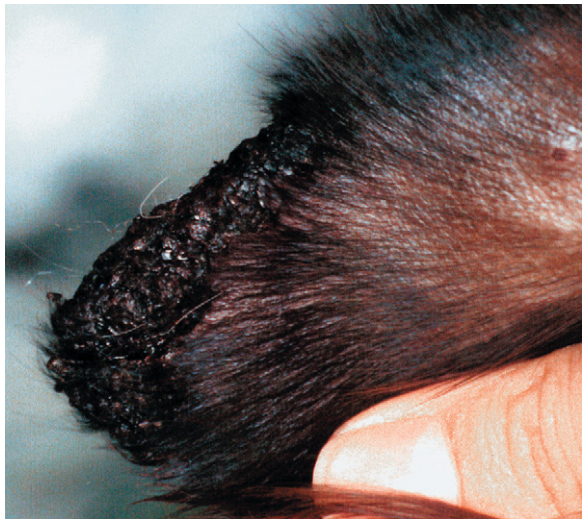

Figure 35-2 Pinnal margin ischemic necrosis in a mixed-breed dog with idiopathic leukocytoclastic vasculitis.

The one form that is very predictable is rabies vaccine–associated vasculitis. These dogs develop an expanding focus of alopecia at the site of previous subcutaneous vaccination that is often not noticed by the owner for 3 to 4 months after vaccination. The skin is typically erythemic and mildly scaly in the acute phase, and becomes atrophic and hyperpigmented with chronicity (see Ghersetich et al.'s article for more complete information). The alopecia is often permanent.

5. How does one tell the difference between purpura and erythema?

Because purpura is caused by leakage of blood from damaged vessels into the surrounding tissue, it will be very dark red. As the lesions age, bruising may become more apparent. However,

I have seen cases in which skin that looked purpuric had no evidence of hemorrhage histologically—just extreme vascular dilation in the dermis. A quick test to help differentiate between purpura and inflammation is to press a glass slide firmly against the lesion. Inflammation should blanch, while hemorrhage does not. This simple test, referred to as diascopy, can be falsely negative in cases with really intense inflammation and vascular dilation, so caution is warranted to avoid overinterpretation.

6. What causes vasculitis in dogs and cats?

Vasculitis and vasculopathy are not specific diseases, but rather clinical signs. Most cases probably result from an antigen-antibody response, where immune complexes become trapped in vessel walls and provoke an inflammatory response (also referred to as hypersensitivity vasculitis). Therefore, the vessels are "innocent bystanders" of a sort. Any foreign antigen that can provoke an immune response could potentially lead to this response. These include infectious agents (bacteria, rickettsia, fungi, protozoa, viruses), drugs and sera, foods and food additives, neoplasia, and sources of autoantibody responses (lupus erythematosus, rheumatoid arthritis, etc.). In my experience, the most common causes in dogs are drugs (a very wide range of drugs!), rabies vaccination, foods, and rickettsial diseases such as ehrlichiosis and Rocky Mountain spotted fever. Rabies vaccination has also been associated with a more generalized ischemic dermatopathy (Figure 35-3). Food sensitivity seems to be associated with many cases of urticarial vasculitis. In cats, vasculitis appears to be extremely rare. The cases I have seen have been associated with routine vaccinations, drugs, and with neoplasia (lymphoma). I am also aware of canine cases that were associated with lymphoma and possibly osteosarcoma. The bad news is that greater than 50% of all cases will be idiopathic! The same is true for human cases.

Figure 35-3 Ischemic dermatopathy associated with rabies vaccine administration in a Chihuahua. Note the alopecic, hyperpigmented, and atrophic skin over the bridge of the muzzle, periocularly, and over the occipital area. The pinnae are alopecic, cyanotic, and curling as a result of atrophy and ischemic necrosis.

7. Are there other skin diseases that can be confused with vasculitis clinically?

Absolutely. I have mistaken cases of eosinophilic dermatitis (Wells-like syndrome) and erythema multiforme for vasculitis. Both of these conditions can produce brightly erythemic lesions that can appear to be purpuric, and may not blanche with diascopy. I have been fooled several times, and the diagnosis was then made by the dermatopathologist. Interestingly, both of these conditions are cutaneous reaction patterns that may be associated with some of the same etiologies that are reported with vasculitis, especially drug reactions.

8. Give some examples of more common types of vasculitis/vasculopathy.

The most common presentations my dermatology group practice sees are leukocytoclastic vasculitis (a histologic category that may result from any of the aforementioned etiologies), and mononuclear vasculopathies associated with either familial dermatomyositis in Collies and Shelties or rabies vaccine–associated vasculitis with alopecia. We can also see predominantly eosinophilic vasculitis, or neutrophilic vasculitis that is non-cytoclastic. Whether there is any difference in etiology between the leukocytoclastic and the non-leukocytoclastic cases is unknown.

9. Are there any other specific breeds that are at risk?

Specific "syndromes" have been reported in the Jack Russell Terrier, German Shepherd, and in the Scottish Terrier breeds. Collies and Shetland Sheepdogs are the "classic" breeds at risk for dermatomyositis, although other breeds (Beauceron Shepherd, German Shepherd, Welsh Corgi, and Kuvasz among others) have been reported.

10. Are there specific drugs that have been implicated?

Many drugs have been implicated in the literature, and drug reactions can be difficult to document definitively, since re-exposing the patient to a potentially reactive drug is considered by most to be unethical. However, the temporal relationship between use of a drug and onset of clinical signs is often impossible to deny. One drug that is well known to be associated with cutaneous vasculitis is itraconazole (Sporanox), and this reaction appears to be dose-dependent.

11. When I suspect a vasculitis, how can I assure a definitive diagnosis when I take the skin biopsy?

First the bad news: there are no guarantees, and clients should be warned that a skin biopsy is a "test" without an absolute "answer" in many cases. Now the good news: with proper site selection and use of a knowledgeable dermatopathologist, the important differential diagnoses (erythema multiforme and eosinophilic dermatitis) can usually be excluded, and signs of vasculitis can usually be seen. Site selection is an art, and dependent upon experience in many cases. One hint: do not biopsy the middle of ulcers or severely crusted central areas. Select areas on the periphery of lesions that appear to be acutely inflamed, edematous, purpuric, or cyanotic.

12. What other laboratory evaluations should be considered "standard" for every case?

The answer to this question can be highly variable, depending on the patient's history and other (systemic) clinical signs. Certainly a skin biopsy is necessary to make the absolute diagnosis of a vasculitis/vasculopathy. Once the diagnosis is in hand, the search for an etiology begins. The minimum database suggested by Nichols et al. is a complete blood cell count with differential, serum biochemical assay, urinalysis, and histopathology. Infectious etiologies (such as rickettsial diseases in dogs and retroviruses in cats) should be ruled out by serology. Because bacterial and fungal infection may cause either localized or more widespread vasculitis, tissue cultures (bacterial, fungal, and mycobacterial) should be recommended when serologic results are negative. To rule out sources of autoantibody, tests such as Coombs', antinuclear antibody, and rheumatoid factor should be considered. In vasculopathy cases with extensive thrombosis, bacterial sepsis should be ruled out with blood culture. Food sensitivity is also an important differential diagnosis, especially for dogs with urticarial vasculitis.

13. What should I do while the biopsy results are pending?

This depends on the physical status of the patient. I typically avoid the temptation to start steroidal treatment, and simply provide good nursing care. Most patients will not be severely ill. If there is a history of drug administration, stop it immediately! If you suspect a rickettsial disease could be the basis for the vasculitis, start appropriate antimicrobial therapy while results are pending.

14. Which drugs are appropriate for treating canine vasculitis/vasculopathy?

This will depend on the clinical and histologic type of vasculitis diagnosed. Obviously, eliminating the primary source of antigen (drugs, foods, infectious agents) may be curative in some cases. Pentoxifylline (Trental) is most commonly recommended for rabies vaccine-induced vasculitis with alopecia, rabies vaccine–associated ischemic dermatopathy, and for dermatomyositis. The dosages used have been variable (Table 35-1). The addition of vitamin E has also been recommended; however, there is no hard evidence to support its added benefit.

Table 35-1 ***Drugs Used in the Treatment of Canine Vasculitis***

DRUG	DOSE/ROUTE	INTERVAL	MONITORING
Pentoxifylline	10-40 mg/kg PO	q 8-12 h	Vomiting/nausea, hyperactivity
Sulfasalazine	15-22 mg/kg PO	q 8-12 h	CBC, LFTs, STT q 2 wk initially
Dapsone	1 mg/kg PO	q 24 h	CBC, LFTs, STT q 2 wk initially
Tetracycline +	22 mg/kg PO	q 8-12 h	Vomiting/nausea
Niacinamide	22 mg/kg PO	q 8-12 h	
Auranofin*	0.1-0.2 mg/kg PO	q 24 h	CBC, Plt, UA q 2 wk initially
Aurothioglucose*	1 mg/kg IM	q 7 d	UA weekly; CBC q 2 wk initially
Azathioprine	10-22 mg/kg PO	q 12-24 h	CBC, Plt, LFTs q 1-2 wk initially
Chlorambucil*	0.1-0.2 mg/kg PO	q 24 h	CBC, Plt. weekly initially, LFTs prn
Prednisone†	2 mg/kg PO	q 12 h	Glucocorticoid side effects
Triamcinolone†	0.22 mg/kg PO	q 24 h	Glucocorticoid side effects
Dexamethasone†	0.22 mg/kg PO	q 12-24 h	Glucocorticoid side effects
Cyclosporine A*	5-10 mg/kg PO	q 12-24 h	Secondary infections and neoplasia; papillomatosis; plasma levels
Mycophenolate	10-20 mg/kg PO	q 8-12 h	CBC q 2 wk initially; diarrhea
Methotrexate	2.5 mg/m^2 PO	q 24 h	CBC, Plt weekly, LFTs q 2 wk

*May be used in cats at the same dosage as dogs.
†May be used in cats; double the dosage listed for dogs. Dosage should be tapered gradually with respect to clinical response, to the lowest possible maintenance dose and frequency of administration.
CBC, Complete blood cell (count); *Plt,* platelet count; *LFTs,* liver function tests; *STT,* Schirmer tear test.

For idiopathic vasculitides, most of which will be granulocytic (i.e., neutrophilic and/or eosinophilic), a number of drugs have been used successfully in a limited number of cases. Antigranulocytic drugs are the first choice of the author, and may include sulfasalazine, dapsone, gold compounds, or a combination of tetracycline/niacinamide. Steroidal anti-inflammatory drugs have long been the mainstay of vasculitis therapy in humans and animals, and will often be prescribed in combination with these other medications due to their rapid effect. For idiopathic cases, which may persist for indefinite periods, nonsteroidal drugs should be used in combination with steroidal drugs for their steroid-sparing effect. Reducing and eventually eliminating the steroid should be the goal. However, the sulfa derivatives (sulfasalazine and dapsone) have serious side-effect profiles of their own which must be respected. These include bone marrow suppression and hepatocellular toxicity (sulfasalazine and dapsone) and renal toxicity (dapsone). Careful laboratory monitoring every 2 weeks initially, then at least quarterly with chronic use, is essential.

Pentoxifylline has not been reported to be successful in managing granulocytic vasculitides; however I still use it when the histologic inflammatory cell type is predominantly mononuclear. It should also be noted that in human beings, the inflammatory infiltrate shifts from granulocytic to mononuclear over 48 hours in most cases of leukocytoclastic vasculitis. Because the skin biopsy is just one picture taken during the lifespan of a lesion, it may be inappropriate to base therapy upon this impression alone.

15. Can these same drugs be used in cats?

The literature is very sparse regarding the treatment of feline vasculitis. My experience has been limited to the use of steroidal drugs and chlorambucil in feline cases. Gold salts (both oral and parenteral) have been used in cats for other immune-mediated diseases, and could also be considered in specific cases.

16. The treatment is not working…now what?

This is not an uncommon occurrence. Vasculitides can be extremely difficult to control! When steroidals, pentoxifylline, and anti-granulocytic drugs have failed, the immunosuppressive drugs can be tried. Included in this class are azathioprine, chlorambucil, cyclophosphamide, methotrexate, cyclosporin A, and mycophenolate mofetil. All of these drugs have been reported in the treatment of human vasculitides, but information is extremely sparse on their use in veterinary medicine. One caveat that the author would add from personal experience: when a vasculitis is not responding to therapy, rule out underlying neoplasia as the source of antigen! This is easier said than done in some cases, as tumors may not cause other clinical signs for several months after a vasculitis has started.

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Section VII
Endocrine and Metabolic Disorders with Cutaneous Manifestations

36. THYROID DYSFUNCTION

Manon Paradis, DVM, MVS*c*, DACVD

1. Name the main thyroid dysfunctions and the species most commonly affected.

- Hypothyroidism and hyperthyroidism.
- Hypothyroidism is the most common endocrinopathy in the dog; however, it is extremely rare as a naturally occurring disorder in cats. Conversely, hyperthyroidism is the most common endocrine disorder in the cat, but quite rare in dogs.

2. What are the physiologic roles of thyroid hormones?

Thyroxine (T4) and triiodothyronine (T3) have a myriad of physiologic effects and are necessary for normal cell metabolism of virtually every tissue and organ. Receptors for these hormones have been identified in almost all tissues, where they increase the metabolic rate and oxygen consumption. In physiologic quantities, thyroid hormones are anabolic. However, in excess (i.e., hyperthyroidism) they have catabolic effects on muscle and adipose tissues. Thyroid hormones stimulate erythropoiesis, and regulate both cholesterol synthesis and degradation.

Thyroid hormones play a major role in the differentiation and maturation of skin as well as maintenance of normal cutaneous functions. They are needed for the initiation of anagen hair follicles and regulation of the cornification process and sebaceous glands secretion. In hypothyroidism, epidermal atrophy and abnormal cornification occur because of decreased protein synthesis, mitotic activity, and oxygen consumption.

In various animal models, it was shown that lymphoid tissue development depends on thyroid gland integrity. Thyroidectomy results in hypoplasia of lymphoid organs, and depletion of thyroid hormones results in alteration in neutrophils as well as B- and T-lymphocyte function.

3. What causes hypothyroidism in dogs?

Hypothyroidism (i.e., decreased production of T4 and T3) can be primary (due to destruction of the thyroid gland itself; this represents more than 95% of clinical cases of canine hypothyroidism), secondary (decreased thyroid-stimulating hormone [TSH] from the pituitary gland, less than 5% of the clinical cases) or tertiary (decreased thyroid-releasing hormone [TRH] from the hypothalamus; not documented in dogs yet). The two most common causes of canine adult-onset primary thyroid dysfunction are lymphocytic thyroiditis (apparently genetically programmed) and idiopathic atrophy of the thyroid gland, which may be the end stage of lymphocytic thyroiditis in an unknown percentage of cases (Box 36-1).

4. Which population of dogs is typically affected by hypothyroidism?

Hypothyroidism occurs most commonly in mid to large-size purebred dogs with an onset between 3 and 8 years of age. Several breeds including Doberman Pinschers, Golden Retrievers, Irish Setters, Airedales, Great Danes, Old English Sheepdogs, Borzoi, and Beagles are reported to be at increased risk of hypothyroidism.

Box 36-1 *Etiologies of Canine Hypothyroidism*

Primary hypothyroidism
Lymphocytic thyroiditis
Idiopathic atrophy
Abnormal hormonogenesis
Destruction by a neoplasm
Iatrogenic (e.g., surgical ablation, antithyroid drugs, radioactive treatment)

Secondary hypothyroidism
Pituitary malformation (e.g., pituitary dwarfism of German Shepherd Dogs)
Pituitary destruction (e.g., neoplasm)
Suppression of pituitary thyrotrope cells (e.g., natural HAC, nonthyroidal illnesses)
Iatrogenic (e.g., exogenous glucocorticoids, hypophysectomy, radiation therapy)

Tertiary hypothyroidism
Congenital hypothalamic malformation
Acquired hypothalamic destruction (e.g., neoplasm, hemorrhage, abscess, granuloma)

Congenital hypothyroidism
Thyroid gland dysgenesis (e.g., aplasia, hypoplasia, ectasia)
Dyshormonogenesis (e.g., defective iodine organification)
Dietary iodine deficiency (congenital goiter)

5. What is the typical signalment of dogs with hypothyroidism?

Hypothyroidism is characterized by a plethora of clinical signs affecting the skin and other organ systems that occur with a deficiency of thyroid hormone activity (Table 36-1). However, none are pathognomonic of hypothyroidism, and their development is generally gradual and insidious.

Table 36-1 *Clinical Signs of Canine Hypothyroidism*

COMMON	UNCOMMON	RARE TO QUESTIONABLE
Dull, dry, brittle hair coat	Alopecia	Hypothermia
Hypotrichosis	Pyoderma	Bradycardia
Seborrhea	Facial myxedema (tragic look)	Ocular disorders
Lack of hair regrowth after clipping	Ceruminous otitis externa	Reproductive disorders
Weight gain/obesity (without polyphagia)	Weakness	Facial nerve paralysis
Lethargy/mental dullness	Cold intolerance	
	Exercise intolerance	

Dermatologic signs of canine hypothyroidism are reported in approximately 80% of cases. The initial dermatologic abnormalities include a dull, dry, brittle hair coat that gradually becomes sparse and easily epilates or fails to regrow after clipping, and generalized seborrhea. If left untreated, a bilaterally symmetric truncal alopecia may eventually develop, as well as alopecia on the bridge of the nose and tail, and myxedema. Ceruminous otitis externa can also

occur, but this is infrequent. Hypothyroid dogs have an increased susceptibility to develop recurrent bacterial pyoderma, which may be the result of altered local immunity and/or impaired systemic immunity. However, by the time pyoderma develops, these immunocompromised dogs usually have other obvious clinical signs associated with hypothyroidism.

In addition to the dermatologic changes, dogs can have clinical signs associated with a decreased metabolic rate: lethargy (which is frequently overlooked until increased activity and alertness is noticed after thyroid hormone supplementation is initiated); obesity or weight gain despite normal or low caloric intake; weakness, and exercise intolerance. Less frequently, findings include decreased heart rate and body temperature; cold intolerance; various neuromuscular disorders (facial and vestibular neuropathies, myopathies, etc.); central nervous system clinical signs; atherosclerosis (due to the altered lipid metabolism); reproductive abnormalities (although not well documented, except for inappropriate galactorrhea in intact females); corneal lipid deposition, etc.

6. How easily can I diagnose canine hypothyroidism?

Hypothyroidism is one of the most frequent endocrinopathies in the dog. However, due to the diversity of the clinical signs and the unavailability of a perfect diagnostic test, hypothyroidism is also the most commonly misdiagnosed endocrinopathy in dogs.

7. Can I diagnose hypothyroidism in a 1-year-old dog?

In a clinical context, hypothyroidism is virtually nonexistent in dogs younger than 2 years of age. Congenital hypothyroidism is rare and results in disproportionate dwarfism with epiphyseal dysgenesis, macroglossia, delayed dental eruption and cretinism, in addition to the aforementioned symptoms.

8. Can hypothyroid dogs be diagnosed on physical examination?

At best, it can only be strongly suspected in very chronic and severe cases when several clinical signs are present. However, despite the numerous clinical signs that can be seen in canine hypothyroidism, it remains difficult to diagnose because none of those symptoms is pathognomonic.

9. What is the ideal test to evaluate canine thyroid function?

Unfortunately, of the many diagnostic tests available to evaluate thyroid function, no single test is optimal at the present time. None can accurately confirm or rule out hypothyroidism in all cases.

Definitive diagnosis of hypothyroidism can best be made, at this time, by a combination of compatible clinical signs, abnormal specific thyroid test results (in absence of diseases or drugs that can affect results), coupled with successful long-term response to levothyroxine supplementation.

10. Which nonspecific laboratory findings am I expected to find in canine hypothyroidism?

A mild, nonregenerative anemia has been noted in approximately 30% of hypothyroid dogs. A fasting hypercholesterolemia is present in up to 75% of hypothyroid dogs. However, these findings can also be associated with other diseases such as hyperadrenocorticism; diabetes mellitus; pancreatitis; and renal, hepatic, or enteric diseases.

11. Should I perform a hemogram, biochemical panel, and urinalysis on every suspected case of hypothyroidism?

These tests are not always part of the initial workup in a dermatologic patient, but are routinely performed if the animal is presented to an internist for vague medical clinical signs. However, these tests should be performed if clinical signs appear multisystemic, and they are strongly recommended before initiating thyroid hormone replacement therapy to support a diagnosis of hypothyroidism and to rule out other disorders.

12. How useful is a skin biopsy in the diagnosis of hypothyroidism?

It is most useful to rule out other diseases such as follicular dysplasia and sebaceous adenitis.

13. What dermatopathologic findings can I expect to find in hypothyroidism?

Most frequently, dermatopathologic findings will reveal nonspecific changes of an endocrinopathy. Occasionally, however, some histologic changes can be more characteristic of hypothyroidism (e.g., dermal thickening, myxedema, hypertrophy and vacuolation (controversial) of arrector pili muscles).

14. List the various diagnostic tests available for a biologic exploration of canine thyroid function.

- Basal serum hormone concentrations
  - Total thyroxine (TT4)
  - Free thyroxine (FT4)
  - Total and free triiodothyronine (TT3 and FT3)
  - Reverse triiodothyronine (RT3)
  - Endogenous canine TSH assays (cTSH)
- Dynamic tests
  - TSH stimulation test
  - TRH stimulation test
- Miscellaneous
  - Antithyroglobulin antibodies (AtgA)
  - Antithyroid hormone antibodies (AT3A/AT4A)
  - Thyroid biopsy
  - Scintigraphy

15. How useful is the measurement of basal total thyroxine (TT4) concentration?

Serum TT4 concentration, which represents the sum of both protein-bound and free circulating hormones, is commonly measured to assess thyroid function, in spite of significant overlap between euthyroid and hypothyroid dogs. It is most frequently analyzed with radioimmunoassay (RIA), although an in-house enzyme-linked immunosorbent assay (ELISA) method is also available.

Basal TT4 concentration remains an excellent screening test for canine thyroid dysfunction. Dogs with TT4 concentrations well within the reference range may be assumed to be euthyroid, unless anti-T4 antibodies are causing a spurious increase in TT4 value. This is a rare phenomenon, and TT4 values are usually extremely high. Overall, with some patient preselection, one can expect a diagnostic accuracy of approximately 80% when evaluating serum TT4 concentration alone:

- ≈99% of dogs with a TT4 concentration >15 nmol/L are euthyroid;
- >95% of the dogs with a TT4 concentration <5 nmol/L are hypothyroid;
- any results between 5 and 15 nmol/L are in the gray zone;
- the reference range for TT4 is usually 15-45 nmol/L for most laboratories.

16. How reliable is the in-house ELISA measurement of TT4 concentration?

The in-house ELISA kit is not accurate for determining serum TT4 concentrations in dogs and cats. Indeed, it was recently shown that there were substantial discrepancies between ELISA and RIA results for TT4 concentration. In addition, the degree of precision of ELISA kit findings was poor. Therefore, measurement of TT4 by RIA is recommended.

17. Can TT4 be used as a single test to confirm hypothyroidism?

Basal TT4 can be an economical and valuable test, even if used alone, to rule out hypothyroidism. However, a low TT4 does not imply hypothyroidism. In healthy euthyroid dogs, the TT4 concentration may decrease below the reference range as much as 20% of the time (with no

predictable diurnal pattern) and over 50% of euthyroid dogs can have low serum basal TT4 at some time during the day, reflecting the risk of establishing a diagnosis of hypothyroidism based on a low TT4 alone.

In addition, serum TT4 concentrations gradually decline with age, and in some breeds such as Greyhounds and Scottish Deerhounds the basal TT4 is lower than in other breeds. Newfoundlands have also been mentioned as having lower basal TT4; however, another study reported TT4 and cTSH values similar to those in other breeds.

In euthyroid dogs, thyroid hormone levels, and particularly TT4, often decreases below the reference values following administration of certain drugs such as trimethoprim-sulfa (dermatologic dose), glucocorticoids, phenobarbital, acetylsalicylic acid, and clomipramine.

18. What is "euthyroid sick syndrome"?

Several nonthyroidal illnesses (NTI) can cause a reduction of serum total T3 and T4 concentrations and an increase of serum rT3 concentrations (an inactive product) in euthyroid dogs. In this situation, called "euthyroid sick syndrome," it is thought that there is a metabolic switch in the sick patient to protect by counteracting the excessive calorigenic effects of T3 in catabolic states. This leads to decreased production of T3 from T4, and decreased rT3 degradation. Indeed, thyroid hormone concentration can significantly decrease below the reference values in the presence of nonthyroidal systemic illnesses such as renal, cardiac, and hepatic insufficiencies, hyperadrenocorticism, diabetes mellitus, pancreatitis, neoplasia, and even pyoderma. This is a common source of misdiagnosis (when basal serum TT3 and/or TT4 concentrations are used to diagnose hypothyroidism). In these circumstances, the patients are euthyroid and in no need of thyroid hormone supplementation.

19. What is free thyroxine?

Free T4 is the active fraction of T4 that is unbound to protein and constitutes less than 1% of TT4.

20. What is the advantage of measuring free thyroxine rather than total thyroxine?

In theory, FT4 is less influenced by nonthyroidal illnesses or medications than TT4. In a small percentage of dogs, FT4 concentration will give a diagnostic precision superior to that of TT4 levels, but only if measured by equilibrium dialysis (ED), a diagnostic technique that is expensive, laborious, and not widely available. Most laboratories offering FT4 assays unfortunately rely on a RIA method, which essentially does not give more precision than a basal TT4 concentration. Nevertheless, even when FT4 is determined with ED, there is an overlap between FT4 results in hypothyroid and euthyroid dogs (sensitivity of ≈0.98 and a specificity of ≈0.92). Equilibrium dialysis assay is unaffected by anti-T4 antibodies.

By routinely measuring serum FT4 (ED) concentration instead of TT4 (RIA) levels, the diagnostic accuracy will increase by a few percentage points, but also the expense in all patients (FT4 by ED is typically two to three times more expensive than TT4 by RIA). Nevertheless, it is advantageous when the presence of anti-T4 antibodies in suspected (because ED assay is unaffected by AT4A).

21. Comment on the usefulness of measuring total and free triiodothyronine concentrations.

Serum TT3 concentration is not reliable as a screening tool to evaluate thyroid function, because there is considerable overlap between values in healthy, hypothyroid and euthyroid sick dogs. One study showed that up to 70% of normal dogs had low serum TT3 concentrations at some time during the day. This parameter is nowadays not often used. No study evaluating the diagnostic usefulness of FT3 is available.

22. Comment on endogenous canine TSH assays (cTSH).

In humans, the diagnosis of primary hypothyroidism is often made when low serum FT4 and

high endogenous TSH concentrations are simultaneously found. Commercial endogenous cTSH assays became available in dogs a few years ago, and their diagnostic potential has since been evaluated in normal, hypothyroid, and euthyroid sick dogs. Unfortunately, the clinical usefulness of cTSH did not meet our expectations:

- ≈25% of hypothyroid dogs have a serum cTSH concentration in the euthyroid range (sensitivity, 0.63-0.87);
- ≈10% of euthyroid dogs have an increased serum cTSH concentration in the hypothyroid range (specificity, 0.75-0.93);
- The usual reference range for serum cTSH concentration is 0.02-0.6 ng/mL.

In early thyroid failure in humans, TT4 is maintained in the normal range by an increase in serum TSH concentration. This phenomenon most likely occurs in dogs as well; however, the thyroid dysfunction should then be subclinical, and thyroid function would not normally be evaluated at that stage.

When assessing thyroid function in dogs, serum cTSH concentration should not be evaluated alone but in association with other parameters such as TT4 or FT4 by ED, keeping in mind, as mentioned previously, that in ≈25% of the hypothyroid dogs cTSH concentration will remain normal and that in ≈10% of euthyroid dogs, cTSH concentration will increase into the hypothyroid zone.

23. Describe the thyrotropin stimulation test.

The TSH test is considered the most reliable, noninvasive diagnostic test to evaluate thyroid function in dogs, allowing differentiation, in most instances, between hypothyroid dogs, euthyroid dogs, and euthyroid dogs with nonthyroidal illness.

The most widely used protocol consists in the measurement of TT4 before and 4-6 hours after administrating 0.1 IU/kg of bovine TSH (bTSH) intravenously. However, a dose as low as 1 IU/dog (post-TSH TT4 sampled 4 hours later) is sufficient to achieve a maximal thyroidal TT4 response in large size (30-40 kg) euthyroid dogs, even if the bTSH had been frozen in aliquots for up to 200 days.

24. Why is the thyrotropin stimulation test not used routinely to evaluate canine thyroid function?

It is because medical grade bTSH is no longer commercially available. A chemical-grade bTSH (Sigma, not licensed for clinical use) is still used by some clinicians in selected cases presenting a diagnostic dilemma, although anaphylactic reactions may occur. However, a recent study, using recombinant human TSH (rhTSH) in lieu of bTSH, has produced promising results, and other studies are in progress.

25. What is the significance of antithyroglobulin autoantibodies?

Antithyroglobulin autoantibodies (ATgA) can be found in up to 60% of hypothyroid dogs and in ≈3% of normal dogs. A positive ATgA titer suggests the presence of autoimmune lymphocytic thyroiditis; however, it is not an indicator of thyroid hypofunction. Clinical signs of hypothyroidism are observed when more than 75% of thyroid function is lost, and this usually occurs a long time after the pathologic process was initiated. Whether all dogs with ATgA ultimately develop clinical hypothyroidism is not known. Therefore, we should never base a clinical diagnosis of hypothyroidism on the sole presence of ATgA because this gives no information on the capacity of the thyroid gland to synthesize thyroid hormones.

However, measurement of ATgA combined with the measurements of serum FT4 (ED) and cTSH concentrations (OFA certification) has been advocated for screening breeding stocks of breeds at risk such as Golden Retriever, Doberman, Beagle, and Borzoi with the aim of ultimately eliminating heritable forms of thyroiditis.

26. What is the significance of antithyroid hormone antibodies (AT3A and AT4A)?

These autoantibodies to T3 or T4 have been found in ≈4% and ≈0.2%, respectively, of

canine sera submitted for thyroid testing. AT3A or AT4A is present in less than 30% of hypothyroid dogs. While probably of little physiological significance, the presence of AT3A or AT4A can interfere with measurement of serum thyroid hormone concentrations, usually resulting in a spurious increase in measured hormone levels.

27. List the most useful specific diagnostic tests for evaluating canine thyroid function and name the main reasons why (Table 36-2).

Table 36-2 ***Diagnostic Tests for Evaluating Canine Thyroid Function***

TT4 (RIA)	Economical
	Relatively reliable in *ruling out* hypothyroidism
FT4 (ED)	Very good diagnostic accuracy in most cases
	No interference with AT4A
	Relatively expensive
cTSH	Useful when combined with TT4 or FT4
TSH stimulation test	Rarely performed
	May regain popularity with rhTSH?
ATgA	For screening breeding stocks (combined with FT4 and cTSH)

28. What test would you recommend to diagnose hypothyroidism in the dog?

Recommendations depend on the availability of tests and the reasons for testing such as (1) clinical signs suggestive of hypothyroidism but diagnosis unlikely; (2) clinical signs suggestive of hypothyroidism and diagnosis probable; and (3) screening asymptomatic breeding stock.

Measurements of serum TT4 concentration along with the measurement of serum cTSH concentration or serum FT4 concentration by ED are currently popular tests for evaluating thyroid function in the dog. However, patient selection and results interpretation are overall more important than which diagnostic test is chosen. Over-interpretation of any thyroid function test should be avoided, especially in clinically ill dogs or in dogs receiving drugs such as sulfonamides, phenobarbital, glucocorticoids, acetylsalicylic acid, and clomipramine.

For example, when serum TT4 and cTSH concentrations are measured, the diagnostic precision will be ≈85%: i.e., ≈85% of the dogs will have either a diagnosis of euthyroidism (T4T >15 nmol/L and cTSH < 0.6 ng/mL) or a diagnosis of hypothyroidism (TT4 < 5 nmol/L and cTSH > 0.6 ng/mL). If there is discordance or if the results are in the gray zone, it is preferable to resubmit blood samples a few weeks to a few months later or to perform additional tests such as a hemogram and a biochemical panel including fasting cholesterol, FT4 by ED, ATgA or, in the near future, thyrotropin stimulation test using rhTSH. As a last resort, a therapeutic trial with levothyroxine can be tried if results are discordant or in the gray zone, but only if reliable clinical signs are present to evaluate response to treatment. One must be careful if the only criterion is the presence of endocrine type alopecia, because hair regrowth may be coincidental (canine recurrent flank alopecia, telogen defluxion). Remember, any thyroid function test result (and response to therapy) in dogs should be interpreted carefully, and always with a healthy dose of skepticism.

29. Before evaluating thyroid function in a dog, what should the clinician do?

The clinician should: (1) select patients with clinical signs and age (>2 years) that are compatible with hypothyroidism; (2) be aware of the several factors (mostly drugs and nonthyroidal illnesses) that can alter the test results; (3) postpone, if possible, thyroid evaluation until resolution of the illness or withdrawal of the drug; and (4) send the samples to a laboratory that has validated assays for dogs and has established reference values.

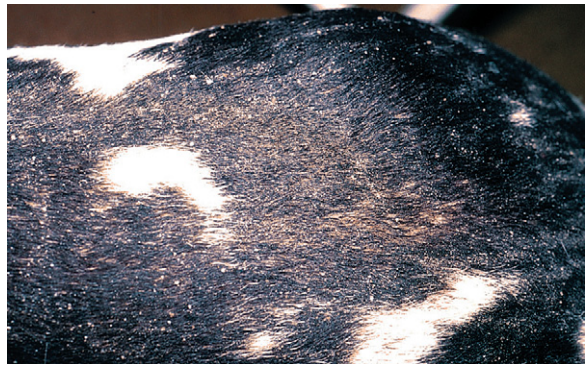

Figure 36-1 Hypothyroidism in a Great Dane. Note the dull, dry, brittle hair coat and hypotrichosis.

30. What is the ideal treatment for canine hypothyroidism?

Levothyroxine (Thyro-Tab, Soloxine, Synthroid) is administered orally, at the induction dose of 22 µg/kg (or 0.5 mg/m^2) every 12-24 hours. For example, using a dose based on body surface, a 30-kg (0.96 m^2) dog would receive a dose of 500 µg instead of 660 µg; a 40-kg (1.17 m^2) dog would receive a dose of 600 µg instead of 880 µg. Although in North America most dogs are initially treated twice a day, it was recently proven that once-a-day administration of an average dose of 22 µg/kg is adequate for most hypothyroid dogs.

31. When can we expect clinical remission?

Development of clinical signs of hypothyroidism is long and insidious; so is the response to treatment. Although lethargy and mental dullness can resolve within a few days, body weight reduction is gradual and it can take a few months for the hair coat to return to its normal appearance.

32. How long do we need to treat?

Treatment of hypothyroidism is lifelong; hence the importance of a definitive diagnosis before initiating treatment.

33. How do we determine if the levothyroxine dose regimen is adequate?

After replacement therapy has been administered for 4-8 weeks or when all the clinical signs have resolved, a post-pill serum concentration can be obtained, 4-6 hours after administration of levothyroxine to determine if adequate concentration of hormone is present in the blood. Typically, we aim for a TT4 in high normal range, or slightly above the normal range. In most hypothyroid dogs, treatment can be reduced to (in dogs treated every 12 hours) or maintained on once-a-day administration (≈22 µg/kg every 24 hours) after an adequate clinical response is noted, without reduction in efficacy.

The usefulness of serum cTSH measurements to determine if the dose of levothyroxine is adequate is limited in dogs, because ≈25% of hypothyroid dogs already have cTSH concentrations within reference values before initiation of therapy. In addition, the assay currently available is not sensitive enough to differentiate a normal cTSH concentration from a decreased one. Because serum cTSH concentration should normalize with appropriate therapy, it can only at best detect hypothyroid dogs that are undertreated. However, the assay cannot distinguish between dogs that are adequately supplemented and those that are oversupplemented.

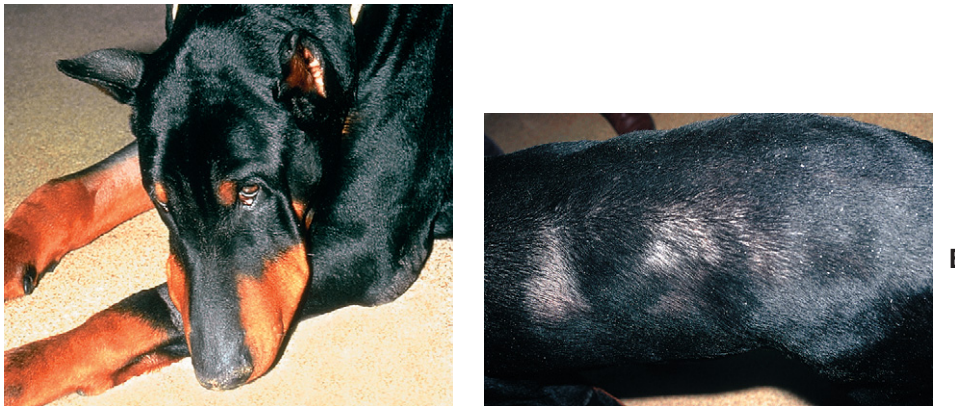

Figure 36-2 **A,** Hypothyroid in a Doberman Pinscher. Note the "tragic" face with myxedema and alopecia on the bridge of the nose. **B,** Trunk of the same Doberman Pinscher. Note the alopecia and seborrhea on the flank.

34. Can I induce thyrotoxicosis if I overtreat or if my diagnosis is erroneous?

Thyrotoxicosis (PU/PD, weight loss, panting, nervousness, and tachycardia) is rare in the dog, due to the rapid metabolism and renal and hepatic excretion of thyroid hormone. However, we should be cautious in dogs suffering with kidney or hepatic diseases, diabetes mellitus, hypoadrenocorticism, and congestive heart failure. In these instances, it has been recommended that levothyroxine therapy be initiated at 5 µg/kg every 12 hours, and then increased progressively over the following 3 to 4 weeks. However, if therapy is induced at 22 µg/kg every 24 hours, instead of every 12 hours, potential complications are unlikely.

35. Can a treated hypothyroid dog be used as a breeder?

Although hypothyroidism holds an excellent prognosis when appropriate and life-long treatment is achieved, affected dogs should not be bred due to the hereditary nature of this disorder.

36. What is the typical signalment of cats with hyperthyroidism?

Feline hyperthyroidism typically occurs in older cats. Common clinical signs include polyphagia, polydipsia, polyuria, weight loss, hyperactivity, tachycardia, vomiting, and diarrhea.

37. What are the cutaneous abnormalities associated with feline hyperthyroidism?

Dermatologic signs, which occur in approximately 30% of cases of feline hyperthyroidism, include excessive shedding, matting of the hair coat and seborrhea, and focal or symmetric alopecia caused by overgrooming. Increased rate of claw growth and thin, hypotonic skin can also be seen.

38. What are the cutaneous abnormalities of feline hypothyroidism?

Hypothyroidism is extremely rare in cats. Dermatological abnormalities, which resemble those of dogs, may include, in addition to dorsal matting of the hair coat due to decreased grooming, dry and dull pelage, seborrhea, and poor hair regrowth after clipping. The skin can be dry, scaly, and thickened, and facial myxedema can also be seen. Alopecia of the pinnae, pressure points, and dorsal and lateral tail base region can develop. Although quite rare, a bilateral, symmetric alopecia may develop.

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37. ADRENAL DYSFUNCTION

Rhonda L. Schulman, DVM, DACVIM

1. **List the dermatologic manifestations of canine hyperadrenocorticism.**
   - Bilaterally symmetrical, truncal alopecia
   - Involvement of the flank region, face, or legs has also been seen
   - Moth-eaten appearance (short-coated dogs)
   - Poor regrowth of shaved hair
   - Thin, easily wrinkled skin; "cigarette paper skin"
   - Hyperpigmentation
   - Comedones
   - Calcinosis cutis
   - Bruising
   - Seborrhea
   - Secondary bacterial infections
   - Adult-onset demodicosis
   - Poor wound healing
   - Striae
   - Cutaneous phlebectasias

2. **What is a phlebectasia?**

Phlebectasias are erythematous vascular lesions, often found over the ventrum and medial thighs. They can be up to 6 mm in diameter. They are asymptomatic. Phlebectasias are seen in up

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   - Striae
   - Cutaneous phlebectasias

2. **What is a phlebectasia?**

Phlebectasias are erythematous vascular lesions, often found over the ventrum and medial thighs. They can be up to 6 mm in diameter. They are asymptomatic. Phlebectasias are seen in up

to 40% of dogs with hyperadrenocorticism. Phlebectasias result from weakening of vascular collagen. They may not regress with treatment for hyperadrenocorticism.

3. Why are some dogs with hyperadrenocorticism itchy?

Approximately 25% of dogs with hyperadrenocorticism are pruritic. The pruritus can be caused by pyoderma, seborrhea, calcinosis cutis, or demodicosis.

4. Why do dogs with hyperadrenocorticism bruise easily?

Fragility of both the skin and blood vessels causes these dogs to readily bruise (Figure 37-1). Additionally, these patients have less subcutaneous tissue and thus less protection from trauma.

5. What causes calcinosis cutis?

It results from calcium deposition in the dermis and subcutis. Lesions are usually found on the head and neck, dorsal midline, and ventral abdomen. The lesions are firm and frequently gritty. The lesions may appear as papules, plaques, or nodules and are yellowish in color (Figure 37-2). The underlying pathogenesis is not known.

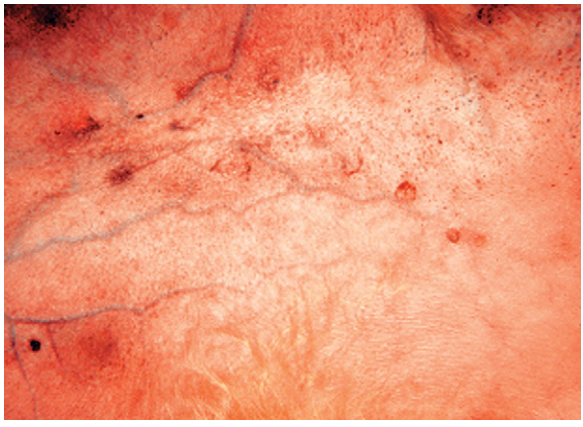
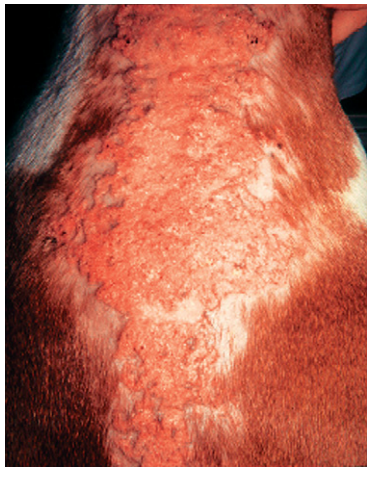


Figure 37-1 Thin skin with fragile blood vessels on the abdomen of a dog with hyperadrenocorticism.

Figure 37-2 Calcinosis cutis on the dorsal neck of a dog with hyperadrenocorticism.



6. List other differential diagnoses for truncal alopecia.

- Hypothyroidism
- Sex hormone imbalance
- Telogen or anagen defluxion
- Demodicosis
- Hyposomatotropism
- Dermatophytosis
- Follicular dysplasia

7. What are the other common clinical signs of canine hyperadrenocorticism?

- Polyuria-polydipsia
- Polyphagia
- Panting
- Pot-bellied appearance
- Muscle weakness
- Lethargy
- Anestrus
- Testicular atrophy

8. List other differential diagnoses for polyuria-polydipsia.

- Primary polydipsia
- Primary central diabetes insipidus (CDI)
- Nephrogenic diabetes insipidus (NDI)
  - Renal insufficiency
  - Pyelonephritis
  - Postobstructive diuresis
  - Hypoadrenocorticism
  - Hyperthyroidism
  - Hepatic insufficiency
  - Pyometra
  - Hypercalcemia
  - Hypokalemia
  - Glucosuria
  - Renal medullary solute washout
  - Primary NDI

9. Give two reasons why a dog with hyperadrenocorticism might become blind.

- Sudden acquired retinal degeneration syndrome
- Pituitary macroadenoma

10. What causes canine hyperadrenocorticism?

Hyperadrenocorticism may be naturally occurring or iatrogenic. In all cases, the clinical signs are the result of hypercortisolemia. Of the naturally occurring cases, 80-85% are due to pituitary-dependent disease. The hyperplastic pituitary secretes excessive ACTH, stimulating the adrenal glands to secrete excessive cortisol. In the other 15-20% of naturally occurring cases, the hyperadrenocorticism is the result of an adrenal tumor. Both adrenocortical adenomas and carcinomas may be hyperfunctional.

11. Other than dermatologic diseases, what significant pathologic complications may result from hyperadrenocorticism?

- Systemic hypertension
- Diabetes mellitus
- Urinary tract infections
- Urinary calculi
- Pulmonary thromboembolism

12. Why might some dogs with hyperadrenocorticism develop neurologic signs? What is the expected percentage of patients to exhibit neurologic signs?

Dogs with pituitary macroadenomas (masses >1 cm in diameter) may develop neurologic signs secondary to their expanding masses. At least 10-15% of dogs with pituitary-dependent hyperadrenocorticism can be expected to do so.

Systemic hypertension is seen in 40% of dogs with well-controlled hyperadrenocorticism and 86% of untreated dogs. Hypertension can precipitate cerebral vascular accidents, which can result in neurologic deficits.

A less common reason for dogs with hyperadrenocorticism to display neurologic signs is as a side effect of mitotane therapy. Signs such as head-pressing, ataxia, mental dullness, and circling can rarely be seen as adverse side effects associated with mitotane therapy.

13. What is the difference between Cushing's syndrome and Cushing's disease?

Cushing's syndrome encompasses all of the clinical and biochemical findings that result from excessive glucocorticoids. Cushing's disease specifies pituitary-dependent hyperadrenocorticism.

14. Is it possible for a dog to have both pituitary-dependent disease and an adrenal tumor?

Dogs with both pituitary-dependent disease and adrenal tumors have been reported. Additionally, dogs have been seen with bilateral adrenocortical tumors. There are also reports of dogs with adrenocortical tumors and adrenomedullary tumors (pheochromocytomas).

15. Are there any age, breed, or gender predilections for canine hyperadrenocorticism?

Hyperadrenocorticism is seen in middle-aged and older dogs. There is a slight female predominance (55-65%). Many breeds are considered to be at increased risk: Poodles, Dachshunds, Beagles, German Shepherds, Labrador Retrievers, and various terrier breeds. Pituitary-dependent disease occurs more frequently in small dogs, with 75% of the patients weighing <20 kg. Conversely, approximately one half of the dogs with adrenal tumors weigh >20 kg.

16. What is a stress leukogram? Why does it occur?

Stress leukograms reflect the effects of cortisol on the different pools of white blood cells. On the complete blood cell (CBC) count, you will see a mature neutrophilia, lymphopenia, and eosinopenia. Corticosteroids cause the release of neutrophils from the bone marrow and decrease their migration into peripheral tissues, resulting in neutrophilia. Cortisol results in decreased release of eosinophils from the bone marrow. The lymphopenia is related to corticosteroid-induced apoptosis and lymphocyte redistribution. A stress leukogram can result from exogenous or endogenous corticosteroids. Any physical or emotional stress can result in excessive endogenous corticosteroids; hypercortisolemia is not diagnostic for hyperadrenocorticism.

17. List the biochemical abnormalities seen in canine hyperadrenocorticism.

- Mild polycythemia possible
- Increased alkaline phosphatase (ALP) (often severe)
- Increased alanine aminotransferase (ALT) (not to the same degree as ALP)
- Hyperglycemia (mild-moderate)
- Hypercholesterolemia and hypertriglyceridemia
- Increased bile acids
- Electrolyte changes (mild)—increased sodium, decreased potassium, decreased phosphorus
- Increased lipase
- Decreased T4, decreased TSH
- Isosthenuria (on urinalysis)

18. List two reasons why dogs with hyperadrenocorticism are more susceptible to urinary tract infections (UTIs). Does this affect how these patients should be monitored?

- Dogs with hyperadrenocorticism often have urine that is isosthenuric or even hyposthenuric. One of urine's protections against infection is being concentrated, thus dilute urine predisposes these animals to urinary tract infections.
- Hypercortisolemia has deleterious effects upon the immune system.

Patients with hyperadrenocorticism may not be able to mount an effective immune response against a UTI. Many of the typical signals for an infection such as pyuria are often not seen. Because of the lack of signs of an active infection in combination with the predisposition to infection, patients with hyperadrenocorticism should routinely have their urine cultured.

19. How do you diagnose hyperadrenocorticism?

Historical and physical examination findings should be consistent with a diagnosis of hyperadrenocorticism. There are three tests used to confirm the diagnosis: urine cortisol: creatinine ratio, adrenocorticotropic hormone (ACTH) stimulation test, and low-dose dexamethasone test (Table 37-1). The urine cortisol:creatinine ratio is very sensitive but lacks specificity. It is most useful as an early screening test. Dogs with excessive amounts of cortisol in their urine will

Table 37-1 ***Assays for Adrenal Dysfunction***

ASSAY	DOG PROTOCOL	CAT PROTOCOL
Screening Tests		
ACTH stimulation test	Draw blood samples at 0 and 60 minutes. Administer synthetic ACTH (Cortrosyn) 5 µg/kg IV or IM immediately following obtaining baseline blood sample. Alternatively, administer ACTH gel 2.2 IU/kg IM and draw post-sample 2 hours later.	Draw blood samples at 0, 60 and 90 minutes. Administer synthetic ACTH (Cortrosyn) 0.125 mg/cat IV immediately following obtaining baseline blood sample. Alternatively, administer ACTH gel 2.2 IU/kg IM and draw post-samples 1 and 2 hours later.
Urine cortisol:creatinine ratio	Have owners collect the first morning urine at home	Have owners collect the first morning urine at home
Low-dose dexamethasone suppression test	Blood samples are collected at time 0, 4, and 8 hours after injection. Administer dexamethasone 0.01 mg/kg IV at time 0.	Blood samples are collected at time 0, 4, and 8 hours after injection. Administer dexamethasone 0.1 mg/kg IV at time 0.
Discriminatory Tests		
Endogenous ACTH level	Collect blood into a prechilled tube containing EDTA and immediately spin in a cold centrifuge. Some laboratories recommend the use of aprotinin as a preservative.	Collect blood into a prechilled tube containing EDTA and immediately spin in a cold centrifuge. Some laboratories recommend the use of aprotinin as a preservative.
Low-dose dexamethasone suppression test	Blood samples are collected at time 0, 4, and 8 hours after injection.	Blood samples are collected at time 0, 4, and 8 hours after injection.

Continued

Table 37-1 *Assays for Adrenal Dysfunction—Cont'd*

ASSAY	DOG PROTOCOL	CAT PROTOCOL
High-dose dexamethasone suppression test (HDDS)	Administer dexamethasone 0.01 mg/kg IV at time 0. Blood samples are collected at time 0, 4, and 8 hours after injection. Administer dexamethasone 0.1 mg/kg IV at time 0.	Administer dexamethasone 0.1 mg/kg IV at time 0. Blood samples are collected at time 0, 4, and 8 hours after injection. Administer dexamethasone 1.0 mg/kg IV at time 0.

need further confirmation before treatment is instituted. The low-dose dexamethasone test has a very high specificity (95%) but is less sensitive than the ACTH stimulation test. This means that there is more chance of false-positive results with a low-dose dexamethasone test whereas there are more chances of a false-negative result with the ACTH stimulation test.

20. What test should be used to differentiate naturally occurring hyperadrenocorticism from iatrogenic causes?

ACTH stimulation test

21. What tests can be used to differentiate between pituitary-dependent hyperadrenocorticism and adrenal tumors?

The low-dose dexamethasone suppression test, the high-dose dexamethasone suppression test, and endogenous ACTH levels can all be used to distinguish between the causes of naturally occurring hyperadrenocorticism.

22. How do you interpret the results from a low-dose dexamethasone suppression test?

The first question to be answered with this test is whether there is evidence of hyperadrenocorticism. To answer this question, the cortisol results obtained 8 hours after dexamethasone administration are analyzed. Normal animals will show suppression of cortisol secretion 8 hours after dexamethasone administration; animals with hyperadrenocorticism will have elevated cortisol levels. The concentration values as determined by the laboratory should be used for this analysis (as opposed to comparing to baseline)—the absolute level of suppression is more important than the percent of suppression.

The second question that can be answered with this assay is whether the hyperadrenocorticism stems from pituitary or adrenal disease. If the 8-hour sample is consistent with hyperadrenocorticism, the 4-hour sample is then examined for evidence of pituitary-dependent hyperadrenocorticism. If one of the following three criteria is met, it suggests the dog has pituitary-dependent hyperadrenocorticism:

1. The 4-hour post-dexamethasone administration cortisol concentration is less than the laboratory's reference range for post-samples.
2. The 4-hour post-dexamethasone administration cortisol concentration is <50% of the baseline concentration.
3. The 8-hour post-dexamethasone administration cortisol concentration is <50% of the baseline concentration.

23. How do you interpret the results from a high-dose dexamethasone suppression (HDDS) test?

This test is used to discriminate between adrenal tumors and pituitary-dependent hyperadrenocorticism. This test is only helpful after a diagnosis of hyperadrenocorticism has been

made. Serum samples are collected 4 and 8 hours after dexamethasone administration. For either sample, if the absolute value for the cortisol concentration is less than the laboratory's cut-off value, this indicates suppression and is consistent with pituitary-dependent hyperadrenocorticism. Similarly, if either cortisol concentration is less than 50% of the baseline cortisol concentration, this would also be indicative of suppression. Up to 25% of dogs with pituitary-dependent hyperadrenocorticism may *not* suppress on a HDDS (a finding more consistent with an adrenal tumor).

24. Explain how endogenous ACTH levels can be used to distinguish between pituitary-dependent hyperadrenocorticism and an adrenal tumor.

In the normal animal, the pituitary secretes ACTH to signal the adrenal glands to secrete cortisol. The increase in cortisol levels negatively feeds back on both the hypothalamus and the pituitary, with a subsequent decrease in ACTH. In animals with pituitary-dependent hyperadrenocorticism, the pituitary releases excessive amounts of ACTH. Conversely, in patients with an adrenal tumor, the hypercortisolemia from the autonomously functioning adrenal gland will result in negative feedback at the level of the pituitary and minimal ACTH will be released. Endogenous ACTH levels <10 pg/mL suggest an adrenal tumor, whereas endogenous ACTH levels >45 pg/mL are consistent with pituitary-dependent hyperadrenocorticism.

25. List potential causes for an enlarged adrenal gland.

- Adrenal cortex adenoma
- Adrenal cortex carcinoma
- Adrenal cortical hyperplasia
- Pheochromocytoma
- Other neuroendocrine tumors
- Cyst
- Lipoma
- Hematoma
- Abscess
- Granuloma
- Metastatic disease
- Pseudoadrenal mass (arising from elsewhere)

26. When a calcified adrenal gland is found, does that indicate a malignant process?

No! Fifty percent of adrenal adenomas are calcified. The same percentage of adrenal carcinomas are also calcified.

27. What are some different treatment options for pituitary-dependent hyperadrenocorticism?

- Mitotane, which is also known as Lysodren or o,p'-DDD
- Ketoconazole
- L-Deprenyl
- Trilostane
- Hypophysectomy

28. Name an advantage to using ketoconazole as therapy for hyperadrenocorticism.

Ketoconazole reversibly inhibits cortisol synthesis. Because it's reversible, its effects can be rapidly altered in case of overdosage.

29. Does the dose of ketoconazole for use in treatment of canine hyperadrenocorticism differ from that used in the treatment of fungal infections?

The dose of ketoconazole used for treating hyperadrenocorticism ranges from 5 to 20 mg/kg orally every 12 hours. It is recommended to start at the lower end of the dosage range and slowly increase to the minimal dose that suppresses cortisol production in the patient. The dose used to treat fungal infections varies with the different fungi but is often in the range of 5-20 mg/kg orally once or twice daily.

30. What monitoring is required for dogs with hyperadrenocorticism being treated with ketoconazole?

Dogs are initially started on a dose of 5 mg/kg orally every 12 hours. If after 1 week, no

adverse effects are noted (anorexia, vomiting, etc.), the dose is increased to 10 mg/kg orally twice daily. After an additional 2 weeks at the higher dose, an ACTH stimulation test should be performed. The goal is for the cortisol levels to be slightly below normal on both the pre- and post-ACTH serum samples. If the cortisol levels are still above the normal reference range, the ketoconazole dose should be increased to 15 mg/kg orally twice daily and the ACTH stimulation test repeated in another 2 weeks. In addition to monitoring for adequate suppression of cortisol levels, dogs should be monitored for adverse drug reactions. Ketoconazole may cause gastrointestinal signs and/or hepatotoxicity. Less common side effects include a whitening of the hair coat and bone marrow suppression.

31. What are the two stages to mitotane therapy?

There are two phases to mitotane therapy: (1) induction and (2) maintenance therapy.

32. Describe the induction phase of mitotane therapy? When should it be stopped?

During induction therapy mitotane is given twice daily at a dosage of 25-50 mg/kg per day. The owners are instructed to carefully monitor their dog for any reduction in appetite or water intake or increased lethargy, vomiting, or diarrhea. Daily contact with the owner is essential during this period. If the owner notices any of these changes, he or she should be instructed to stop the mitotane therapy immediately and to re-present the dog the next morning for another ACTH stimulation test. If the owner does not observe any of these changes in their pet, the induction phase should be stopped after a maximum of 7-10 days and an ACTH stimulation test repeated. The goal for the ACTH stimulation test obtained at the end of the induction phase is to achieve subnormal results. Ideally the results will not be consistent with complete hypoadrenocorticism, but instead show partial hypoadrenocorticism. Both the pre- and post-corticotropin administration cortisol values should fall within the acceptable range for baseline cortisol. If the ACTH stimulation test is not consistent with hypoadrenocorticism, mitotane therapy is continued. ACTH stimulation tests should be repeated frequently until the desired result is achieved (e.g. test weekly or sooner if the dog shows any adverse signs). The clinician should also re-examine his or her initial diagnosis of hypoadrenocorticism for patients who fail to respond to mitotane in the first 10 days of therapy.

33. Discuss maintenance mitotane therapy.

Dogs who respond to mitotane quickly (within the first week) or have very low cortisol concentrations after induction should receive 25 mg/kg of mitotane weekly divided into two or three doses. Dogs that require an induction phase of longer than 1 week or have higher cortisol concentrations post-induction should receive 50 mg/kg of mitotane weekly divided into two or three doses. An ACTH stimulation test should be repeated after 1 and 3 months of maintenance therapy and then every 6 months. If the cortisol concentrations begin to increase over time, it may be necessary to increase the maintenance dose of mitotane by 10-25%. If overt signs of hyperadrenocorticism reoccur, the patient may require a repeat of the induction phase of mitotane therapy.

34. Is concurrent glucocorticoid therapy required during mitotane induction therapy?

There are varied opinions regarding the use of supplemental glucocorticoids during the induction phase. They are sometimes recommended to mitigate the deleterious effects of the rapid fall in cortisol concentrations. The concern is that the routine use of physiologic doses of glucocorticoids will mask the early signs of iatrogenic hypoadrenocorticism. Owners may not witness a decrease in thirst or appetite and may only recognize a problem when the patient suffers a hypoadrenocortical crisis. Regardless of whether they are instructed to routinely supplement with glucocorticoids, owners should have a supply of prednisone or prednisolone on hand in case a crisis develops.

35. If a patient suffers from a mitotane overdose, is that patient likely to permanently suffer from hypoadrenocorticism? Will that patient require both glucocorticoid and mineralocorticoid supplementation?

Permanent hypoadrenocorticism is rare and occurs in less than 5% of mitotane-treated dogs. These dogs may require both glucocorticoid and mineralocorticoid supplementation. More frequently, dogs on mitotane therapy will need transient glucocorticoid supplementation.

36. Other than overdosage, describe the potential side effects of mitotane.

Mitotane can cause central nervous system dysfunction such as apparent blindness, ataxia, dullness, and circling. Mitotane can also cause gastrointestinal upset and lead to anorexia, vomiting, diarrhea, weakness, and lethargy. Because these signs develop soon after mitotane therapy is initiated, these side effects of the drug will have to be separated from those of an overdose.

37. What is a medical adrenalectomy?

A medical adrenalectomy is purposefully, permanently destroying the adrenal cortices with mitotane. To accomplish this requires using doses of 50-100 mg/kg daily for 25 consecutive days. Treatment for hypoadrenocorticism (mineralocorticoid and glucocorticoid supplementation) needs to be instituted on the third day of mitotane therapy. The rationale for this approach is that it is easier to treat hypoadrenocorticism than hyperadrenocorticism. Concerns include the expense and the fact that hypoadrenocorticism can be much more life-threatening if not adequately treated. Many dogs treated with the "medical adrenalectomy" protocol later relapse and need further treatment for hyperadrenocorticism.

38. What do owners of dogs with hyperadrenocorticism need to monitor their pets for?

Pets being treated for hyperadrenocorticism need to be watched for both signs of hypoadrenocorticism and hyperadrenocorticism. The risk of the patient developing hypoadrenocorticism is greatest during induction therapy with mitotane but can happen at any point in treatment. Owners must be instructed to monitor for decreases in appetite or water intake as well as the development of vomiting, diarrhea, muscle trembling, or lethargy. It is crucial that the owners understand that a hypoadrenocortical crisis could be fatal if not treated appropriately.

Owners should also monitor for evidence that the hyperadrenocorticism has become poorly controlled. This will result in a resurgence of clinical signs such as polyuria-polydipsia and polyphagia.

39. I've heard the average lifespan of dogs treated with mitotane for hyperadrenocorticism isn't very different from that for non-treated dogs. What are the benefits of treatment?

Mitotane therapy will reduce the side effects of hyperadrenocorticism that are observable to the owner and that may improve the dog's quality of life. The most noticeable improvements are a reduction in polyuria-polydipsia, polyphagia, weakness, alopecia, and panting.

40. How does L-deprenyl work?

L-deprenyl irreversibly inhibits monoamine oxidase type B. Inhibiting this enzyme increases dopamine in the central nervous system. Dopamine inhibits the release of ACTH from the pars intermedia in the pituitary gland. This drug may be sporadic in effectiveness in the dog because 70% of the pituitary adenomas arise in the pars distalis, which is not under dopaminergic control.

41. What are the pros and cons regarding the use of L-deprenyl for the treatment of canine hyperadrenocorticism?

The major advantage to L-deprenyl is that it has few adverse side effects. Gastrointestinal side effects such as anorexia, vomiting and diarrhea have been rarely reported. Other adverse reactions that have been noted include disorientation, restlessness, and hearing loss. The most significant concern with the use of L-deprenyl is that it is often not effective.

42. What monitoring is required for dogs with Cushing's disease being treated with L-deprenyl?

Patients being treated with L-deprenyl need to be monitored for an improvement in clinical signs. This medication has little effect on cortisol levels or biochemical values.

43. Are there possible drug interactions that clinicians need to be aware of when prescribing L-deprenyl?

This medication should NOT be used in combination with other medications affecting CNS neurotransmission. Thus do not use it in combination with antidepressants (e.g. tricyclic antidepressants and serotonin re-uptake inhibitors). It should also not be used in combination with any other monoamine oxidase inhibitors (e.g., amitraz) or with ephedrine.

44. Discuss the treatment options for functional adrenal cortical tumors.

If surgical removal of the affected adrenal gland is possible, that is the preferred route of treatment. Dogs may require presurgical stabilization with ketoconazole (to lower their cortisol levels). Dogs with adrenal tumors can also be treated with mitotane. Adrenal tumors may be more resistant to the effects of this medication. Longer induction periods and/or higher doses may be necessary.

45. How should patients with both hyperadrenocorticism and diabetes mellitus be managed?

In patients presenting for the first time for these diseases, the diabetes mellitus should be addressed first. Poor regulation of diabetes may skew results of adrenal function tests. Once the diabetes is somewhat controlled, testing of the pituitary-adrenal axis can occur. Dogs with both conditions will require higher insulin doses. When treatment begins for the hyperadrenocorticism, the patient's insulin needs will change. Owners must be warned that the insulin requirements can drop rather precipitously. Diabetic patients beginning induction mitotane therapy have to be closely monitored. Urine samples should be checked two to three times daily for the presence of glucose; if glucosuria is absent, the insulin dose needs to be decreased by 10-20%. Induction therapy typically lasts the same time as in other dogs. Once the hyperadrenocorticism is under control, the diabetes will need to be readdressed.

46. What are the signs of a pituitary macroadenoma? How are they treated?

Pituitary macroadenomas may cause both endocrine signs and signs consistent with a space-occupying mass. In addition to the changes typical of hyperadrenocorticism, dogs with macroadenomas may be mentally dull, lethargic, ataxic, and pace aimlessly. Signs may progress to obtundation, blindness, seizures, head tilt, and circling. Macroadenomas are best treated with radiation therapy. This will control the signs related to the space-occupying mass. Patients may still require specific therapy to treat the endocrine imbalances.

47. Why are dogs with hyperadrenocorticism predisposed to pulmonary thromboembolism?

Dogs with hyperadrenocorticism appear to have both an increase in procoagulation factors II, V, VII, IX, X, XII, and fibrinogen as well as decreased levels of antithrombin.

48. Do cats get hyperadrenocorticism? What type?

Hyperadrenocorticism is much rarer in cats versus dogs. A similar percentage of cats have pituitary-dependent hyperadrenocorticism (75-80%) with the rest having adrenal tumors.

49. What are common concurrent diseases in cats? Does this affect clinical signs?

The majority of cats with hyperadrenocorticism also have diabetes mellitus. The polyuria-polydipsia and polyphagia that they display can more likely be attributed to the diabetes as opposed to the hypercortisolemia. Dermatologic signs are also commonly seen in cats (Figure 37-3).

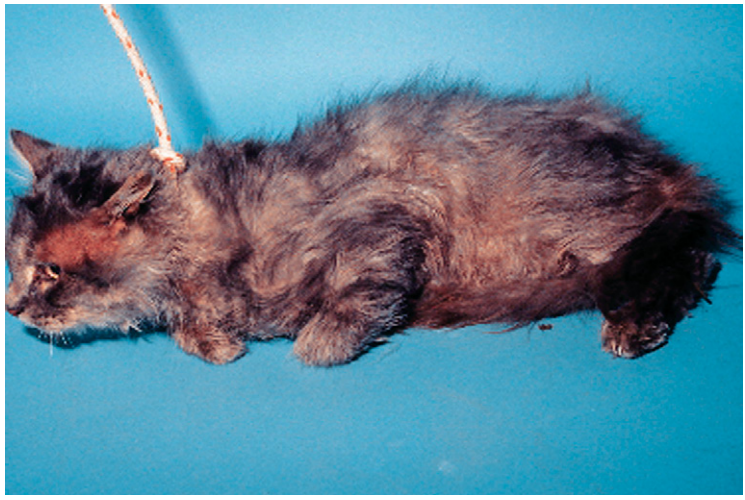


Figure 37-3 This sparse unkempt hair coat is a feature of feline hyperadrenocorticism.

50. What are the dermatologic manifestations of hyperadrenocorticism in cats?

- Alopecia
- Thin skin
- Fragile, easily torn skin
- Rough or dry hair coat
- Seborrhea
- Hyperpigmentation
- Folded pinnae

51. What percentage of cats with hyperadrenocorticism also have diabetes mellitus?

>80%

52. Why is it less common for cats to have an increased alkaline phosphatase?

Cats do not have a corticosteroid-induced isoenzyme. The increases in liver enzymes may reflect the diabetes mellitus, not the hyperadrenocorticism.

53. How does performing an ACTH stimulation test differ in cats versus dogs?

The ACTH stimulation test is considered to be less sensitive than the dexamethasone suppression test. Cats often have earlier peaks in cortisol values. Collecting two samples after administration of ACTH is recommended (after 30 minutes and 1 hour if using Cortrosyn; 1 and 2 hours after administration of ACTH gel).

54. Are there any differences in dexamethasone suppression testing for cats? Why?

Cats receive a tenfold higher dose of dexamethasone (0.1 mg/kg for a low-dose dexamethasone suppression test, 1 mg/kg for a high-dose dexamethasone suppression test). Cats have fewer receptors for glucocorticoids than dogs and their receptors have weaker binding affinities.

55. What is the treatment of choice for hyperadrenocorticism in cats?

Surgical adrenalectomy is the treatment of choice. For cats with pituitary-dependent hyperadrenocorticism, bilateral adrenalectomy is performed, whereas in cats with a functional adrenocortical tumor, only the affected adrenal gland is removed.

56. How are these cats managed postoperatively?

Cats that have undergone bilateral adrenalectomy will require mineralocorticoid and glucocorticoid supplementation for life. Cats that have one adrenal gland removed will need glucocorticoid supplementation for approximately 2 months. Those cats should have their electrolyte levels closely monitored as well.

57. What are the complications associated with adrenalectomy?

The most common postoperative complications are sepsis, pancreatitis, and thromboembolism.

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38. SEX HORMONE DERMATOSES

Linda A. Frank, MS, DVM, DACVD

1. What causes sex hormone dermatoses?

Sex hormones are produced from cholesterol by the zona reticularis of the adrenal cortex and by the gonads. Pathways and intermediates in steroid hormone production are similar in all steroid-producing tissues (Figure 38-1). Sex hormone dermatoses are due to the overproduction of one or more of the sex hormones. This overproduction may arise from the gonads in intact animals, the adrenal glands, or from exogenous administration.

2. How common are sex hormone dermatoses in the dog?

Sex hormone dermatoses are an uncommon cause of endocrine alopecias in the dog. Cushing's syndrome and hypothyroidism are much more common.

56. How are these cats managed postoperatively?

Cats that have undergone bilateral adrenalectomy will require mineralocorticoid and glucocorticoid supplementation for life. Cats that have one adrenal gland removed will need glucocorticoid supplementation for approximately 2 months. Those cats should have their electrolyte levels closely monitored as well.

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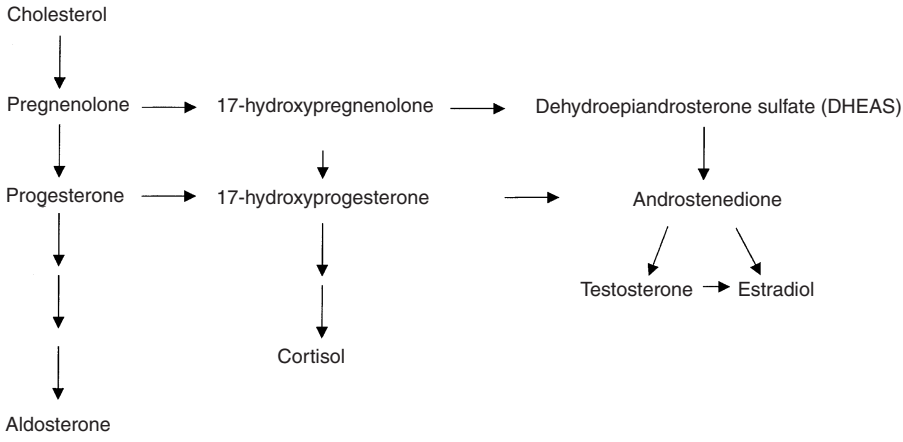

Figure 38-1 Schematic of adrenal steroid hormone intermediates.

3. How common are sex hormone dermatoses in the cat?

Sex hormone dermatoses are rarely seen in the cat, probably because there are so few intact felines. Most reports of sex hormone dermatoses in cats have been associated with exogenous hormone administration such as megestrol acetate. There are also more recent reports of cats presenting with clinical signs of Cushing's disease in which hyperprogesteronemia was found in association with an adrenal tumor. This is discussed later in this chapter.

4. What are the major causes of overproduction of gonadal hormones in the dog?

In the male, testicular tumors are the most common cause of sex hormone dermatoses. The most common hormone abnormality is hyperestrogenism usually arising from a Sertoli cell tumor. Hyperandrogenism may also occur. It has been seen in association with interstitial cell tumors and seminomas.

In the female, cystic ovaries and granulosa cell tumors are the most common causes of hyperestrogenism.

5. Describe the clinical signs associated with Sertoli cell tumor in the dog.

Clinical signs associated with Sertoli cell tumor are due to hyperestrogenism. Dogs often present with an endocrine pattern of alopecia (similar to Cushing's syndrome), which is a symmetrical alopecia that affects trunk and perineum, sparing the head and extremities (Figure 38-2). The coat may have a generalized dry or oily seborrhea. Comedones, representing a follicular seborrhea, may be noted in the inguinal region. Variable degrees of hyperpigmentation may occur. This may be in the form of diffuse hyperpigmentation in areas of alopecia or as macular melanosis, which are hyperpigmented nonraised lesions of the ventrum and perineum (Figure 38-3). In addition, feminization of the male dog may occur, consisting of enlargement of nipples and attraction of other male dogs. When interpreting the enlargement of the nipples, be careful! Chronic inflammation can also cause this presentation. In addition, the testicles will be abnormal on palpation (Figure 38-4).

A clinical presentation highly suggestive of hyperestrogenism in the male dog is linear preputial dermatosis (Figure 38-5). This appears as a narrow stripe of hyperpigmentation along the ventral midline that extends from the tip of the prepuce towards the scrotum.

Elevations of estrogen, whether endogenous or exogenous, have been associated with bone marrow suppression and aplastic anemia.

Figure 38-2 Truncal alopecia in a 7-year-old intact male poodle with Sertoli cell tumor. (Case material courtesy of University of Tennessee.)

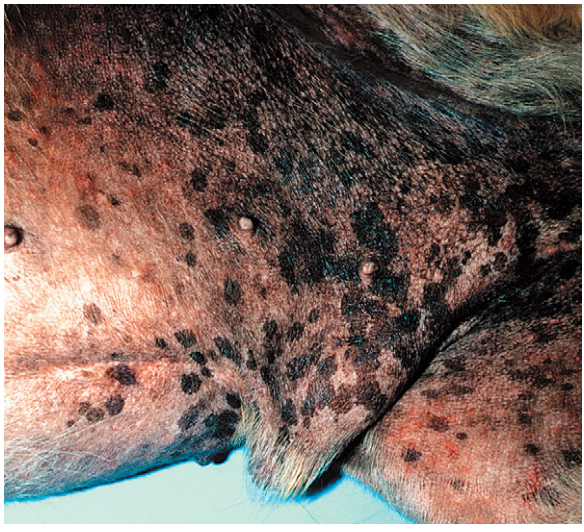

Figure 38-3 Macular melanosis of the ventrum in an 11-year-old intact male Golden Retriever with interstitial cell tumor. (Case material courtesy of University of Tennessee.)

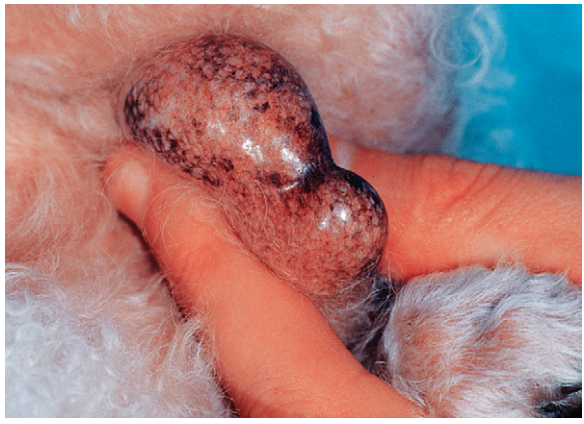

Figure 38-4 Asymmetrical testes in a 7-year-old intact male Poodle with Sertoli cell tumor (dog shown in Figure 38-2). (Case material courtesy of University of Tennessee.)

Figure 38-5 Linear preputial dermatosis in an 8-year-old intact male Pomeranian with testicular asymmetry.

6. **Would the clinical presentation of a female dog with hyperestrogenism be different from that of a dog with Sertoli cell tumor?**

A female dog with hyperestrogenism would have a very similar dermatological presentation to the male dog. In addition, we would also see abnormalities in her heat cycle such as persistent estrus and a swollen vulva.

7. **How does hyperestrogenism result in the alopecia?**

Estrogen is a known inhibitor of anagen initiation. Therefore, we assume that the alopecia is due to the fact that the hair is no longer cycling. As hairs are shed, there are no new hairs to replace them.

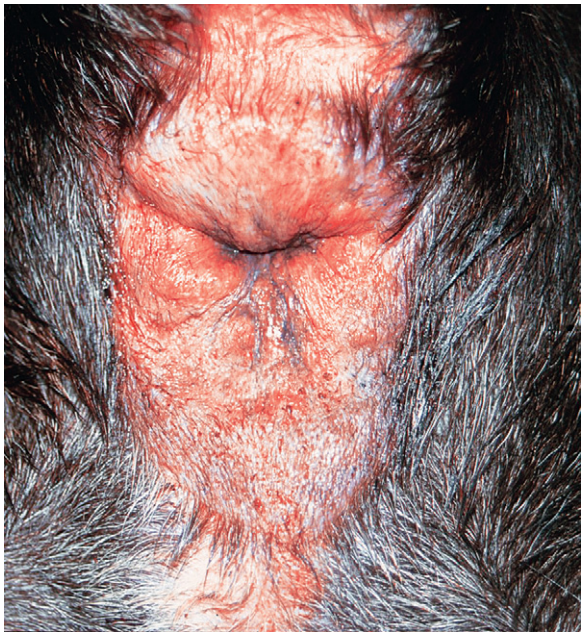

Figure 38-6 Perianal hyperplasia in a 10-year-old intact male mixed-breed dog. (Case material courtesy of University of Tennessee.)

8. Can other hormones arise from Sertoli cell tumors?

This is controversial. Sertoli cell tumors arise from estrogen-secreting cells. There is one report of a dog with hyperprogesteronemia associated with a Sertoli cell tumor. The presenting clinical signs were an endocrine pattern of alopecia and irregular, asymmetrical testes. It is unknown if the Sertoli cell tumor was truly producing progesterone or inducing progesterone synthesis by other tissues. It is also possible that some Sertoli cell tumors produce an estrogen-like hormone that is physically active but does not cross-react with the existing hormone assays.

9. Describe the clinical signs associated with hyperandrogenism arising from a gonadal tumor.

Hyperandrogenism is only rarely associated with alopecia. Instead, the clinical signs are associated with hyperplasia and overproduction of the sebaceous and circumanal or hepatoid glands. Typical lesions consist of perianal gland hyperplasia resulting in a "donut" ring around the anus (Figure 38-6), which can result in anal sac impactions. Dogs may also present with diffuse seborrhea oleosa. In addition, alopecia and seborrhea may be seen on the dorsal aspect of the tail approximately one third the distance from the base (Figure 38-7). This is the location of the tail gland (supracaudal gland), an area of simple follicles with specialized sebaceous glands similar to those found in the perianal tissue. These glands also become hyperplastic in response to excess androgen stimulation.

Because hyperandrogenism in the intact dog arises most often from interstitial cell tumors, the testicles may be abnormal on palpation.

10. How do you diagnose sex hormone imbalances in the intact animal?

First, a thorough history and physical examination will possibly lead you to suspect a sex hormone imbalance because of findings such as asymmetrical testes in the male, or irregular heat

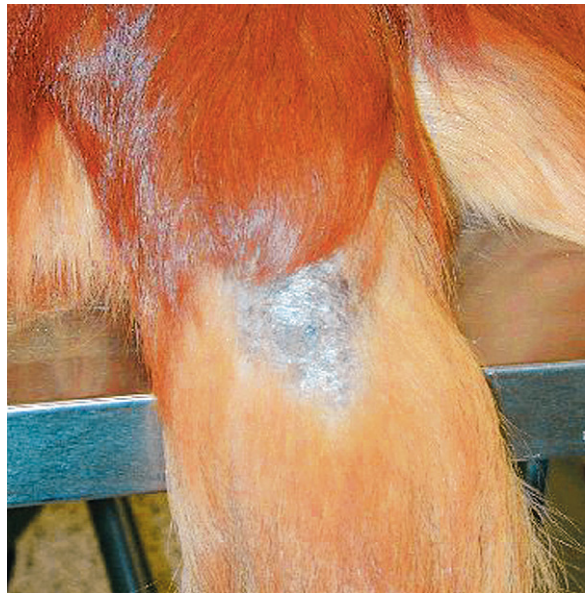

Figure 38-7 Tail gland hyperplasia in an 8-year-old intact male Golden Retriever. (Case material courtesy of University of Tennessee.)

cycles in the female. If these clinical signs exist in an intact animal, then often response to ovariohysterectomy or castration will be enough to diagnose the condition.

If physical examination findings are normal with the exception of the dermatitis, then the approach would be to first rule out the common causes of endocrine alopecias such as Cushing's syndrome or hypothyroidism and then investigate sex hormone imbalances. Once this is done, the simple approach would be to neuter the animal and watch for resolution of the clinical signs. If the owner is unwilling to neuter the animal, the diagnosis may sometimes be made by measuring baseline estradiol, progesterone, and testosterone concentrations. If any of these hormones are substantially elevated, then there is good reason to suspect a sex hormone imbalance as the cause of the dermatosis. Again, confirmation is based on response to neutering! An alternate means of confirmation would be treatment with an antagonistic hormone such as use of androgens in a dog suspected of having hyperestrogenism. This latter approach is not recommended since the number one cause of sex hormone imbalances in the intact animal is gonadal tumors.

11. Can you see sex hormone imbalances in neutered animals?

Definitely, yes. The source of the sex hormones would be either originating from the adrenal glands or from exogenous administration.

12. What are some common exogenous hormones that result in sex hormone dermatoses?

Diethylstilbestrol (DES) is a hormone commonly used to control urinary incontinence in neutered female dogs. Excessive use of this hormone has been reported to cause an endocrine pattern of alopecia.

Megestrol acetate is a progestational compound that has been used to treat various dermatoses in cats from allergic disease to psychogenic alopecia. Unfortunately, the side effects of this drug are many and include an endocrine-like alopecia in cats.

13. Are there any other potential side effects of using diethylstilbestrol or megestrol acetate?

Yes, excessive estrogen concentrations can cause bone marrow suppression. Therefore, monitoring of complete blood cell counts while an animal is on estrogen supplementation is extremely important.

Chronic administration of a progestational compound can induce diabetes mellitus and mammary carcinomas. In addition, it may cause a Cushing-like disease via stimulation of the glucocorticoid receptors. It can also stimulate growth hormone production, resulting in acromegaly.

14. What sex hormone imbalances are associated with the adrenal glands?

Because the adrenal glands produce many of the same sex hormones as the gonads, we could see increases of progesterone, testosterone, or estradiol originating from the adrenal glands.

15. What conditions may be associated with sex hormone imbalances of the adrenal glands?

The primary differential when we suspect excess hormone production from the adrenal glands is Cushing's syndrome, either from an adrenal tumor or adrenal hyperplasia secondary to a pituitary adenoma. With hypercortisolemia, sex hormone precursors may also be produced in excessive amounts, resulting in some of the clinical signs we have discussed. In addition, we are now just recognizing some forms of Cushing's disease in which the dog or cat presents with signs typical of hypercortisolemia; however, increased concentrations of cortisol are not detected on routine screening tests for Cushing's disease. Instead, these animals have increased concentrations of cortisol precursors such as progesterone or 17-hydroxyprogesterone. There are two reports in cats in which hyperprogesteronemia from an adrenal tumor was associated with the clinical presentation. In addition, there have been a few reports of dogs with both adrenal tumors and pituitary adenomas in which cortisol was normal but there were substantial increases of 17-hydroxyprogesterone.

Another condition that may be associated with adrenal sex hormone imbalance is alopecia-X. This is discussed further in Chapter 40.

16. How does hyperprogesteronemia cause alopecia?

The action of progesterone on hair growth is unknown. One mechanism may be due to its ability to bind to the glucocorticoid receptor in the dog, thus blocking hair growth. Progesterone can also cross-react with the testosterone receptor, which may either block or stimulate the receptor.

17. Are there any other clinical signs that may be associated with hyperprogesteronemia in cats?

Because progesterone stimulates the glucocorticoid receptors, the clinical signs in the cat reflect those seen with Cushing's disease. Cats may present with progressive truncal alopecia, thin skin, and increased skin fragility. In addition, they often have overt diabetes mellitus.

18. If you see clinical signs of hyperandrogenism in a neutered dog, what differential diagnoses should you consider?

Again, the first disease to investigate is that of Cushing's disease. Overproduction of androgens can occur concurrently with hypercortisolemia. The other concern would be an androgen-secreting adrenal tumor.

19. How do you diagnose sex hormone imbalances in neutered animals?

Because sex hormones in neutered animals are originating from the adrenal glands, the best method to document abnormal sex hormone concentrations would be to run a panel of steroid hormone intermediates and cortisol. This panel includes the following hormones: progesterone, 17-hydroxyprogesterone, estradiol, testosterone, androstenedione, and cortisol.

20. Can sex hormone imbalances still be the diagnosis in the face of normal hormone concentrations?

Yes. It can be difficult to document specific sex hormone abnormalities. This is partly because some sex hormones may be metabolized in the peripheral tissues to more potent hormones (e.g., androgens to estrogens; testosterone to dihydrotestosterone). Measuring more hormones increases the chances of finding an abnormality.

In addition, baseline hormone concentrations may be normal in the face of adrenal hyperplasia or adrenal tumors. Abnormalities may only be detected with dynamic testing such as using ACTH to stimulate the adrenal glands and measure a panel of sex hormones and intermediate precursors to cortisol before and 1 hour after stimulation, just as you would for Cushing's disease. Care must be taken in interpreting these results because of wide variations in normal subjects for some hormones and apparent breed variations. For definitive diagnosis, look for values substantially greater than the normal range in post-stimulation samples.

21. Will histopathologic findings facilitate diagnosis of these conditions?

Histopathology is valuable to help you confirm your suspicion of an endocrine dermatosis and to rule out non-endocrine causes of alopecia such as sebaceous adenitis or follicular dysplasia. However, with few exceptions, histopathologic findings won't differentiate between the various endocrine dermatoses.

22. Can a normal heat cycle be associated with alopecia?

In certain individuals of both dogs and cats, excessive shedding may occur during estrus, pseudopregnancy, or pregnancy. This shedding can resemble a partial to complete molt. The exact pathomechanism of the hair loss is not known. One possible explanation is a telogen defluxion resulting from a prolonged anagen phase and a synchronizing of the hair follicles, as can be seen in women postpartum. In cats, the breeds most frequently affected by this include the Cornish and Devon Rex. I am unaware of any specific dog breeds in which this routinely occurs.

23. Is pruritus ever associated with a sex hormone dermatosis?

Yes, pruritus can be seen in dogs with sex hormone dermatoses. There are a number of possible explanations for this. First, concurrent pyoderma or seborrhea can cause pruritus in dogs with an endocrine dermatosis. Second, the animal can have concurrent allergies. Third, there are reports of hormonal hypersensitivity that may induce pruritus. This latter possibility is less well described. A number of dermatologists have recognized bitches that developed pruritus during estrus that resolved at the completion of their cycle or upon spaying. Whether or not this is a true hormonal hypersensitivity remains to be proven.

24. Are there any reports of hypoandrogenism or hypoestrogenism associated with dermatoses?

While anecdotal reports exist of neutered dogs with alopecia that respond to hormone supplementation, it is suspected that this does not represent a true deficiency but a "responsive" condition (see Chapter 39).

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39. MISCELLANEOUS HORMONE-RESPONSIVE ALOPECIAS

Manon Paradis, DVM, MVSc, DACVD

1. How common are hormone-responsive alopecias?

Well, it depends on the species. In cats, with the exception of rare cases of hyperadrenocorticism (HAC), hormone-responsive alopecia is virtually inexistent. Moreover, to be purist, HAC is due to an "excess of hormones" (e.g., glucocorticoids) rather than being "hormone-responsive."

In the dog, alopecia is a frequent reason for veterinary consultation. Its major causes are self-trauma associated with pruritus and alopecia due to infections (Figure 39-1). However,

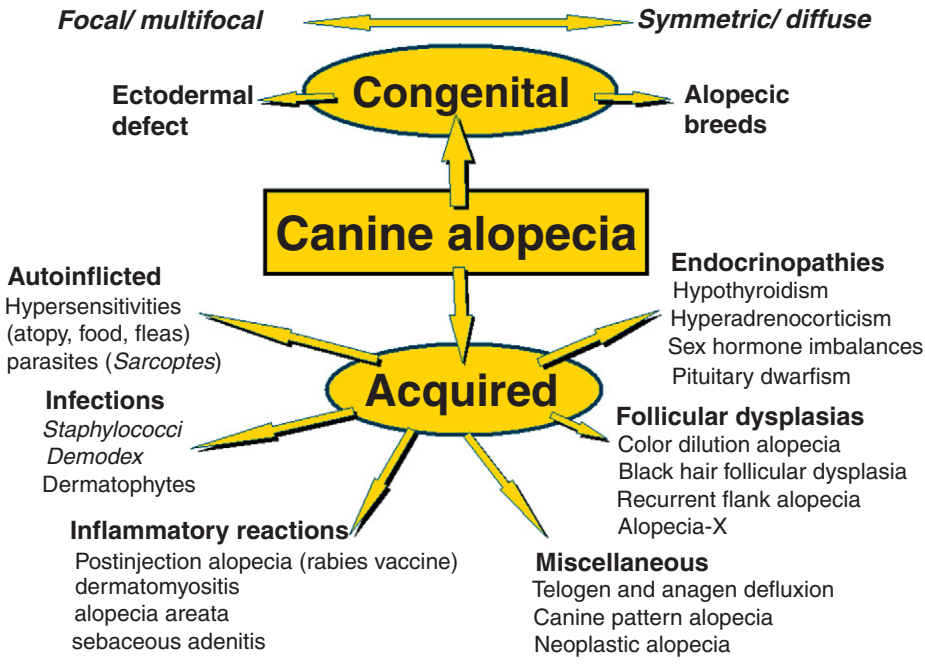

Figure 39-1 Schematic for the diagnosis of alopecia in the dog.

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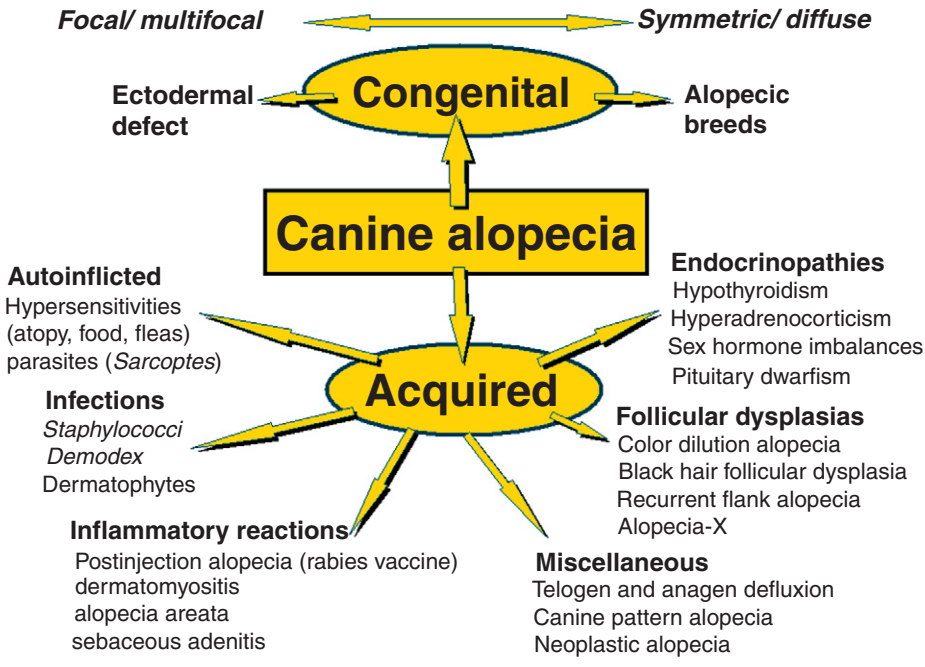

Figure 39-1 Schematic for the diagnosis of alopecia in the dog.

disorders manifested by noninflammatory, nonpruritic symmetrical alopecia are relatively common.

2. How do we define hormone-responsive alopecia?

It could be defined as an acquired alopecia, usually symmetrical/diffuse and nonpruritic that would improve/resolve following a specific hormonal treatment regimen, implying there was a hormonal deficiency. We realize, however, that we can observe improvement following non-specific hormonal treatment (e.g., melatonin) in "non-endocrine" alopecic disorders, such as color dilution alopecia and black hair follicular dysplasia.

3. Name the various hormonal responsive alopecias of the dog.

- Endocrinopathies such as hypothyroidism, hyperadrenocorticism, sex hormone imbalances due to functional gonadal neoplasms and pituitary dwarfism (see Chapters 36-38).
- Follicular dysplasia such as canine recurrent flank alopecia and alopecia-X
- Canine pattern alopecia

4. What is canine recurrent flank alopecia?

Canine recurrent flank alopecia (CRFA) is a skin disorder of unknown etiology characterized by episodes of truncal hair loss that often occur on a recurrent basis. It has previously been described under several synonyms such as seasonal flank alopecia, seasonal growth hormone deficiency, canine idiopathic cyclic flank alopecia, and cyclic follicular dysplasia.

5. Describe the clinical features of canine recurrent flank alopecia.

CRFA is characterized by a nonscarring alopecia, most often confined to the thoracolumbar region. Lesions are usually bilaterally symmetric, but in occasional dogs (or episodes) only one side of the body is affected, or one side is more affected than the other. Alopecic lesions are typically "geographic" in shape with well-demarcated borders and often markedly hyperpigmented (Figures 39-2 and 39-3). Occasionally, a more generalized pattern of alopecia involving the dorsum of the nose, base of the ears, base of tail, and perineum can be seen in addition to the thoracolumbar distribution. Alopecia in these unusual areas also manifests a cyclic pattern and spontaneous regrowth.

For the majority of dogs, the onset of alopecia is between November and March (in the Northern Hemisphere). Spontaneous regrowth of hair usually occurs in 3 to 8 months (range, 1 to 14 months). New hair usually consists of normal pelage density. Some individuals (particularly Boxers) can grow darker hair in the previously affected areas and some Miniature Schnauzers

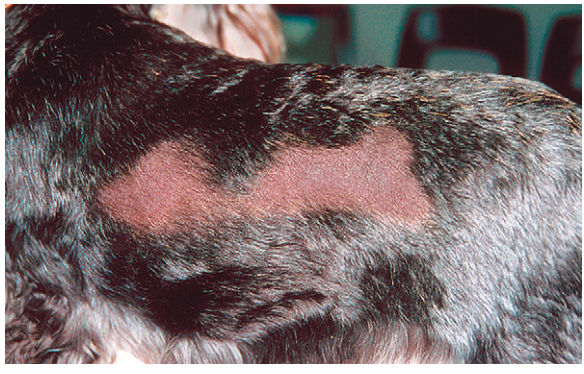

Figure 39-2 Miniature Schnauzer with canine recurrent flank alopecia.

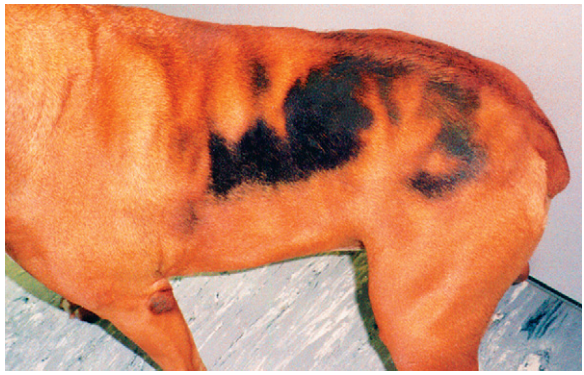

Figure 39-3 Boxer with canine recurrent flank alopecia. Note the marked hyperpigmentation.

may grow hair of a golden color (aurotrichia). In a few dogs, hair regrowth may become less complete following several episodes. Rarely, some dogs eventually progress to an end stage—permanent flank alopecia and marked skin hyperpigmentation.

Approximately 20% of CRFA cases may have only one isolated episode of flank alopecia during their life. However, the majority of cases will develop recurrent alopecic episodes for years. Some dogs have an occasional year when the alopecia does not recur. The degree of alopecia is variable, with some dogs developing a virtually identical hair loss (size and duration) year after year, and other dogs developing larger areas and/or longer episodes of hair loss as years go by.

6. Name the breeds of dogs that are predisposed to recurrent flank alopecia.

CRFA is most commonly seen in Boxers, which may account for approximately half of all cases, but other predisposed breeds include Airedale Terriers, English Bulldogs, and Schnauzers (Miniature, Standard, and Giant). Although CRFA seems to affect virtually any breed, this condition appears to be rare to absent in the plush-coated Nordic breeds, German Shepherd Dogs, and Cocker Spaniels.

7. Are females more frequently affected in canine recurrent flank alopecia?

Although initial reports suggested that CRFA was more frequent in ovariohysterectomized females, dogs of either sex and of any reproductive status can be affected.

8. What is the age of onset for canine recurrent flank alopecia?

Mean age at the onset of the first episode is around 4 years, but it can be quite variable (range, 8 months to 11 years).

9. What is the etiopathogenesis of canine recurrent flank alopecia?

The cause of CRFA is unknown. However, the high incidence in some breeds and the familial character of CRFA observed in Boxer, Airedale, Griffon Korthals, Affenpinscher, and Bearded Collie, suggests a genetic predisposition.

The seasonal nature and annual recurrences also suggest that photoperiod may be involved. There is definitely a higher incidence of CRFA at higher latitude (around or north of the 45 degrees parallel). In Australia and New Zealand, the onset of CRFA appears to be the reverse of what we see in the Northern Hemisphere (also during their short photoperiod season), supporting the importance of light exposure to this disorder.

10. Name other diseases in which we can see spontaneous hair regrowth.

Spontaneous hair regrowth can be observed in anagen and telogen defluxion, post-clipping alopecia, erythema ad igne (radiant heat dermatitis), and some cases of demodicosis and dermatophytosis. However, the distinctive history and clinical aspect of CRFA generally allow differentiating from these conditions.

11. Name other differential diagnoses.

In a dog presenting with its first episode, other causes of alopecia, such as endocrinopathies (hypothyroidism, hyperadrenocorticism) or other types of follicular dysplasias, need to be considered. Hypothyroidism is an important differential diagnosis for CRFA. Moreover, hypothyroidism and CRFA can both occur in the same animal, and this can represent a real diagnostic and therapeutic challenge!

12. How do you diagnose canine recurrent flank alopecia?

For most cases of CRFA, the diagnosis is based on history, clinical signs, exclusion of hypothyroidism (in dogs older than 2 years of age), and skin biopsies. Histopathologic findings ("witch's feet" or "octopus-like hair follicles") are suggestive, but not pathognomonic, of CRFA. Moreover, these findings are not always present in cases of CRFA and they may be found with low frequency in other alopecic diseases.

13. How do we treat canine recurrent flank alopecia?

The unpredictable course of CRFA and the spontaneous regrowth of hair render the evaluation of any therapeutic agent extremely difficult, whether used to prevent CRFA or to shorten an existing episode of alopecia. To date, melatonin is the only treatment that appears efficacious. The current recommendation is to use oral melatonin at the rate of 3-6 mg/dog every 8 to 12 hours for 1 to 2 months. The treatment should be initiated 1 to 2 months before or shortly after the onset of alopecia.

14. What is the prognosis for canine recurrent flank alopecia?

CRFA is only an esthetic problem and benign neglect is a valid management alternative. In addition, one must keep in mind that some dogs will have only one or a few episodes of flank alopecia during their life.

15. What is alopecia-X?

Alopecia-X is a disorder on which much has been said and written but for which little is really known or understood. This name was coined a few years ago to refer to the following disease(s): pseudo-Cushing, adult-onset growth hormone deficiency, hyposomatotropism of the adult dog, growth hormone–responsive alopecia, castration responsive dermatosis, gonadal sex hormone alopecia, sex hormone/growth hormone dermatosis, biopsy-responsive alopecia, post-clipping alopecia (of plush-coated breeds), adrenal sex hormone imbalance, adrenal hyperplasia syndrome, Lysodren responsive dermatosis, follicular dysplasia of Nordic breeds, Siberian Husky follicular dysplasia, follicular growth dysfunction of the plush-coated breeds, and black skin disease of Pomeranians. The diversity in names is merely descriptive and based on the differences in endocrine evaluation results and/or clinical responses to various therapeutic modalities.

16. Describe the clinical features of alopecia-X.

Initial clinical signs consist in loss of primary hairs (with retention of secondary hairs) in the frictional areas (around the neck, caudomedial thighs, and tail). Gradually, all hair is lost in those regions and eventually the truncal primary hairs are also lost, giving the remaining coat a puppy-like appearance (or very old sheepskin rug appearance). With time (several months to years) the secondary hairs become sparse, and hyperpigmentation of the exposed skin and/or color change in the remaining hair coat may be seen (Figure 39-4).

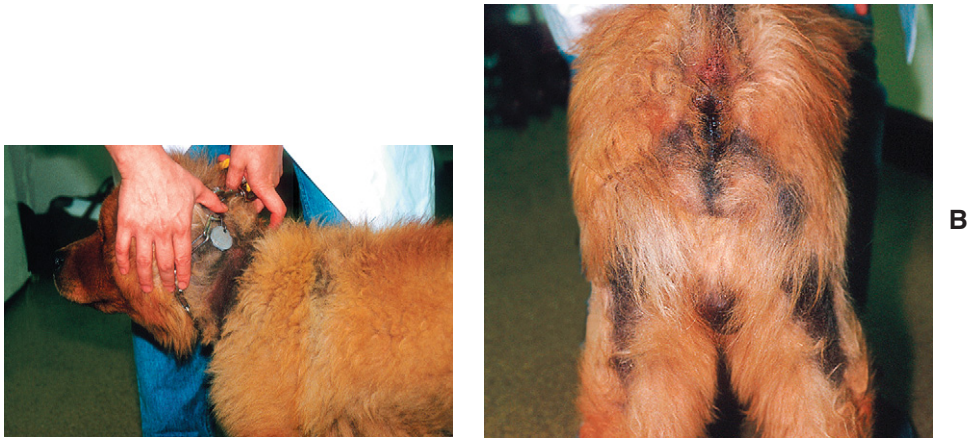

Figure 39-4 Neck **(A)** and hindquarters **(B)** of a Chow with alopecia-X.

The head and legs are usually spared. A tendency to regrow hair at the biopsy site following skin biopsy or other external traumatic stimuli (skin scraping, sunburn, etc.) is a common finding in this syndrome.

17. What is the age of onset for alopecia-X?

The age of onset is quite variable. It is seen more often in young adults, but has been seen in dogs as young as 9 months to as old as 11 years. It is seen more frequently in neutered dogs.

18. Name the breeds of dogs that are predisposed to alopecia-X

Nordic breeds with plush coats such as Pomeranians, Chow Chows, Keeshonds, Samoyeds, Malamutes, and Huskies have a higher risk of developing this syndrome. However, Miniature Poodles are also predisposed to this disorder.

19. What is the etiopathogenesis of alopecia-X?

Etiopathogenesis of alopecia-X remains obscure. A genetic predisposition to an unidentified hormonal imbalance and/or a change in receptor sensitivity at the hair follicle level is plausible. Adrenal sex-hormone imbalance has been a popular hypothesis over the past decade.

Alopecia-X occurs most commonly in breeds bred for hirsutism, and it may be caused by a primary follicular defect, similar to male pattern baldness, but with a sex hormone–related signal for expression. Indeed, men with pattern baldness do not have elevated sex hormone concentrations; instead their hair follicles respond abnormally to a normal hormonal signal (e.g., receptor problems). In any case, if the problem is a primary disorder of the hair growth cycle, various stimuli (including different hormones) could draw hair follicles into anagen phase.

It is conceivable that Miniature Poodles (anagen predominant hair cycle) have a different clinicopathological entity than the plush-coated breeds (telogen predominant hair cycle). Ironically, however, it was found recently in a retrospective evaluation of adrenal hormone panels that adrenal sex hormone levels in Miniature Poodles most resemble those of Pomeranians.

It was recently suggested that the alopecia might be due to a mild but prolonged increase in basal cortisol concentration, instead of adrenal sex hormone imbalance. This postulated pathogenesis is based on work done in Miniature Poodles and Pomeranians with alopecia-X that had increased urinary cortisol/creatinine ratios but normal post-ACTH stimulation cortisol levels.

20. What is the differential diagnosis of alopecia-X?

It includes hypothyroidism, hyperadrenocorticism (natural or exogenous), sex hormone imbalance due to functional gonadal neoplasms, telogen defluxion, other follicular dysplasias, and sebaceous adenitis.

21. How do you diagnose alopecia-X?

The diagnosis is based on history, physical examination findings, ruling out of other diseases (e.g., hypothyroidism and hyperadrenocorticism), skin biopsies, and response to therapy. No specific hormonal diagnostic tests are currently available. An ACTH stimulation test measuring various reproductive hormones before and following ACTH administration has been proposed. However, the main limitation to the routine use of this testing is the cost and difficulty in details of shipping. In addition, the results are often inconsistent. Moreover, even when an abnormality is demonstrated (after hypercortisolemia is ruled out), it rarely changes the treatment approach or the outcome. Indeed, hypercortisolemia must first be ruled out because it was recently demonstrated that concentrations of one or more adrenal sex hormones were substantially greater than reference range values before and after administration of ACTH in neutered dogs with hypercortisolemia. Therefore, these hormonal assays may be more useful in trying to understand alopecia-X than in guiding treatment for a specific patient.

22. Name the dermatohistopathological changes associated with alopecia-X.

Examination of skin biopsies reveals changes consistent with endocrinopathies. Decreased amount and size of dermal elastin fibers were reported (in chronic cases) in initial reports of growth hormone deficiencies. Later, the presence of "flame follicles" (excessive trichilemmal keratinization) gained popularity over the elastin fibers. It is not known whether the flame follicle is simply a nonspecific expression of follicular growth arrest in these plush-coated breeds, or whether haircoat abnormalities featuring flame follicles are united by a common etiopathogenesis. However, even though flame follicles are neither pathognomonic nor observed in every case of alopecia-X, histopathologic evaluation should confirm atrophic/endocrine changes and rule out other disorders such as sebaceous adenitis or other follicular dysplasias.

23. How do you treat alopecia-X?

Once hypothyroidism and hyperadrenocorticism have been ruled out, the following approach is usually recommended. Castration or ovariohysterectomy is generally the treatment of choice in intact dogs, offering up to 75% chance of success, with hair growth achieved either for a few years or permanently. Unfortunately, gonadectomy has already been performed in the majority of dogs before the hair loss/alopecia-X develops.

In neutered animals, various treatment modalities such as exogenous estrogen, testosterone, or growth hormone have been proposed. However, these therapies are no longer popular due to adverse effects, cost, availability, and/or poor effectiveness.

O,p'-DDD (Lysodren) is a relatively effective alternative when administered at 15-25 mg/kg, once daily for 5 days, then every 7-14 days as maintenance (lower dose than for Cushing's disease). Owners must be warned of the potential side effects (hypoadrenocorticism) before initiating this treatment.

Recently, new drugs have been used in an attempt to stimulate hair regrowth in dogs with alopecia-X. Leuprolide acetate, an antigonadotropin, and L-deprenyl (Anipril), a dopamine agonist, have been used with very limited to no success, respectively.

Trilostane, a competitive inhibitor of 3β-hydroxysteroid dehydrogenase, which interferes with adrenal steroidogenesis, has produced very encouraging results in Pomeranians and Miniature Poodles, with approximately 80% success rate. This drug affects adrenal function only if therapeutic levels are maintained, thus minimizing the potential risk of excessive adrenal suppression. Finasteride, a type II 5 α-reductase inhibitor, which prevents conversion of testosterone into its most potent metabolite dihydrotestosterone, is currently being investigated in the treatment of alopecia-X.

Melatonin has been used by several veterinary dermatologists over the last few years in several dogs with alopecia-X. The current recommendation is to use oral melatonin at the rate of 3-6 mg orally every 8 to 12 hours for up to 3 months. Success is achieved in approximately 33% of the cases. If effective, this course of treatment can be reinstituted as needed. In spite of this modest success rate, melatonin is a valuable therapeutic alternative to try because of its safety and low cost. The hair growth observed in alopecic dogs treated with melatonin might be due to either modulation of sex hormone levels; interference with cortisol production; action at the hair follicle level by blocking estrogen receptors (estrogen can inhibit anagen initiation); or actual melatonin deficiency. However, all of these proposed mechanisms are based on generalization of work done in other species.

24. What is the prognosis for alopecia-X?

Alopecia-X is only an esthetic problem and historically, due to cost, availability, and/or side effects related to various treatments, owners often choose not to have their dogs treated. Indeed, it is important to state that benign neglect is considered a valid management alternative. Rather than promoting aggressive treatments (e.g. o,p'-DDD), one's efforts should be toward client education and promotion of acceptance of the alopecia (i.e., buy your dog a sweater).

25. What is canine pattern alopecia?

Canine pattern alopecia (canine pattern baldness, CPA) is a relatively common disorder, with unknown etiology, which presents clinically with several different syndromes.

26. Describe the most common syndrome of pattern alopecia.

The most common syndrome is characterized by an acquired alopecia developing at the postauricular regions, along the ventral neck, thorax and abdomen, and on the caudomedial thighs (Figure 39-5).

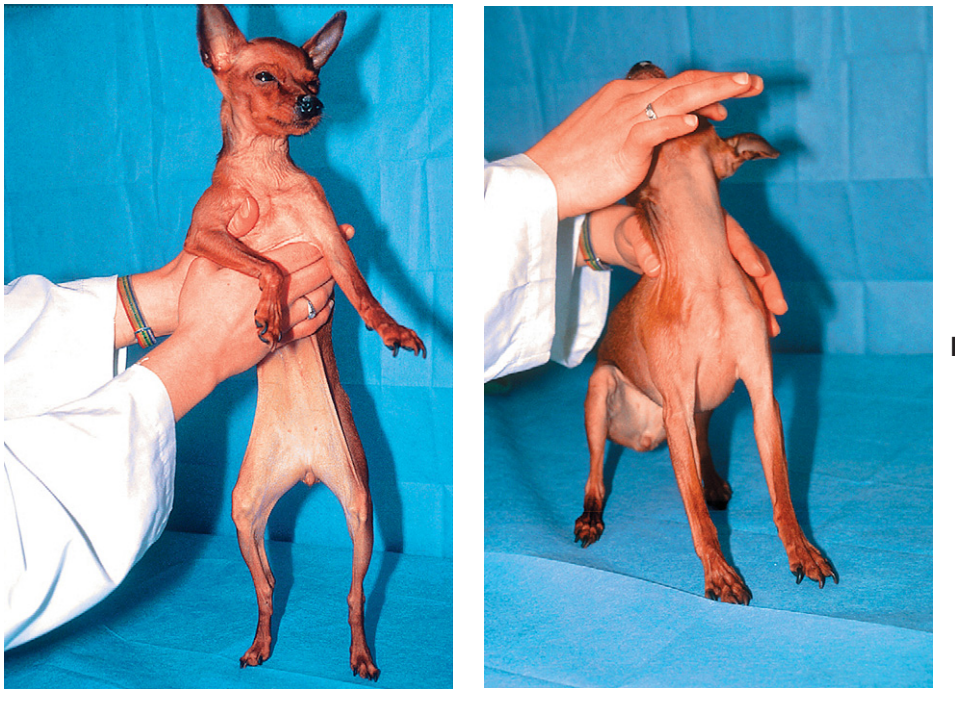

Figure 39-5 Chihuahua with canine pattern baldness (ventral type).

27. What is the age at onset of canine pattern alopecia?

The hair loss starts around 6 months of age and gradually progresses over the following year, but remains restricted to the described areas.

28. Name the breeds of dogs that are predisposed to canine pattern alopecia.

It is seen primarily in Dachshunds, but it is also recognized in several short-coated breeds such as Chihuahuas, Miniature Pinschers, Whippets, Greyhounds, Boston Terriers, and Boxers.

29. What is the differential diagnosis of canine pattern baldness?

Other causes of noninflammatory alopecia such as alopecia areata (pelade), follicular dysplasias and endocrinopathies (hypothyroidism, hyperadrenocorticism) are part of the differential diagnosis. The bald thigh syndrome of Greyhound dogs is also included in the differential diagnosis of CPA. It is characterized by hair loss at the caudolateral aspect of thighs but often extending to the ventral abdomen and chest. It is most often seen in racing Greyhounds and hair generally regrows (at least at the lateral aspect of thighs) when racing activity is stopped. It is likely that most of these Greyhounds indeed have CPA but in a few of them the alopecia may be due to either hypothyroidism, hyperadrenocorticism, or alopecia associated with exogenous testosterone administration.

30. How can we differentiate canine pattern alopecia from estrogen-responsive alopecia?

We cannot! It is probable that most cases of "classical" estrogen-responsive alopecia diagnosed in the past were in reality cases of CPA. Indeed, the description of estrogen-responsive alopecia in the literature seems to include cases of CRFA, alopecia-X and, more often, CPA. The existence of a distinct disorder named "estrogen-responsive alopecia" is therefore unlikely.

31. How do you diagnose canine pattern alopecia?

The diagnosis of CPA is based on the history, the dermatological examination, and exclusion of other diagnosis. Histopathological findings are characterized by miniaturization of hair follicles.

32. How do you treat canine pattern alopecia?

To date, no effective treatment has been reported for this disorder aside from the possible beneficial effect of melatonin. The current recommendation is to administer oral melatonin at the rate of 3-6 mg/dog orally every 8 to 12 hours for 1 to 2 months, repeated once or twice a year. This treatment regimen produces good to excellent results in over 50% of dogs (Figure 39-6).

Estrogen could also be effective if cases of so-called "estrogen responsive alopecia" were indeed CPA. However, because of serious adverse reactions seen with exogenous administration of estrogen, therapeutic trial with that hormone is not recommended for such a benign disease.

33. Can I use a dog affected with CRFA, CPA, or alopecia-X for breeding purposes?

Because these three disorders appear to be genetically programmed, it is probably better to avoid breeding affected animals.

34. How does melatonin work in the treatment of these various alopecias?

Melatonin is involved, by ill-defined mechanism, in the neuroendocrine control of photoperiod-dependent molting and/or pelage color in many mammals. The hormone may act directly on hair follicles, or within the central nervous system to alter secretion of melanocyte-stimulating hormone or prolactin secretion, or both. Melatonin, because of its effect on hair growth in dogs, is now part of the treatment modality for various types of acquired alopecias in dogs.

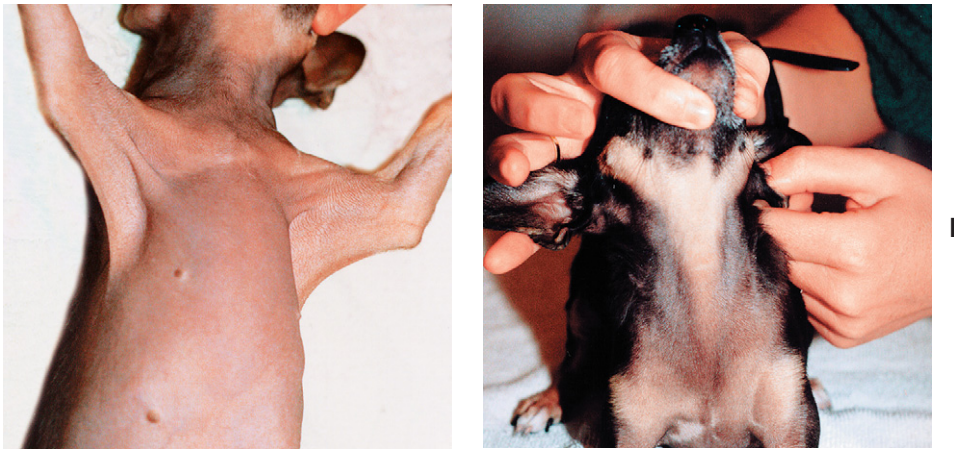

Figure 39-6 **A,** Chihuahua with canine pattern baldness before melatonin treatment. **B,** After melatonin treatment.

35. Where can I find melatonin?

Melatonin tablets are sold over the counter in health stores and drugstores in the United States and several other countries, where it is considered a dietary supplement rather than a drug (so it is not regulated as such). Constant-release melatonin implants are available in several countries for mink and foxes to modulate fur growth cycle, or for sheep, goats, and deer to modulate reproductive cycles. Melatonin implants (12 mg) intended for foxes have been used in dogs. Unfortunately, some dogs developed sterile abscesses or granulomas at the site of implantation. Therefore, oral administration is more convenient and is recommended at the present time.

36. How safe is melatonin in dogs?

Melatonin appears to be a very safe drug in dogs, although it should be used with caution in diabetic dogs because it may cause insulin resistance. Due to the experimental nature of the treatment, it is preferable to have a written consent from the owner.

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40. METABOLIC EPIDERMAL NECROSIS

Stephanie R. *Bruner,* DVM, ACVD

1. What is metabolic epidermal necrosis?

Metabolic epidermal necrosis (MEN) refers to a collection of dermatologic clinical signs and histologic changes associated with an internal disease process. MEN has historically been referred to as superficial necrolytic dermatitis (SND), diabetic dermatosis, necrolytic migratory erythema (NME), and hepatocutaneous syndrome. In humans, NME is most often associated with a functional pancreatic α-cell tumor (glucagonoma) but has also been observed with various hepatopathies, Crohn's disease, celiac sprue, malabsorption syndrome, and pancreatitis. Alternatively, MEN in dogs is most commonly associated with a hepatopathy and, much less frequently, with glucagon-secreting tumors. The cause of the liver disease is idiopathic in most affected dogs; however, anticonvulsant medications, copper storage disease, and mycotoxin ingestion have been implicated in rare cases.

2. What causes the cutaneous changes of MEN?

Several pathophysiologic mechanisms are proposed for the dermatologic features of MEN. The most frequently discussed are hyperglucagonemia, hypoaminoacidemia, and hypoalbuminemia. Hyperglucagonemia may be due to a glucagonoma or hepatic impairment with decreased degradation of glucagon fractions. Elevated glucagon levels result in excessive gluconeogenesis and hypoaminoacidemia. Deprived of a protein source, epidermal cells undergo necrosis.

Abnormal hepatic function results in hypoalbuminemia. Because albumin is an important plasma carrier protein, decreased albumin levels lead to altered zinc and fatty acid metabolism and subsequent cutaneous changes. Parakeratosis, a histologic feature common to both MEN and the zinc-responsive dermatoses, is an example of these changes.

3. What are the differential diagnoses for MEN?

The primary dermatologic differential diagnoses for MEN include pemphigus foliaceus, zinc-responsive dermatoses, demodicosis, dermatophytosis, bacterial folliculitis, contact dermatitis, toxic epidermal necrosis, and systemic lupus erythematosus. Many of these are ruled out based on the history, clinical signs, and initial diagnostic screening tests (e.g., skin scrapings, cutaneous cytology, dermatophyte cultures, complete blood cell count, biochemical profile, and urinalysis). With the exception of systemic lupus erythematosus, the differential diagnoses seldom have the clinicopathologic changes anticipated with MEN.

4. What are the signalment and clinical signs of dogs with MEN?

Dogs with MEN are typically middle-aged to geriatric animals with a history of relatively acute onset of alopecic, erythematous, exudative, coalescing papules or plaques with crusts, ulcers, and occasionally vesicles or bullae. Lesions may be located on the muzzle, distal extremities, pressure points, and mucocutaneous junctions of the oral cavity, eyes, anus and genitalia. The flanks and ventral abdomen may also be affected. Footpad hyperkeratosis with fissure formation is a very common feature. Some owners report foot pain or lameness as the chief complaint. Other chief complaints may include polyuria, polydipsia, lethargy, decreased appetite, or weight loss. Dermatologic changes may precede the onset of clinical signs of internal disease. No gender predilections occur. Mixed-breed dogs and Terrier breeds are over-represented in the literature.

5. What is the minimum database for initial evaluation of a patient suspected of having MEN?

The minimum database includes a complete blood cell count, serum chemistry panel, urinalysis, deep skin scrapings, cytologic evaluation of the skin, and a dermatophyte culture. MEN candidates with liver disease may demonstrate a nonregenerative anemia of chronic inflammation, leukocytosis, elevated alanine aminotransferase and alkaline phosphatase, hypoalbuminemia, mild-to-moderate hyperglycemia, and in some cases, glucosuria. Some patients have overt diabetes mellitus.

Skin scrapings will typically be negative for ectoparasites, although concurrent demodicosis may be present. This is especially true in a debilitated animal with a history of corticosteroid therapy. Cutaneous cytology will often indicate a secondary *Malassezia* or bacterial overgrowth. If vesicles are present, cytologic evaluation of their contents is acellular. Dermatophyte culture results are classically negative for the growth of pathogenic organisms.

6. How is the diagnosis of MEN confirmed?

Further evaluation for MEN candidates includes skin biopsies, to be submitted for dermatohistopathologic evaluation, liver function testing (fasting and postprandial bile acids), abdominal ultrasound, and subsequent lesion (usually liver) biopsy for histologic evaluation.

Skin biopsy specimens are obtained from lesional but not ulcerated or openly fissured body areas. Multiple specimens are collected, routinely fixed in 10% formalin, and submitted to a veterinary dermatohistopathologist for evaluation. Because the affected areas, particularly the footpads, are painful, appropriate postoperative analgesia is imperative (Figure 40-1). The histologic cutaneous changes of MEN are characterized by a red, white, and blue pattern, representing lymphoplasmacytic perivascular dermal infiltrates with lower epidermal hyperplasia (staining blue), intercellular and intracellular edema due to keratinocyte vacuolation in the upper levels of the epidermis (staining white), and parakeratotic hyperkeratosis (staining red). The dermatohistologic diagnosis of MEN is not specific for either liver or pancreatic disease.

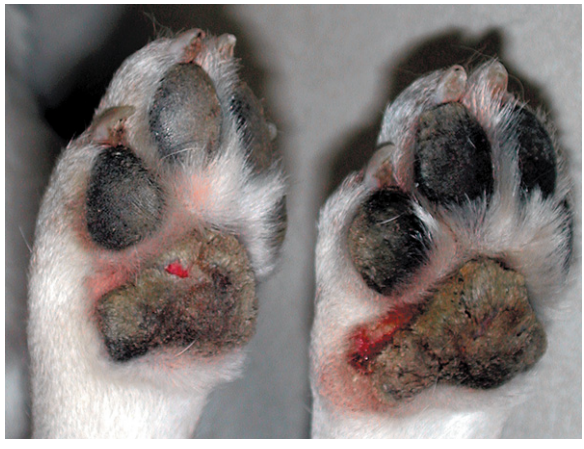

Figure 40-1 Hyperkeratotic fissured footpads of a dog with metabolic epidermal necrosis.

Elevations in fasting and postprandial bile acids are frequently noted. If the liver enzymes and bile acids are normal but other clinical and laboratory parameters (i.e., hyperglycemia) are suggestive of MEN, consider glucagonoma as the primary cause.

Abdominal ultrasound should evaluate all possible intra-abdominal structures, with particular attention to the pancreas and liver. Hepatic architecture changes are most commonly observed in

the dog. Classically, a honeycomb or Swiss cheese liver echotexture represents a hyperechoic network surrounding hypoechoic areas of parenchyma (Figure 40-2). Abdominal ultrasonography is frequently unremarkable in patients with glucagonomas. Occasionally pancreatic tumors or hepatic metastases are detected.

Ultrasound-guided biopsies are indicated if any liver abnormalities are noted. Histologic evaluation usually demonstrates an extensive portal-portal vacuolar hepatopathy with parenchymal collapse and stromal condensation. Other reports have described these changes as hepatic cirrhosis, vacuolar hepatopathy with cirrhosis, and vacuolar hepatopathy with parenchymal collapse and nodular hyperplasia. Rare cases are consistent with toxic hepatopathy.

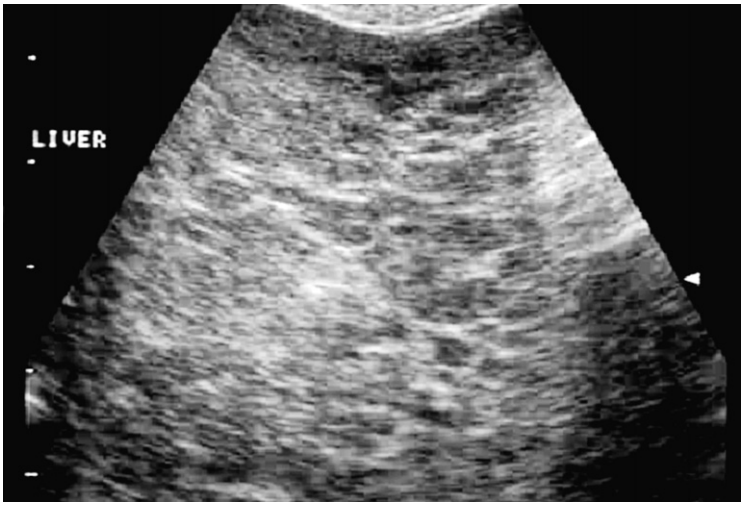

Figure 40-2 Hepatic ultrasound image shows the honeycomb pattern characteristic of dogs with metabolic epidermal necrosis.

Plasma amino acids, plasma glucagon, and serum insulin concentration assays have all been evaluated in dogs with MEN. Hypoaminoacidemia, hyperglucagonemia, and hyperinsulinemia in varying degrees have been reported with both liver- and pancreatic-associated MEN. Due to a lack of specificity, the utility of these tests in diagnosing or treating MEN is limited at this time.

7. How is MEN treated?

Treatment of dogs with MEN requires a twofold approach: management of the internal disease process (when possible) and palliative care of the dermatologic manifestations. The results of abdominal ultrasonography and histologic findings dictate the management of the internal disease. Surgical excision of glucagonomas generally results in remission of all clinical signs, although postoperative complications such as pancreatitis and biliary obstruction may occur. Disease relapse is not uncommon and may be associated with the development of metastatic disease.

Therapy for the dermatologic lesions is directed at pain management, treatment of any secondary skin infections, and replacement of the nutritional deficits presumed to be the cause of the primary skin lesions. The latter includes a high-quality protein diet rich in egg yolks or Prescription Diet i/d or Prescription Diet a/d (Hill's Pet Products), dietary zinc supplementation (zinc sulfate 10 mg/kg per day), and dietary fatty acid supplementation. Intravenous amino acid supplementation, available as a hypertonic 10% crystalline solution (Aminosyn, Abbott Laboratories) or the mixed amino acid/electrolyte solution Procalamine (B. Braun), is advocated as a

means of more rapidly decreasing pain and enhancing healing time of the skin lesions. Dosages are empirical. Aminosyn is infused at a rate of 500 mL/dog or 25 mL/kg body weight intravenously over 6-8 hours for 1-3 days and repeated on an as-needed basis. Ideally, hypertonic solutions are administered via a central venous catheter to avoid thrombophlebitis, although short-term use of a peripheral vein may be feasible. Because Procalamine is less hypertonic, I administer this product through a peripheral venous catheter at $1\frac{1}{2}$-2 times maintenance fluid rate over a 24-hour period with satisfactory outcomes. Procalamine is less cost-prohibitive than Aminosyn.

The use of somatostatin and its analogues for palliative control of glucagonoma-induced MEN is anecdotal at this time. Expense and drug-resistance limit their use. Corticosteroids aid in the resolution of the skin lesions but may exacerbate hyperglycemia and result in a diabetic crisis.

8. What is the prognosis for dogs with MEN?

The long-term prognosis for dogs with MEN, particularly if associated with end-stage liver disease, is guarded to poor. Many dogs respond temporarily to palliative care but ultimately succumb to their internal disease process.

9. Does MEN occur in cats?

MEN is rarely reported in the cat. Pancreatic carcinoma, hepatopathies, and thymic amyloidosis have been associated with dermatologic changes characteristic of MEN. Clinical, histologic, and post-mortem findings are similar to those seen with MEN in dogs. The clinical evaluation and proposed therapies are also comparable. To date, the prognosis for cats with MEN is poor.

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41. PARANEOPLASTIC SKIN DISEASES

Jennifer L. *Matousek*, DVM, MS, DACVD

1. Give the definition of a paraneoplastic disorder.

A paraneoplastic disorder is a marker for cancer, in which clinical signs develop at a site that is distant from the primary tumor or its metastases. Cutaneous paraneoplastic diseases are rare in small animals.

2. Name two malignant tumors reported to cause feline paraneoplastic alopecia.

Pancreatic carcinoma and bile duct carcinoma.

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2. Name two malignant tumors reported to cause feline paraneoplastic alopecia.

Pancreatic carcinoma and bile duct carcinoma.

3. What is the pathogenesis of the alopecia seen in feline paraneoplastic alopecia?

The pathogenesis of paraneoplastic alopecia has not been determined. It is possible that the alopecia is caused by an unknown circulating tumor-derived factor.

4. What is the typical signalment of cats with paraneoplastic alopecia?

These cats are usually older (9 to 16 years of age). There is no breed or gender predilection.

5. List the systemic and cutaneous clinical signs that are associated with feline paraneoplastic alopecia.

- Systemic: lethargy, anorexia, weight loss.
- Cutaneous: alopecia of the ventrum, legs, and face (Figure 41-1)
  - The alopecic areas have a characteristic shiny appearance.
  - The fur epilates easily.
  - Erythema and scale (Figure 41-2)
  - The paw pads may be shiny and smooth, with crusts and fissures.
  - Some cats have secondary *Malassezia* spp. yeast infections
  - Generally nonpruritic unless there is a secondary infection

6. How is feline paraneoplastic alopecia diagnosed?

1. Results of a complete blood cell (CBC) count, biochemical profile, and urinalysis are nonspecific.
2. Feline leukemia virus (FeLV) and feline immunodeficiency virus (FIV) test results are negative.
3. Skin biopsy and histopathology is suggestive. The most remarkable change is marked hair follicle atrophy and telogenization. The surface keratin layer may consist of alternating orthokeratotic and parakeratotic hyperkeratosis, or hypokeratosis. There may also be a mild superficial lymphocytic perivascular dermal infiltrate.
4. To date, abdominal radiographs have been normal in the cats with paraneoplastic alopecia.
5. Abdominal ultrasonography can be used to evaluate for a mass or nodular lesions consistent with neoplasia of the pancreas or liver. The absence of abnormalities does not preclude a diagnosis of pancreatic or hepatic neoplasia.

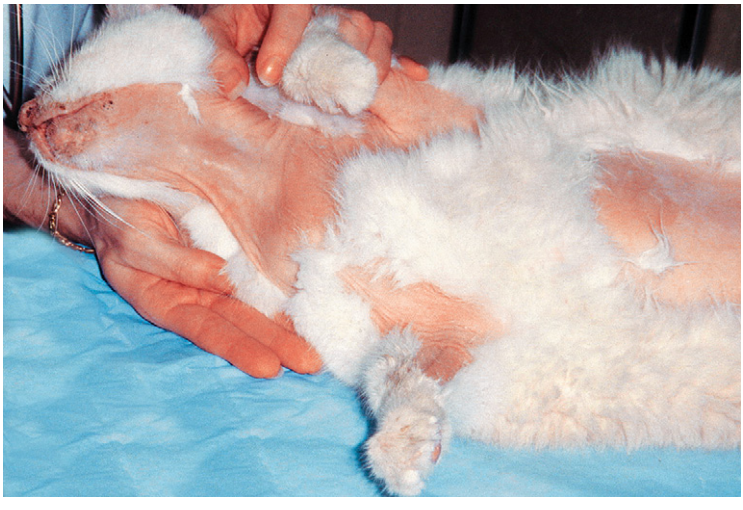

Figure 41-1 A cat with paraneoplastic alopecia; note the ventral alopecia and shiny skin.

Figure 41-2 Feline paraneoplastic alopecia; note the alopecia and scale on the rear limb.

6. Abdominal exploratory surgery with biopsies and histopathologic studies of abnormal tissue may be required to identify the internal malignancy in some cats with paraneoplastic alopecia.

7. What is the prognosis for cats with paraneoplastic alopecia?

The prognosis for cats with paraneoplastic alopecia is grave because the tumor has often metastasized by the time of diagnosis. Unfortunately, current chemotherapy is ineffective in cats with primary pancreatic or hepatic malignancies.

8. Name and describe a dermatologic syndrome that is associated with thymoma in cats.

Exfoliative dermatitis

- Affects middle-aged to old cats
- Nonpruritic erythema, scale, and alopecia
- Primarily affects the head and ear pinnae, but may progress to involve the entire body
- Brown waxy debris may accumulate around the mucocutaneous areas and clawbeds

9. List some differential diagnoses for feline exfoliative dermatitis.

- Hypersensitivity (environmental, dietary, contact)
- Infectious (dermatophytosis, bacterial dermatitis, FeLV infection)
- Parasitic (*Demodex, Otodectes, Cheyletiella*)
- Adverse drug reaction
- Autoimmune disorder (pemphigus foliaceus, systemic lupus erythematosus)
- Neoplasia (cutaneous T-cell lymphoma)
- Paraneoplastic (thymoma)

10. What tests should be done if feline exfoliative dermatitis with thymoma is suspected?

- Results of a CBC count, biochemistry panel, and urinalysis are usually nonspecific.
- FIV and FeLV negative.
- Cutaneous histopathology: cell poor interface dermatitis with apoptotic keratinocytes in the stratum basale and stratum spinosum of the epidermis and in the follicular outer root sheath.
- Thoracic radiographs may reveal a mediastinal mass.

11. How is feline exfoliative dermatitis associated with thymoma treated?
Surgical removal of the thymoma should be curative.

12. Paraneoplastic pemphigus has relatively recently been described in dogs. What types of tumors have been associated with paraneoplastic pemphigus in dogs and humans?
Paraneoplastic pemphigus is most often associated with lymphoma. Other malignancies reported in dogs include a Sertoli cell tumor and mammary carcinoma. Other malignancies reported in humans include thymoma, bronchogenic squamous cell carcinoma, poorly differentiated sarcoma, and round cell liposarcoma.

13. What is the proposed pathogenesis of paraneoplastic pemphigus?
The pathogenesis is not known. One theory is that the animal's immune response to tumor antigens cross-reacts with normal epithelial antigens. Another theory is that the tumor is secreting excessive amounts of cytokines (i.e., IL-6) that stimulate the immune system, leading to immune-mediated disease.

14. How are the target antigens and histopathology of paraneoplastic pemphigus different from pemphigus foliaceus and pemphigus vulgaris?
See Table 41-1.

Table 41-1 ***Distinction of Forms of Pemphigus***

PARAMETER	PEMPHIGUS FOLIACEUS	PEMPHIGUS VULGARIS	PARANEOPLASTIC PEMPHIGUS
Target antigen	Desmoglein I (150 kd)	Desmoglein III (130 kd)	Envoplakin (210 kd) Periplakin (190 kd) Desmoglein III (130 kd)
Histopathology	Subcorneal or intragranular acantholysis	Suprabasilar acantholysis	Intraepithelial acantholysis, apoptotic keratinocytes, vacuolar interface dermatitis
Indirect immuno-fluorescence	Stratified squamous epithelia	Stratified squamous epithelia	Stratified squamous and nonstratified squamous epithelia

15. What is the prognosis for an animal with paraneoplastic pemphigus?
Paraneoplastic pemphigus has a grave prognosis because it is generally unresponsive to therapy. If the tumor can be completely cured, the prognosis may be better.

16. What tumors have been associated with nodular dermatofibrosis?
Refer to Chapter 13.

17. What are the cutaneous manifestations of adrenal adenocarcinomas in cats and dogs?
Refer to Chapter 37.

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42. ZINC-RELATED DERMATOSES

Rod A.W. Rosychuk, DVM, DACVIM

1. What skin diseases have been associated with zinc?

Several clinical syndromes have been associated with either proven or suspected zinc deficiencies or response to zinc supplementation. The most common is seen in Siberian Huskies and Malamutes. It has been suggested that affected individuals may have a defect in the gastrointestinal absorption of zinc. Most respond to zinc supplementation. A zinc-responsive dermatosis is seen in young, rapidly growing puppies who have been fed diets low in zinc, or high in calcium, phytates (e.g., cereal grain, soy-based, corn-based diets) or iron (well water), which may bind zinc and prevent its absorption. Growing dogs do require more zinc than adults. Affected individuals respond to the elimination of these dietary influences and zinc supplementation. Following clinical remission, the supplementation can usually be discontinued. Bull Terriers with acrodermatitis have been hypothesized to have a defect in the cellular uptake or utilization of zinc, which is thought to play a significant role in the development of clinical signs. However, perhaps because of this defect, these individuals do not respond to oral or intravenous zinc supplementation. Metabolic epidermal necrosis (superficial necrolytic dermatitis, necrolytic migratory erythema, hepatocutaneous syndrome) is a cutaneous manifestation of hepatic disease or pancreatic neoplasia. Skin changes are multifactorial in origin. Zinc deficiencies and/or response to zinc therapy have been suggested to potentially play a role. Because zinc is an integral part of many enzyme systems within the body (a cofactor in over 100 metalloenzymes), both systemic and topical therapy with zinc have been suggested to improve overall coat and skin condition, reduce pruritus, enhance wound healing, and have anti-microbial effects. While much of these data is anecdotal or has been examined in other animal models, there are data to suggest that zinc supplementation in clinically normal dogs on complete and adequate diets may improve coat gloss and reduce both scale and transepidermal water loss if used in conjunction with linoleic acid. This effect was significantly greater than if the diet was supplemented with linoleic acid only.

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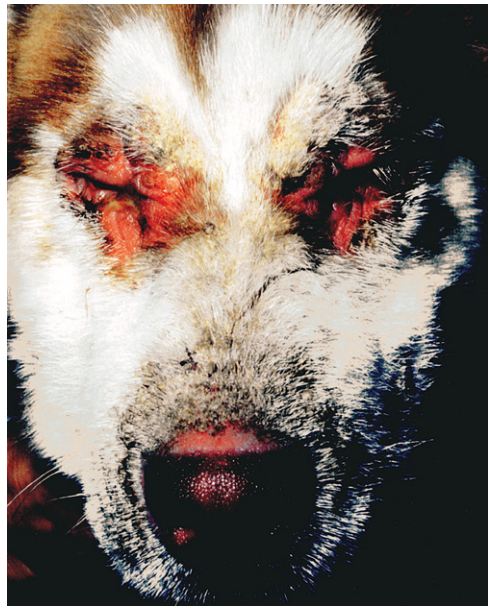

Figure 42-1 Two-year-old neutered male Siberian Husky with alopecia, inflammation, and adherent crust around the eyes and over the bridge of the nose.

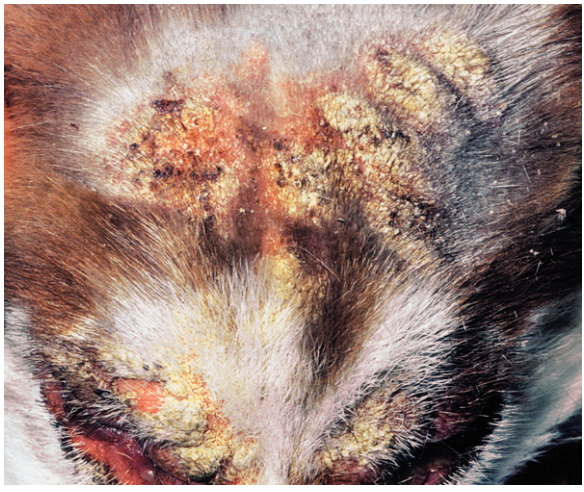

Figure 42-2 Close-up of clipped lesions on the head of the dog in Figure 42-1. Note inflammation and characteristic adherent scale.

2. What are the clinical signs associated with zinc-responsive dermatoses in Siberian Huskies and Malamutes?

Lesions are usually first noted in younger individuals (1-3 years of age), although any aged individual is susceptible. In one retrospective study of 43 cases, age of onset ranged from 2 months to 11 years. Lesions consist of focal areas of adherent crusts and scale with attendant variable degrees of hair loss (Figures 42-1 and 42-2). The involved skin is inflamed. Lesions are

Figure 42-3 Four-year-old spayed female Siberian Husky with characteristic periocular alopecia, inflammation, and adherent scale.

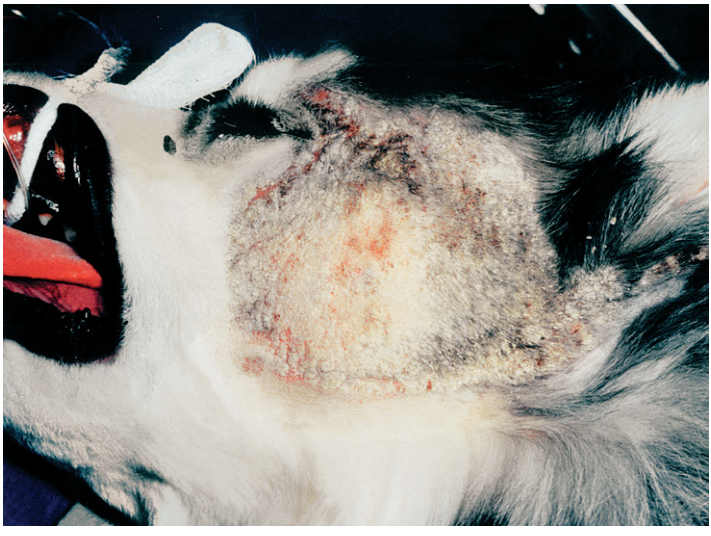

Figure 42-4 Five-year-old neutered male Malamute with asymmetric alopecia, inflammation, and adherent crusts related to zinc-responsive dermatosis.

Figure 42-5 Hyperkeratosis of footpads related to zinc-responsive dermatosis.

most commonly symmetric, primarily involving the periocular regions, chin, peri-oral muco-cutaneous junctions, and both the medial and, less commonly, the lateral aspects of the pinna (Figure 42-3). Other areas of involvement include pressure points (lateral elbows and stifles), scrotum, prepuce, and vulva. Involvement of the trunk and distal extremities is also possible. Whereas the lesions are often symmetric on presentation, asymmetric lesions, especially around the eyes and mouth, may be noted (Figure 42-4). Lesional pruritus is noted in approximately 50% of the cases and is variably severe. The footpads may become hyperkeratotic (Figure 42-5). The coat may take on a dry, generally dull appearance. Occasionally, an oily coat may be noted. Secondary bacterial and *Malassezia* infections are possible. Decreased ability to smell and/or taste may be noted in some individuals.

3. Is zinc-responsive dermatosis seen in other breeds?

Yes, but rarely. It has been seen in Samoyeds, American Eskimos, White German Shepherd Dogs, flat-coated retrievers, the Boston Terrier, Great Dane, Doberman Pinscher, Labrador Retriever, and in mixed-breed dogs.

4. Do the lesions tend to wax and wane?

Yes, they may. Exacerbations of the problem have been associated with stress, estrous cycles, and pregnancy. Seasonal variation has also been noted (usually worse in winter).

5. Why do they keep calling these problems zinc-responsive dermatoses rather than zinc deficiencies?

The pathogenesis of these problems, with respect to documentation of true zinc deficiency, has been difficult. There is some suggestion that the benefit of supplementation may be related to a pharmacologic effect of zinc on keratinization and dermal inflammation (anti-inflammatory).

Until the pathogenesis has been better established, the syndromes are perhaps best described by their response to therapy.

6. What differential diagnoses must be considered for these clinical signs?

Major differential diagnoses include bacterial pyoderma, dermatophytosis, demodicosis, *Malassezia* dermatitis, pemphigus foliaceus and metabolic epidermal necrosis.

7. Is the footpad disease similar to what is seen with pemphigus or metabolic epidermal necrosis (MEN)?

While the footpads do become variably hyperkeratotic with zinc responsive dermatoses, they do not progress to the crusting and fissuring seen with pemphigus or metabolic epidermal necrosis. In addition, whereas pad involvement may be the only presenting problem with MEN or pemphigus, with zinc responsive dermatoses, more widespread skin lesions always accompany the pad lesions

8. What are the clinical signs associated with this disease in young, rapidly growing dogs?

The clinical signs are similar, with lesions most commonly noted over pressure points. Affected individuals may be somewhat stunted.

9. What are the clinical signs in Bull Terriers with acrodermatitis?

This is an inherited, autosomal recessive trait that is usually lethal for affected individuals. Clinical signs are noted within weeks of birth and include a failure to grow; splayed feet; hyperkeratosis and fissuring of the footpads; interdigital dermatitis and paronychia, a crusty dermatitis of the muzzle, periauricular areas, and mucocutaneous junctions; and onychodystrophy (abnormal nails). Affected individuals are very prone to secondary *Malassezia* infections and bacterial pyoderma. They may also develop chronic diarrhea or respiratory infections. Left untreated, most die within several months. With treatment for secondary infections (both *Malassezia* and bacteria), survival may be prolonged for months to years.

10. How are zinc-responsive dermatoses diagnosed in Siberian Huskies, Malamutes, and the less commonly affected breeds?

The diagnosis is based on history, clinical signs, rule-out (especially *Demodex*, dermatophytosis, bacterial pyoderma, and *Malassezia* dermatitis), and by assessing response to zinc supplementation. Because zinc concentrations in serum, plasma or hair are variable in affected individuals (may be low or normal) and because of technical problems with sampling, the measurements of zinc concentrations are usually not used as a diagnostic aid. Skin biopsies should include samples from both lesional areas and the margins of lesions. Careful attention should be given to obtaining crusts with the biopsies (i.e., biopsy through crusts). The most common changes that suggest this disease are marked diffuse and follicular parakeratotic hyperkeratosis, eosinophilic "laking" within keratinocytes and epidermal papillae with parakeratotic "capping." Other concurrent, but less common changes include acanthosis (thickening of the epidermis), epidermal and follicular orthokeratotic hyperkeratosis, and superficial epidermal pallor. It is common to see dermal inflammation that is diffuse, perivascular and/or perifollicular and consists of lymphocytes, plasma cells, eosinophils, and macrophages. In addition, histologic abnormalities may suggest the presence of secondary bacterial or *Malassezia* dermatitis. Although the above histologic changes may suggest the presence of a zinc-responsive dermatitis, the diagnosis of a zinc-responsive dermatosis is confirmed by observing response to zinc supplementation.

11. How is the disease treated?

Several forms of oral zinc supplementation have been noted to be effective. The two most commonly used are zinc methionine and zinc sulfate. Zinc gluconate has also been effective. It

Table 42-1 ***Recommended Zinc Dosages***

ZINC SUPPLEMENT (ZINC SALT OR AMINO ACID COMPLEX)	DOSAGE (MG/KG/DAY)*	RELATIVE ELEMENTAL ZINC CONTENT OF SALT OR AMINO ACID COMPLEX (%)
Zinc methionine	2	30
Zinc gluconate	5	14.3
Zinc sulfate	10*	23

*Important that this dosage be divided and given twice daily with food.

would appear that similar degrees of success have been associated with each, although most data are available for zinc methionine and zinc sulfate. Recommended dosages for these supplements vary because each formulation has a different degree of gastrointestinal absorption. In general, the gastrointestinal absorption of zinc is poor. Zinc methionine, as a complex with the amino acid methionine, has much more bioavailability than zinc sulfate. The bioavailability of zinc gluconate appears to fall between the two. There is also some confusion with respect to dosing because some recommendations are based on the amount of elemental zinc in the product, whereas others are based on the amount of the zinc salt or amino acid complex. Interconversions between the two can be made, noting the amount of elemental zinc in each as outlined in Table 42-1. However, in reality, trying to make the conversions often does not correlate with the actual recommended dosages that are given in the literature. Recommended starting dosages for elemental zinc are from 1 to 3 mg/kg per day. In one study, the dosage range of zinc methionine required for control (based on elemental zinc) was 1.2-6.8 mg/kg per day (mean, 3.1 mg/kg per day). For zinc sulfate, it was 1.25-11.36 mg/kg per day (mean, 4.5 mg/kg). The author starts at 2 mg/kg/day. Recommendations for the combinations are outlined in Table 42-1. The dosages of the combinations are most commonly used in clinical practice. If zinc sulfate is used (the most poorly absorbed source), then it is ideal to divide the dosage into two administrations over the day and have the powder mixed with food. Although dosages for zinc methionine or zinc gluconate are often divided and given twice daily, this is less imperative because they are better absorbed. These are starting dosages; individual requirements may vary.

12. Are there any deleterious side effects of zinc administration?

In general, zinc salts are of very low toxicity. The most common side effect is gastric irritation, which is manifest as nausea, vomiting, inappetence. This side effect is most commonly noted with zinc sulfate. Giving the zinc supplement with food will decrease this tendency. Problems may also be circumvented by decreasing the dosage or switching to a different zinc source (especially to zinc methionine or gluconate). The hemolytic anemia and associated nephropathy that has been associated with the ingestion of pennies and zinc oxide in large quantities has not been noted with the zinc supplementation regimens previously recommended.

13. Are there any adjunctive therapies that may enhance response to supplementation?

Fatty acid therapy (combination omega 3 and omega 6 supplements) has been noted to be a benefit for some individuals, perhaps due to concurrent defects in fat absorption in affected individuals. Routine dosages of any one of a number of commercial supplements may be considered. In one case, fatty acid therapy allowed for the discontinuation of zinc supplementation.

14. How long before one should expect to first see response to therapy?

The onset of benefit should be noted within 6 weeks. Significant improvement is often noted within the first 3-4 weeks.

15. Should all the lesions resolve on therapy?

Yes, lesions resolve in the vast majority of patients. Some lesions may not totally resolve but will have degrees of disease that are very acceptable. Total remission may be interspersed with minor flares that spontaneously resolve, without dosage changes. These remissions usually occur within a couple of weeks.

16. How is zinc supplementation managed on a long-term basis?

Therapy at the dosages noted above should be maintained until all lesions have resolved and for at least several weeks beyond. It has been noted that discontinuation of medication at this time may result in prolonged remission in as many as 25% of cases. In my experience, this percentage is high. It is certainly reasonable to slowly reduce and then discontinue the medication. Recurrence of signs would suggest the need for long-term maintenance therapy. Dosages may also vary over time (may require more supplementation at times of stress or with seasonal changes) in some individuals. Minor "flares" will often resolve with continuation of the maintenance dosages. Intact females who are spayed may occasionally come off all supplementation.

17. What if my patient fails to respond to the previously mentioned supplementation?

The first consideration would be to re-evaluate your diagnosis. However, failure to respond is not uncommon. Factors that could complicate therapy (use of zinc-binding dietary supplements, females remaining intact) should be addressed. Consideration should then be given to increasing the dosage of the supplement by 50-100% and re-assessing in 3-4 weeks. If this should fail, then consideration should be given to changing zinc supplements. Patients that have failed to respond to zinc methionine have been noted to respond to zinc sulfate and vice versa. Oral glucocorticoids have been suggested to enhance zinc absorption and may benefit otherwise refractory cases. Dosages used to initiate therapy are in the 0.5-1.0 mg/kg per day range for prednisone or prednisolone, with the goal being to gradually reduce this over 3-4 weeks to the lowest every-other-day dose required to control signs (goal is <0.2 mg/kg once every other day). Some patients, however, must be maintained on low daily dosages. In my case files, two Siberian Huskies requiring adjunctive glucocorticoid therapy were placed on a novel protein; non–fatty acid–supplemented restrictive diet and quickly went into remission. Zinc supplementation was soon thereafter stopped and they remained in remission. This may suggest that food sensitivity, perhaps through the initiation of low-grade inflammatory bowel disease, may play a role in some individuals.

18. Do you see patients that fail to respond even to these manipulations?

Yes, this also occurs and is seen most commonly in Siberian Huskies. In these patients, consideration would then be given to treatment with intravenous zinc sulfate to circumvent the need for gastrointestinal absorption. Sterile zinc sulfate is given intravenously (IV) at a dosage of 10-15 mg/kg as weekly injections for at least 4 consecutive weeks (until lesions resolve), then once every 1-6 months as maintenance dosages. A maintenance dose is given at the first sign of recurrence of the problem. The zinc sulfate is diluted 1:1 with saline and given slowly IV over 10-15 minutes. Deleterious signs are few but include panting and cardiac arrhythmias. It is imperative to note that zinc sulfate is very irritating and if allowed to leak into the perivascular tissues will cause extensive necrosis. Oral zinc therapy is usually maintained to hopefully increase the time between IV infusions. For those patients refractory to even this, or for whom IV zinc therapy is not an option or glucocorticoids are not well tolerated, consideration should be given to the use of topical tacrolimus. The ointment (tacrolimus; Protopic 0.1%; Fugisawa) is applied very sparingly twice daily to initiate therapy until remission of the lesions is noted. Frequency of application is then reduced to once daily and finally once every other day. Affected areas are maintained with once every 1- to 3-day therapy. It may be possible to stop treating a given area (remains in remission). Owners are left to chase lesions as they arise. This therapy appears to be very well tolerated and has been of benefit when all other manipulations have failed.

Although tacrolimus is expensive, one 30-g tube of this medication tends to last a long time (weeks to months) and is worth the investment.

19. How are young, growing dogs on potentially zinc-binding diets or supplements or zinc-deficient diets usually treated?

Zinc dosages are as noted in Table 42-1. A good quality diet is instituted. Supplements are discontinued. Once clinical signs have resolved, supplementation may be slowly discontinued over a few weeks. On a rare occasion, supplementation may be required until adulthood.

20. What are the dosages of zinc used to treat metabolic epidermal necrosis?

The dosages are as noted in Table 42-1. Zinc is usually given in conjunction with essential fatty acids.

21. Should we consider using topical zinc therapy to increase wound healing, reduce pruritus and for its antimicrobial effects, as has been suggested by some?

There are some experimental data to support these claims, but clinical experience in small animals is largely anecdotal. As long as these products are monitored closely and more conventional alternatives are concurrently used or are readily available, then further clinical trials utilizing zinc appear to be warranted.

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Section VIII
Miscellaneous Dermatoses

43. ENVIRONMENTAL DERMATOSES

Rod A.W. Rosychuk, DVM, DACVIM

1. **I have often heard the term actinic used when issues regarding solar damage to the skin are discussed. What does actinic mean?**

Actinic is synonymous with sunlight, or more specifically, sunlight that causes photochemical effects.

2. **What are the solar dermatoses that are seen most commonly in clinical practice?**

Sunburn is seen in naturally nonpigmented or lightly pigmented skin that is thinly haired. It can also be seen in skin that has depigmented due to diseases such as discoid lupus erythematosus or vitiligo. Acute sunburning is characterized by erythema and variable degrees of pain. Lesions are self-limiting. Chronic sun exposure results in further changes to the epidermis and dermis referred to as solar (actinic) dermatitis. In the dog, solar dermatoses tend to be divided into two categories based on their distribution of involvement. Nasal solar dermatitis is most commonly noted over the nasal planum and/or bridge of the nose, but may affect any area of the face that is poorly pigmented (Figure 43-1). On a rare occasion, these lesions may undergo malignant trans-

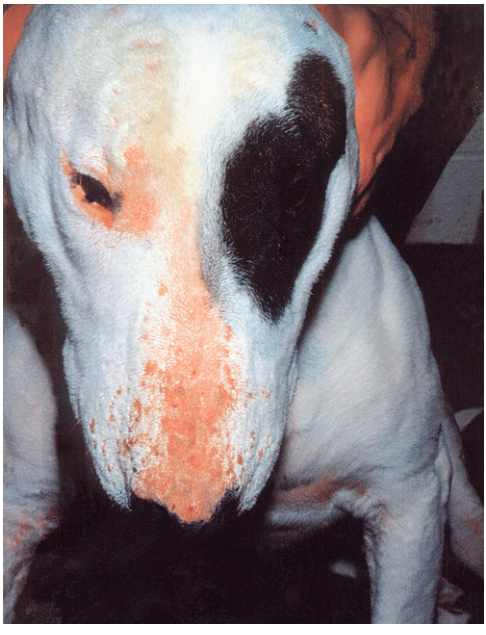

Figure 43-1 Five-year-old neutered male Bull Terrier with nasal solar dermatitis.

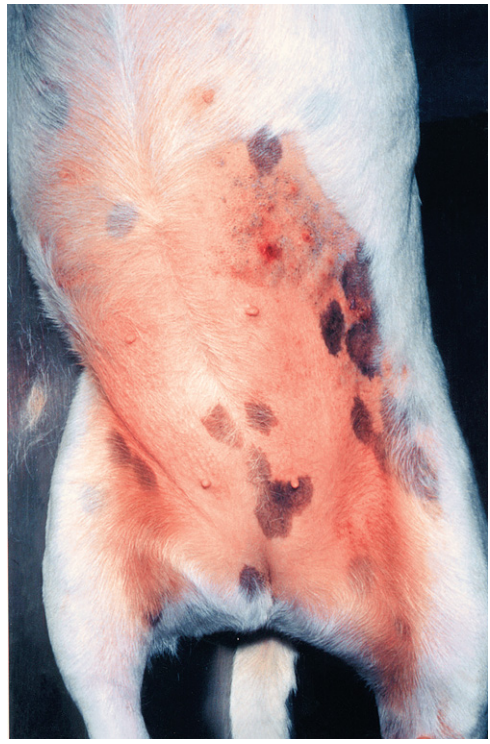

Figure 43-2 Six-year-old spayed female Bull Terrier. Note the erythema, comedo formation, and deep pyogranulomatous dermatitis as a result of solar damage.

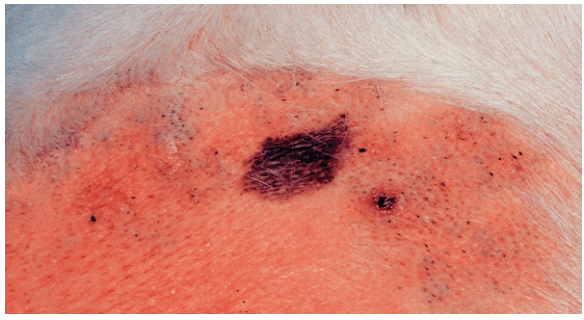

Figure 43-3 Comedo formation and deep pyogranulomatous dermatitis as a result of solar damage.

formation, resulting in the development of squamous cell carcinoma. Solar dermatitis of the trunk tends to involve the ventral abdomen, axilla, perineum, and flanks. Certain breeds appear to be at greater risk, including the Dalmatian, Bull Terrier, American Staffordshire Terrier, White Boxer, Whippet, Beagle, and German Shorthaired Pointer. In these areas, chronically affected lesions may become thickened, fibrotic, and develop follicular plugging and a pyogranulomatous furunculosis (Figures 43-2 to 43-4). Malignant transformation is possible. Squamous cell carcinoma, hemangioma, and hemangiosarcoma have been noted as sequelae to actinic damage in these

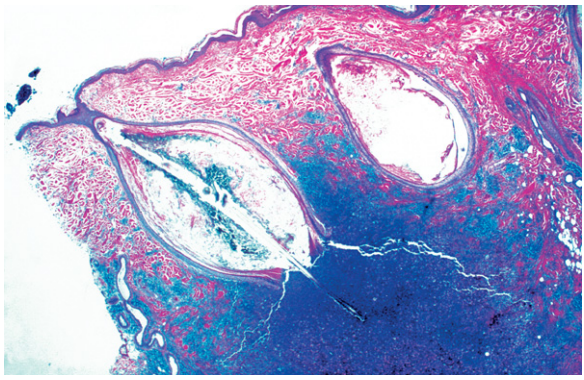

Figure 43-4 Histopathologic section of skin from patient in Figure 43-2 showing follicular dilation and hyperkeratosis plus a deep pyogranulomatous dermatitis as a result of follicular rupture.

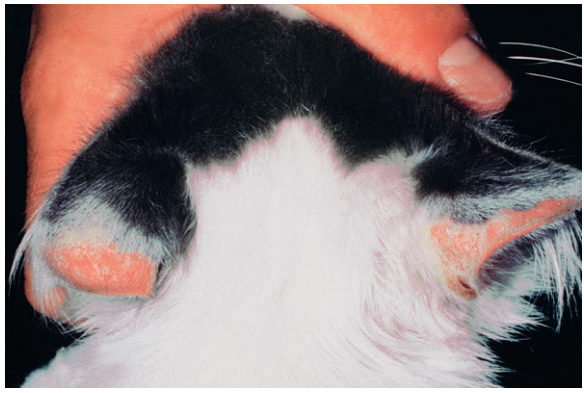

Figure 43-5 Actinic dermatitis characterized by erythema restricted to nonpigmented skin.

areas. In cats, solar dermatitis is seen most commonly in white cats (especially if they have blue eyes) or colored cats with white-haired areas (Figure 43-5). Lesions are most commonly noted over the tips of the ears, lower eyelids, nose, and lips. Chronic lesions are also prone to the development of squamous cell carcinoma (Figure 43-6).

3. What is it in sunlight that results in sunburning and these other more serious sequelae?

The sunburn reaction is a classic phototoxicity related to light within the ultraviolet spectrum (primarily UVB; to a lesser degree, UVA). Exposure results in vacuolation and apoptosis of keratinocytes ("sunburn cells"). Damage to epidermal DNA may result in neoplastic transformation. There is dermal vascular dilatation and leakage with the release of various mediators of inflammation (e.g., prostaglandins, leukotrienes, and inflammatory cytokines) and the generation of various oxygen intermediates (e.g., hydrogen peroxide, superoxide radicals), which are destructive to tissues. Dermal collagen and elastin is damaged and fragmented. Normal immunologic functions of the skin are compromised, which may also predispose to neoplastic transformation.

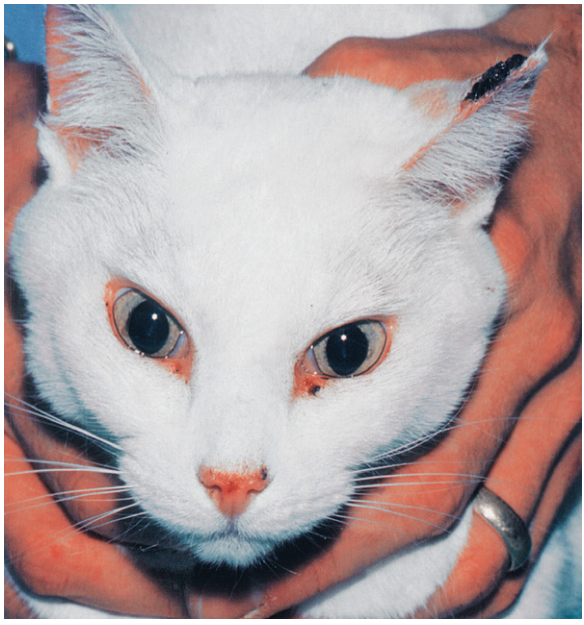

Figure 43-6 Squamous cell carcinoma involving predilection sites for solar damage: nasal planum, eyelids, and tips of ears.

4. What do the lesions look like as they progress?

Affected areas are initially erythematous and scaly. With chronicity, alopecia, thickening of the skin, exudation and crusting, erosion, and ulceration may be seen. With more severe lesions, healing usually results in scarring rather than a normalization of tissue. Previously damaged tissues appear to be more prone to continued alteration by ultraviolet (UV) light. The process may wax and wane with seasons (e.g., more severe in summer) and be more problematic at higher altitudes or with reflected light from the snow. Adjacent pigmented skin should be normal. This is a helpful tip-off to the presence of an actinic dermatitis.

5. What are the major differential diagnoses for canine nasal solar dermatitis?

The major differential diagnoses include those diseases that depigment the skin and make it more UV light sensitive. They include discoid lupus erythematosus (DLE; the most common differential), pemphigus foliaceus (PF), pemphigus erythematosus, systemic lupus erythematosus, dermatomyositis, and vitiligo.

6. How is sunburn of the planum or bridge of the nose differentiated from diseases like DLE or PF on a clinical basis?

When sunburn is more likely to be the culprit, the owners should note that the affected areas had never been pigmented. Inflammation, crusting, erosion, and ulceration develop slowly over years. Adjacent skin should not be affected. For most cases of DLE or PF, the affected skin is initially pigmented. The autoimmune diseases themselves cause depigmentation, which in turn results in the relatively rapid loss of the cobblestone pattern of the planum, and with time, inflammation, exudation, crusting, and erosion/ulceration. Once depigmented by these autoimmune diseases, affected skin is more prone to sunburn. There may also be a greater than expected response to UV light exposure in that these diseases are also capable of sensitizing affected skin

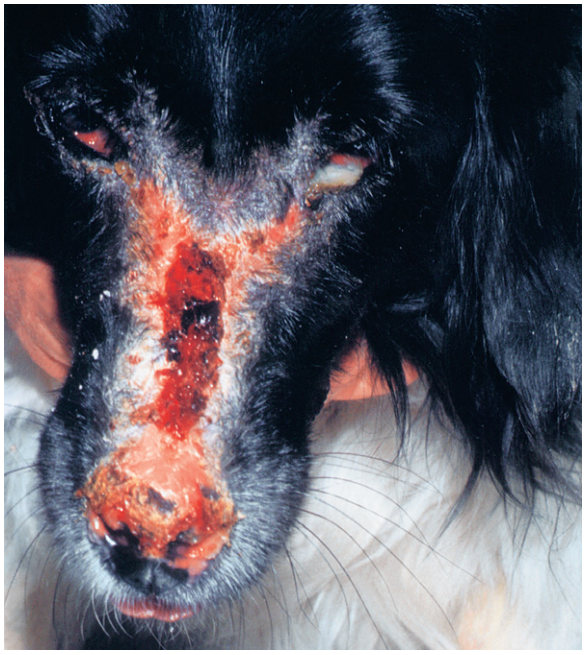

Figure 43-7 Pemphigus erythematosus at initial presentation.

to UV light damage (Figures 43-7 and 43-8). If owners are not aware of the natural progression of early disease, differentiation of a solar dermatitis from an underlying autoimmune disease may be difficult. It is often left to skin biopsy.

7. **Is increased sun sensitivity noted in all dogs with DLE?**
   No. There appears to be significant individual variation. Some dogs are not sensitized at all.

8. **How often does one see significant sunburn-related disease versus discoid lupus and discoid lupus-like diseases affect the planum of the nose in the dog?**
   It is much more common to see DLE, primarily because most dogs normally have pigmented nasal planums.

9. **How common is it to see malignant transformation in chronic actinic lesions affecting the planum or bridge of the nose?**
   As compared to solar dermatoses in the cat and truncal solar dermatoses, malignant transformation is rare. It is usually heralded by tissue that becomes inordinately thickened and usually ulcerated. The lesion is often asymmetric.

10. **Why does chronic actinic damage over the ventrum and flanks of dogs result in comedo formation and deep pyogranulomatous lesions in some dogs such as the Bull Terrier?**
    As the affected inflamed skin becomes more thickened (a combination of epidermal thickening and dermal inflammation and scarring), it has been hypothesized that solar damage causes a weakening of the opening of the follicular structure. Keratogenous debris accumulates

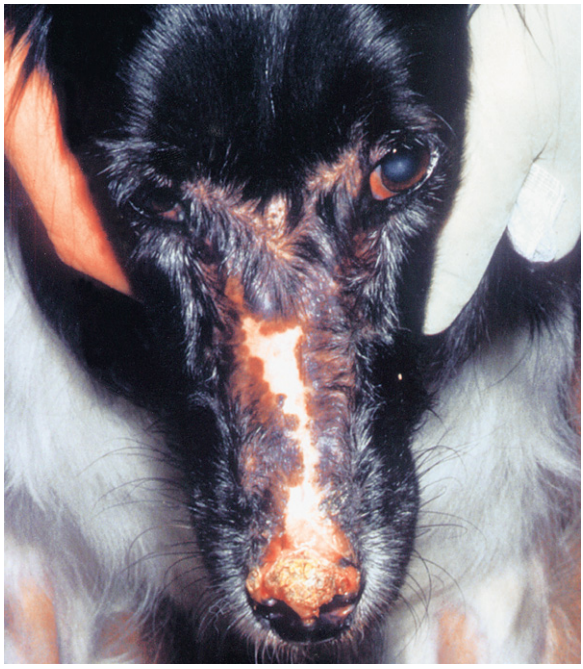

Figure 43-8 Pemphigus erythematosus 10 weeks after nothing but total restriction from sunlight exposure.

within the follicle, resulting in comedo formation (see Figure 43-3). Eventually the follicular wall is breached, resulting in variable degrees of inflammation within the surrounding dermis (furunculosis) (see Figure 43-4). Bacteria within the follicles may predispose to a secondary deep bacterial pyoderma.

11. What is solar dermatitis over the ventrum of dogs most likely to be confused with on a clinical basis?

It most closely resembles an allergic dermatitis with an associated deep pyoderma.

12. Can these lesions be noted in other areas of the body?

Yes, it is possible to see similar lesions on the bridge of the nose, ear tips, or distal extremities.

13. What should herald the transformation to malignancy?

More dramatic, usually focal skin thickening wherein the surface of the skin is irregular, eroded and/or ulcerated should always make one think of either a premalignant or malignant transformation. A biopsy specimen should be obtained from any suspicious lesion for confirmation.

14. What does solar dermatitis look like in cats?

The earliest changes are erythema, scaling, and hair loss (see Figure 43-5). With progression, there is serum exudation and crusting. Lesions may be painful and/or pruritic. Neoplastic transformation is often difficult to differentiate from inflammation. Neoplastic lesions are crusty, hemorrhagic, eroded, and ulcerative and indurated (see Figure 43-6).

15. What are the histologic changes that suggest the presence of solar dermatitis?

Changes that are common to all forms (nasal, truncal, and feline solar dermatitis) include epidermal hyperplasia, intraepidermal edema, and variable numbers of vacuolated and singly apoptotic keratinocytes (sunburn cells). One of the most common changes is fibrosis within the superficial dermis. There is usually a perivascular accumulation of inflammatory cells within the dermis. Solar elastosis, which is a basophilic degeneration of elastin noted in the superficial dermis and is commonly seen in humans, is not commonly seen in the dog and cat. If present, it is better observed with special stains. With truncal solar dermatitis there may also be solar induced folliculitis, follicular cysts, and pyogranulomatous furunculosis.

16. I often hear the terms "actinic keratosis" and "squamous cell carcinoma in situ" mentioned in relation to solar dermatoses. What do these terms mean?

An actinic keratosis is a focal area of marked epidermal hyperplasia, which is very prone to neoplastic transformation. It is most commonly seen with canine truncal and feline solar dermatitis and is manifest as a focal area of skin thickening. Squamous cell carcinoma in situ refers to epidermis that has undergone neoplastic transformation (marked cellular atypia and disorganization of cells), but no invasion of the underlying basement membrane. Invasive squamous cell carcinoma disrupts the basement membrane and has invaded the dermis.

17. What are the therapies for nasal solar dermatitis in the dog?

Whenever possible, emphasis should be placed on sun restriction (indoors or in the shade), especially during times of peak ultraviolet light exposure (9:00 AM to 4:00 PM). Although windows are noted to screen out the majority of UVB light, UVA light is only partially blocked. Sun bathing in a window may still be a significant perpetuator in susceptible individuals. Where restriction is not possible, the use of a sunscreen or sunblock is recommended. Sunscreens absorb ultraviolet light, thereby protecting the skin. Sunscreens should be labeled "broad spectrum" to protect both from UVB and UVA light. A UVB sun protective factor (SPF) rating of 30 or greater (absorbs > 96%) is recommended. For best results, the sunscreen should be applied 30-60 minutes before exposure to the sun. For individuals that are outdoors throughout the day, the sunscreen should be applied at least twice daily. Sunblocks contain titanium dioxide and/or micronized zinc oxide and provide wide spectrum UVA and UVB protection. While very effective, they tend to be messy. When inflammation is moderate to severe, consideration should be given to treating with oral glucocorticoids, beginning at 1 mg/kg per day prednisone or prednisolone and decreasing over 1-3 weeks. Consideration can be given to artificially pigmenting the skin. This can be done in a transient fashion with a permanent felt-tipped black marker or stamp pad ink. Tattooing can be of benefit for prolonged periods (months to sometimes years), but emphasis must be placed on normalizing the skin as much as possible before tattooing and spending enough time to do a very thorough job. The procedure requires general anesthesia and can be very time-consuming for all but the smallest of lesions.

18. What if therapy for nasal solar dermatitis appears to be failing?

In most cases, this is because an underlying disease, commonly discoid lupus erythematosus, is missed. Emphasis should be on obtaining biopsy specimens from affected individuals.

19. What are therapies for truncal solar dermatitis?

They are as above for sun restriction (including restricted sunbathing through windows) and the use of sunscreens. Consideration should also be given to using t-shirts or UV-light protective clothing that is manufactured specifically for the canine (e.g., www.doggles.com, www.pawgear.com). Systemic antibiotics for secondary bacterial infections are often of benefit. Systemic glucocorticoids at anti-inflammatory dosages (i.e., prednisone or prednisolone beginning at 1 mg/kg orally every 24 hours) can be used for more severe inflammation. Some have suggested that β-carotene (30 mg orally every 12 hours for 30 days, then every 24 hours for life), in combination

with anti-inflammatory doses of prednisone or prednisolone, can be used to control inflammation and prevent progression to neoplasia in early cases. Nonsteroidal alternatives include the use of the nonsteroidal anti-inflammatory drug (NSAID) piroxicam, given at a dosage of 0.3 mg/kg orally once every other day. This therapy has been of particular benefit to palliate those patients with significant dysplastic changes or already established squamous cell carcinomas that cannot be managed by other means. Dogs on piroxicam therapy should be monitored closely for gastrointestinal toxicity (complete blood cell counts monthly for development of anemia). Retinoids, which have both anti-inflammatory effects and help to normalize the epidermis, have also been of benefit for those individuals with dysplastic changes and/or folliculitis/furunculosis but are very expensive for maintenance therapy. Acitretin is recommended at a dosage of 0.5-1 mg/kg orally every 24 hours.

20. What can be done for cats with solar dermatitis?

Again, sun restriction (including window sun bathing) and the use of sunscreens are recommended as for the dog. β-Carotene or canthaxanthin at a dosage of 25 or 30 mg/cat orally once per day or 30 mg/cat orally every 12 hours may be of benefit on a maintenance basis if squamous cell carcinoma has not developed. The retinoid Acitretin can be used at 5-10 mg/cat orally every 24 hours. Piroxicam can also be used in cats at a dosage of 0.3 mg/kg (usually 1 mg/cat) orally every 24 to 48 hours. The piroxicam can be mixed with cod liver oil to facilitate administration, but is less stable in tuna-based formulations. For problematic ear margin dermatitis, consideration should be given to cosmetic ear tip amputation. For established squamous cell carcinoma, consideration should first be given to surgical, laser, or cryosurgical removal. Alternatives include radiation therapy and photodynamic therapy.

21. What agents are most frequently associated with burns to the skin?

Thermal burns are most commonly associated with fires, boiling liquids, hot semiliquids (e.g., tar), steam, hot metals (e.g., stoves), electric heating pads, and surgical lights. Both the temperature and length of exposure are of paramount importance in determining the degree of damage to the skin. Burns may also be electrical or associated with various chemicals.

22. Do we use the terms *first-, second-,* and *third-degree* to quantitate the amount of burn damage to the skin?

Usually not. In dogs and cats, burns have most commonly been categorized as partial thickness (epidermis or epidermis and superficial dermis) and full thickness (epidermis, dermis and all structures therein).

23. How would a partial-thickness burn present clinically?

Superficial partial-thickness burns that affect the epidermis only are initially erythematous, thickened, and painful. The epidermis desquamates and usually heals by re-epithelialization over 3-6 days. Deeper partial-thickness burns are relatively more inflamed and edematous. Over 24 to 48 hours, areas of superficial tissue death will be better demarcated. Necrotic tissue will harden and will often remain adhered to underlying tissue. As long as the tissue appears clean and relatively dry, there is no need to remove this adherent eschar. Suppuration suggests the possibility of secondary bacterial infection. This should be explored cytologically. With healing, the eschar will simply peel off.

24. How are partial-thickness burns managed?

Affected areas should be gently clipped and kept clean (0.05% chlorhexidine diacetate; 0.1% povidone-iodine; hydrotherapy). Application of chilled saline or water immediately after the burn may reduce pain and the progression of the burn. For superficial burns, topical aloe vera may be of benefit (antithromboxane effect helps prevent vasoconstriction and microcirculatory

emboli). Especially for deeper partial thickness burns, topical silver sulfadiazine (broad-spectrum antibiotic) is applied twice daily.

25. What is the prognosis for partial-thickness burns?

The prognosis is good. Even for deeper burns, re-epithelialization occurs from the hair follicles and sebaceous glands and scarring is minimal to absent. Hair regrowth is usually good, although with deeper dermal burns, there may be some hypotrichosis in affected areas.

26. How would a full-thickness burn present clinically?

With thermal burns, affected skin is initially inflamed and somewhat thickened, but quickly forms a dark brown, insensitive, leathery covering (eschar) over subcutaneous tissues. With chemical or electric burns, lesions may be obviously severe and deep with overt tissue necrosis. Individuals may also present with a more insidious course wherein overt signs are not noted until about 48-72 hours after the burn (e.g., heating pad or surgical light burns) when the affected skin becomes hard and dry.

27. How are full-thickness burns managed?

Special attention must be given to the extent of the burns (body surface area involved) and the systemic signs being manifest by the patient. Patients with very extensive burns may develop fluid and electrolyte imbalances. They are more prone to shock, septicemia, anemia and renal failure. Management of these systemic complications is discussed elsewhere. Lesions should be kept clean (0.05% chlorhexidine, 0.1% povidone-iodine; hydrotherapy) and are treated with twice-daily topical silver sulfadiazine. The eschar should be monitored closely for suppuration, which may herald secondary infection. Once areas of necrosis are well defined, the eschar should be removed as soon as possible. The remaining defect can then be managed with a wet to dry bandage (gauze wet in saline or 0.01% povidone-iodine, covered by dry gauze; held down by ties through stent sutures) which is initially changed a couple of times daily. This management is maintained until a good bed of granulation is noted. Gauze impregnated with hypertonic saline (commercially available) may also be used over the wound for the first 2-3 days to hasten the development of granulation. Although hypertonic saline is bactericidal, it may prove very irritating and painful. The need for systemic antibiotics is controversial. The presence of suppuration should indicate the need for cytology and culture and susceptibility testing and a choice of a systemic antibiotic based on these data. A reasonable empiric choice pending culture data would be a fluoroquinolone. Once a bed of granulation is established, a decision can be made as to whether to resect the area and try for primary closure (if possible), consider skin grafts, or manage the lesion with topical silver sulfadiazine and allow for second intention healing with scar formation and scar retraction. Scars will likely be hairless and potentially prone to sunburn.

28. What is the difference between a contact irritant dermatitis and a contact hypersensitivity dermatitis?

A contact irritant dermatitis is an inflammatory/degenerative process initiated and perpetuated by the noxious aspect of the material coming in contact with the skin. A contact hypersensitivity dermatitis has an immunologic pathogenesis, primarily mediated by lymphocytes.

29. What causes contact irritant dermatitis?

Examples include disinfectants, insecticide sprays, fertilizers, carpet cleaners, the ingredients in various shampoos and soaps, flea collars, strong acids, and alkalies.

30. What causes contact hypersensitivity dermatitis?

The allergens that initiate these immunologic reactions are small molecules (referred to as haptens) that bind to proteins to become complete antigens. These antigens then initiate a cell-mediated (lymphocytic) immunologic response. Only relatively few cases have been well docu-

mented in the veterinary literature. They include various plants (wandering Jew, the leaves and bulbs of Amaryllidaceae, spreading dayflower, doveweed, Asian jasmine, dandelion leaves), cedar wood, cobalt chloride, nickel sulfate, rubber, wood alcohols, epoxy resin, formaldehyde, cement, bleach, and neomycin. Others suggested to be problems include poison ivy, poison oak, plastic products, detergents, cat litter, collars (leather, metal), other topical agents (bacitracin, thiabendazole, tretinoin, miconazole, povidone iodine, tetracaine), shampoos (tars and benzoyl-peroxide), petrolatum, lanolin, disinfectants, insecticides (shampoos, dips, sprays, "top spots"), flea and tick collars and medallions.

31. How frequently are contact hypersensitivities seen in clinical practice?

They appear to be rare to uncommon in the dog and even less common in the cat, likely because of the widespread hair cover in the cat. Their incidence is significantly higher in humans. Contact irritant dermatitis is seen more commonly than true contact hypersensitivities. Contact hypersensitivities appear to occur more commonly in atopic individuals.

32. Is it easy to differentiate a contact hypersensitivity from an irritant dermatitis?

No. The history, physical findings, and even histopathologic findings may be very similar.

33. What clinical findings are common to both contact irritant and contact hypersensitivity dermatitis problems?

The distribution of lesions is similar, because areas affected are relatively hairless (making them more prone to exposure to irritants and allergens), including the ventral abdomen, thorax, axilla, flanks, scrotum, perineum, ventral neck and tail, point of the chin, interdigital spaces and medial aspect of the pinna (in floppy-eared dogs). If the allergen/irritant is in liquid form, it may penetrate through hairs and be seen on any area of the body. The distribution of lesions may also be very restricted, depending on the areas of contact (e.g., ears for otic preparations; lips, chin for plastic food bowl hypersensitivities). Lesions are manifest as erythema, macules, papules, crusts, hyperpigmentation, lichenification, and excoriation (Figures 43-9 and 43-10). Lesions may spread out of the classic contact areas as the problem becomes more chronic and severe. Both forms of contact dermatitis vary in severity of pruritus (may be mild to severe). Both are prone to secondary bacterial and *Malassezia* infections.

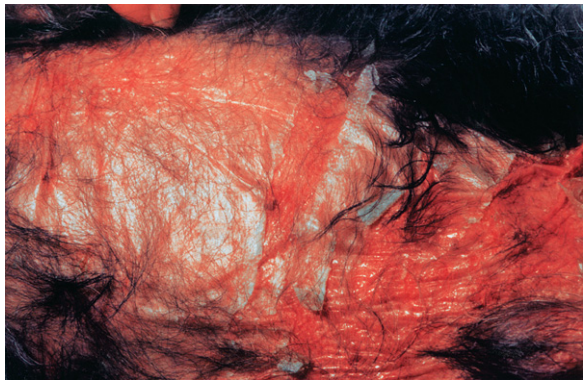

Figure 43-9 Contact hypersensitivity dermatitis manifest as diffuse dermatitis with superficial epithelial desquamation related to chronic topical neomycin application.

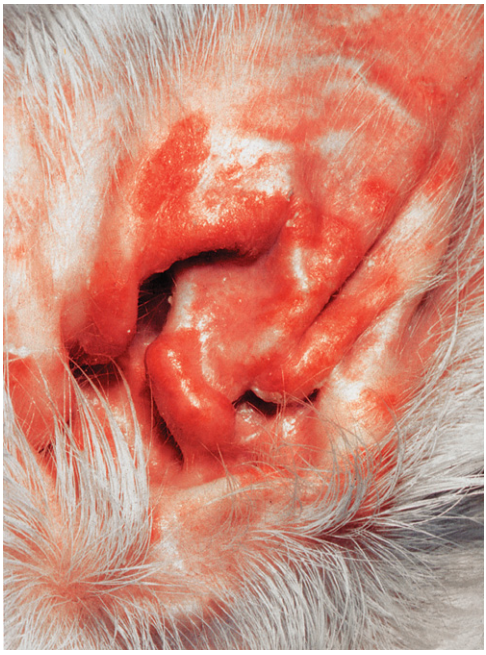

Figure 43-10 Macular erythema caused by topical contact hypersensitivity to propylene glycol.

34. How are contact irritant and hypersensitivity dermatitis problems differentiated?

Differentiation may be very difficult. Contact irritant dermatitis usually occurs rapidly, depending on the nature of the irritant, its concentration, and contact time (minutes to days to weeks). Milder irritants may require repeated exposure to create significant pathology. Contact hypersensitivities usually develop after weeks (minimum of 3-5 weeks) to months or even years. With respect to the feet, exposure to an irritant may produce pad lesions, whereas contact hypersensitivities should not. Contact hypersensitivities usually only involve one sensitized individual. Irritant dermatitis problems are more likely to affect multiple individuals if they have similar exposure. Histopathology may help to differentiate cases early in their course (see below), but changes are very similar with more chronic skin changes.

35. How are contact irritant dermatitis problems diagnosed and managed?

They are diagnosed primarily on the basis of history and physical examination, histopathology, and provocative exposure. Histopathologic changes associated with more acute lesions include epidermal edema (spongiosis) and the presence of neutrophils within the epidermis and dermis. In milder reactions, neutrophils and lymphocytes predominate. In more chronic lesions, lymphocytes and macrophages may predominate. If provocative exposure is used to document the irritant, then suspected irritants should be applied to both normal and diseased skin. Therapy includes avoidance, bathing the affected areas to remove irritants, keeping the areas dry (maceration enhances the effects of irritants). More severe lesions may require topical or systemic glucocorticoids. Pentoxifylline (10 mg/kg orally every 8 to 12 hours) may also be of benefit as for contact hypersensitivities (see below).

36. What are common differential diagnoses for contact hypersensitivities?

These include contact irritant dermatitis, atopy, food sensitivity, canine scabies, hookworm dermatitis, peloderma dermatitis, staphylococcal pyoderma, and *Malassezia* dermatitis.

37. How are contact hypersensitivities diagnosed?

Diagnosis is based on history, physical findings, histopathology, provocative exposure, and patch testing. The changes seen in skin biopsies are relatively variable and often nonspecific. They include superficial perivascular dermatitis, with lymphocytes and macrophages predominating. Eosinophils may be present in significant numbers. Diagnosis by provocative exposure involves first bathing to remove allergens, then isolating the patient from potential allergens for a period of 14 days. Suspected individual allergens are re-introduced once every 7-10 days. This technique is controversial because it may not differentiate contact hypersensitivity from atopy or an irritant dermatitis. Patch testing is performed by clipping hair over the dorsolateral thorax, then applying a small amount of the test allergen to the skin. If it is difficult to keep the material localized in the area, it can be mixed with a small amount of petrolatum. This is covered with a piece of sterile, non-adhesive gauze sponge. The corners of the sponge are taped down. The procedure is repeated for all the test materials. The test sites are bandaged with gauze and secured with an elastic bandage. An "E" collar should be worn to prevent self-trauma. The materials are removed in 48-72 hours. The test sites are marked with a felt-tipped pen and then evaluated for induration, erythema, and vesiculation every 24 hours for at least 3 days. Biopsy specimens should be obtained when there are questionable reactions. False-positive results may be noted if the material is too concentrated or irritating, if the test is done on inflamed skin, or if the site is self-traumatized. It is ideal to perform the test in a control animal to ensure that the test materials are not irritants. Standardized patch test kits are available for humans and can be used for dogs. They use small wells (Finn Chambers), which are taped to the skin. They are prone to false-positive results and often do not have the spectrum of allergens necessary for screening in the dog. Allergens can be added to the kit by mixing each with a small amount of petrolatum. Bandaging and reading are as noted previously. Open patch testing is mostly used for evaluating sensitivities to liquids. The test material is rubbed into clipped skin and examined daily for 5 days. The patient must wear an "E" collar throughout the test time to prevent self-trauma.

38. How are contact hypersensitivities best managed?

Avoidance is the ideal management technique. Because this may not be possible, the use of topical glucocorticoids or oral glucocorticoids (starting at 0.5-1 mg/kg per day orally for 5-7 days, then gradually reducing to the lowest dose required to control the problem) may prove necessary. Pentoxifylline has been noted to prevent the development of contact hypersensitivities in the dog, but may not work as well in managing already existent lesions. It is given at a dosage of 10-15 mg/kg orally every 8 to 12 hours. Frequency of administration may be reduced for longer term, maintenance therapy. Hyposensitization to contact allergens is not effective. Routine bathing and the use of conditioners may be of some benefit.

39. What conditions predispose to the development of frostbite?

Exposures to freezing temperatures or very cold metals are most commonly incriminated. Several factors are noted to exacerbate this tendency at less severe temperatures. These include cold winds, wetting of the tissue, a lack of acclimatization to cold temperatures, or the presence of a vasculopathy or cryoglobulinemia.

40. Where and how is frostbite most likely to be manifest?

The tips of the ears, the tail tip, scrotum and digits are more prone, likely due to the relative lack of hair cover and tissue covering blood vessels in these areas. After thawing, the skin may be erythematous, edematous, vesicular, painful and scaly. The tips of the pinnae may curl. In severe cases, tissue may develop an eschar and partially slough or become completely gangrenous and slough.

41. How is frostbite best managed in the acute situation?

Tissues should be rapidly thawed with warm water. It has been suggested that the parenteral use of aspirin and pentoxifylline (10-15 mg/kg orally every 8-12 hours) and the topical use of

aloe vera for the first few days may improve tissue survival. It is imperative that patience be employed while the demarcation between necrotic and viable tissue is established. This may take as long as 3-6 weeks. Once the line of demarcation is established, necrotic tissue should be removed. Previously frozen tissue may be more susceptible to future freezing. Amputation should be performed up to haired skin, thereby allowing the hair to provide protection from future cold exposure.

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44. PSYCHOCUTANEOUS DISORDERS

Adam P. Patterson, DVM

1. What are psychocutaneous disorders (psychogenic dermatoses)?

Psychocutaneous disorders are self-induced skin conditions associated with underlying behavioral problems, not primary dermatologic or physiologic diseases. Skin lesions are the result of stereotypic behaviors that may be manifestations of an anxiety-related disorder and/or obsessive-compulsive disorder (OCD). However, some skin lesions may be the result of boredom or attention-seeking behavior.

2. What are the differences (if any) between stereotypic behaviors, anxiety, obsessions, and compulsions?

- Stereotypic behaviors are excessive, relatively unchanging, repetitious motions with no obvious intention or function that interfere with normal behavioral function. The pattern of behavior is usually derived from normal behaviors. Examples include excessive licking, sucking, chewing, biting, scratching, and hair pulling.

aloe vera for the first few days may improve tissue survival. It is imperative that patience be employed while the demarcation between necrotic and viable tissue is established. This may take as long as 3-6 weeks. Once the line of demarcation is established, necrotic tissue should be removed. Previously frozen tissue may be more susceptible to future freezing. Amputation should be performed up to haired skin, thereby allowing the hair to provide protection from future cold exposure.

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2. What are the differences (if any) between stereotypic behaviors, anxiety, obsessions, and compulsions?

- Stereotypic behaviors are excessive, relatively unchanging, repetitious motions with no obvious intention or function that interfere with normal behavioral function. The pattern of behavior is usually derived from normal behaviors. Examples include excessive licking, sucking, chewing, biting, scratching, and hair pulling.

- Anxiety is the apprehensive anticipation of impending doom. Anxiety may lead to displaced (out of context) stereotypic behaviors.
- Obsessions are repeated impulses or thoughts that are interpreted as inappropriate, and cause great anxiety. Although it is near impossible to prove in companion animals, some behaviorists believe that animals experience obsessions.
- Compulsions and stereotypic behaviors are used relatively synonymous in veterinary medicine.

3. Why do animals with psychocutaneous disorders engage in stereotypic behaviors?

Although there is no definitive answer, neurochemicals, neurochemical metabolism, neurochemical-receptor interactions, and altered receptor sensitivity in the central nervous system are believed to be involved in anxiety, OCD, and other related behavioral disorders. Genetics probably play a role as well. Current theories include dopamine hypersensitivity, reduced serotonin concentrations, and chronic opioid receptor stimulation by endogenous endorphins. Perhaps internal or external stress associated with these behavioral disorders, and/or continued stereotypic behaviors, stimulate endorphin release which helps the animal cope with its perceived problem(s). Unfortunately, endorphins may sensitize dopaminergic systems, thus reinforcing stereotypic behaviors. Additionally, the animal might become chemically dependent on endogenous endorphins. Concurrent cutaneous trauma from stereotypic behaviors (licking, sucking, etc.) can result in secondary infections, leading to pruritus as well. Consequently, stereotypic behaviors are continued and a vicious circle develops.

4. List the syndromes thought to represent psychocutaneous disorders in dogs and cats.

- Acral lick dermatitis (lick granuloma)
- Feline psychogenic alopecia and dermatitis
- Tail dock neuroma
- Tail sucking (cats) and tail biting (dogs)
- Flank sucking
- Foot licking
- Self-nursing
- Anal licking
- Preputial licking

5. List stressors that may provoke compulsive behaviors in dogs and cats.

- Inadequate socialization
- Isolation or confinement
- Inadequate exercise
- Boring environment
- New environment
- Status disputes
- Overcrowding
- Territorial disputes
- Addition of family member or pets
- Loss of family member or pets
- Change of daily routines
- Hospitalization

6. What type of information should one acquire from the client when faced with a patient who might have a psychocutaneous disorder?

- Source of the pet
- Chronologic progression of problem behavior/signs
- Frequency and duration of problem behavior/signs
- Seasonal associations with problem behavior/signs
- Presence of skin lesions before problem behavior/signs
- Previous skin and/or ear infections
- Other household pets experiencing problem behaviors/signs
- People in household developing skin lesions
- Appropriate flea control used on all in-contact pets
- Dietary history
- Medical history
- Previous and current medications
- Response to any previously prescribed medication for problem behavior/signs

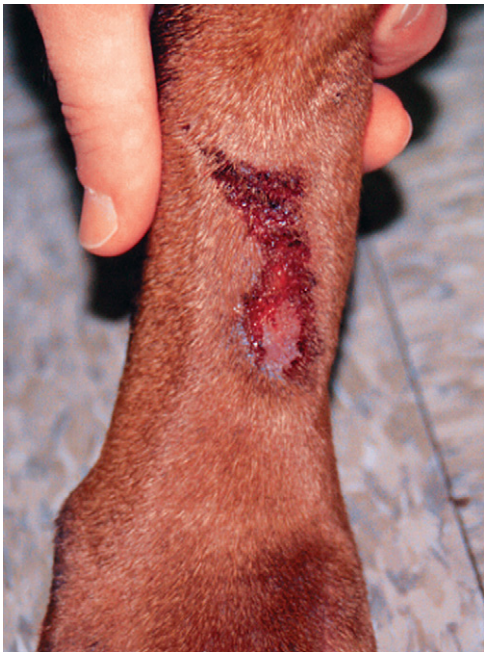

Figure 44-1 Acral lick dermatitis on the anterior metatarsus of a male Doberman Pinscher.

- Ease with which problem behavior may be interrupted
- Problem behavior elicited while the client is in the presence/absence of patient
- Deduce all potential social and environmental stressors
- Social interactions with people and animals
- Sleeping habits

7. **Define acral.**
   Affecting the extremities.

8. **Describe the age of onset, gender predilections, breed predispositions, distribution of skin lesions, and types of skin lesions of acral lick dermatitis and feline psychogenic alopecia and dermatitis.**
   See Figures 44-1 and 44-2 and Table 44-1.

9. **What are possible differential diagnoses of acral lick dermatitis?**
   - Folliculitis/furunculosis (bacterial, demodecosis, dermatophytosis)
   - Underlying allergies (flea, food, environmental)
   - Underlying endocrinopathy (hypothyroidism, hyperadrenocorticism)
   - Granulomas (pressure point, calcinosis circumscripta, fungal, mycobacterial)
   - Neoplasia (histiocytoma, mast cell tumor, fibrosarcoma, melanoma)
   - Underlying musculoskeletal disease (arthritis, osteomyelitis, implant pain or failure)
   - Underlying nerve damage
   - Trauma

10. **List the possible differential diagnoses of feline psychogenic alopecia and dermatitis.**
    - Folliculitis (bacterial, demodecosis, dermatophytosis)
    - Underlying allergies (flea, food, environmental)

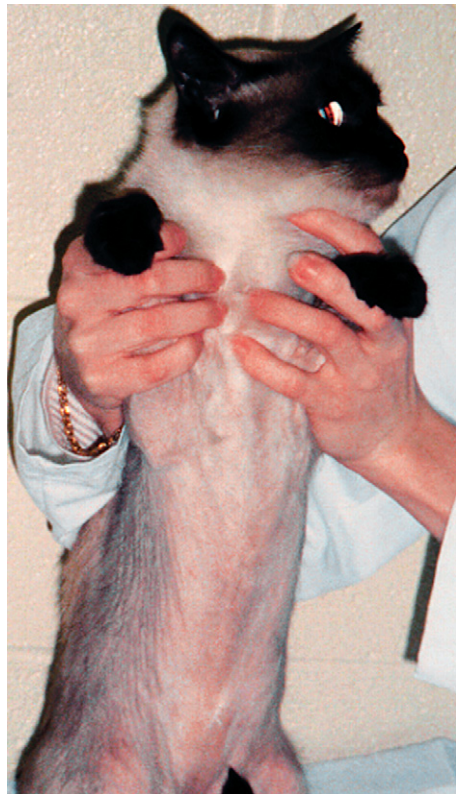

Figure 44-2 Feline psychogenic alopecia. This cat had bilaterally symmetric generalized alopecia.

Table 44-1 ***Characteristics of Acral Lick Dermatitis and Feline Psychogenic Alopecia and Dermatitis***

CHARACTERISTICS	ACRAL LICK DERMATITIS	FELINE PSYCHOGENIC ALOPECIA AND DERMATITIS
Age of onset	Any age	Any age
Gender predilection	Males are affected twice as often as females	None
Breed predispositions	Medium to large breed dogs; Doberman Pinscher, Great Dane, Labrador Retriever, Irish Setter, Golden Retriever, German Shepherd Dog	Emotional and oriental breeds (Siamese, Abyssinian, Oriental)
Distribution	Usually unilateral; cranial carpal, metacarpal, radial, metatarsal, and tibial regions	Easily accessible regions for cat to lick; medial forelegs and thighs, caudal abdomen, inguinal region, dorsolumbar and tail regions

Continued

Table 44-1 ***Characteristics of Acral Lick Dermatitis and Feline Psychogenic Alopecia and Dermatitis—Cont'd***

CHARACTERISTICS	ACRAL LICK DERMATITIS	FELINE PSYCHOGENIC ALOPECIA AND DERMATITIS
Lesions	Firm, thick, alopecic, erosive to ulcerative, well-circumscribed, erythematous to brown nodular plaque that may ooze; may have a hyperpigmented perimeter; surrounding hair is saliva-stained	Symmetrical alopecia (broken hairs) with areas of hair regrowth (short, stubby hairs that do not epilate easily), ± excoriations, ± hyperpigmentation, ± lichenification, ± bright red, elongated, oval plaque (eosinophilic plaque)

- Underlying parasites (internal, *Demodex gatoi, Cheyletiella, Otodectes, Notoedres*)
- Underlying systemic disease or endocrinopathy (hyperthyroidism)
- Paraneoplastic alopecia
- Eosinophilic plaque or granuloma

11. What diagnostics should be performed before a diagnosis of psychocutaneous disorder is given?

It is paramount that causes of pruritus and infection are eliminated before the diagnosis is made. Psychocutaneous disorders are diagnoses of exclusion not first time clinical impressions. However, a secondary psychogenic component may be a contributing factor to one of the possible differential diagnoses, specifically pruritic dermatoses. Additionally, a self-induced psychocutaneous lesion may become secondarily infected because of chronic irritation. Consequently, diagnostics should first focus on ruling out a potential primary dermatologic or physiologic disease. Diagnostics to consider are: skin cytology (microorganisms?), skin scrapings (mites?), dermatophyte culture, trichogram (broken/barbered hairs?), response to topical flea preventative, response to ectoparasite therapy, deworming, elimination diet trial, environmental allergy testing, complete blood count, chemistry profile, urinalysis, endocrine testing, skin lesion aspirate cytology ± acid fast staining, skin biopsy for histopathology, bacterial/fungal culture and sensitivity, and extremity radiography (bone involvement?). Occasionally, response to antihistamines and antipruritic doses of steroids may be beneficial to rule out allergic dermatoses. If results of selected diagnostics for the given patient are negative or inconclusive, then a psychocutaneous disorder becomes more likely.

12. Describe the histopathologic features of acral lick dermatitis.

There is irregular epidermal hyperplasia with rete ridge formation that interdigitates with the superficial dermis (Figure 44-3). The superficial epidermis is often ulcerated with an overlying crust. There is a marked transition between the ulcerated and nonulcerated epidermis. A superficial perivascular dermatitis consisting of neutrophils and mononuclear cells is usually present. There is prominent superficial dermal fibrosis. Collagen fibers in the dermal papillae are perpendicular to the epidermis. It is not uncommon to see evidence of perifolliculitis, folliculitis, or furunculosis. Hair follicles and sebaceous glands can appear hyperplastic. Varying numbers of plasma cells may surround the epitrichial sweat glands. Note that there is no evidence of granulomatous inflammation. The term lick granuloma is a clinical description of acral lick dermatitis, not a histopathologic description.

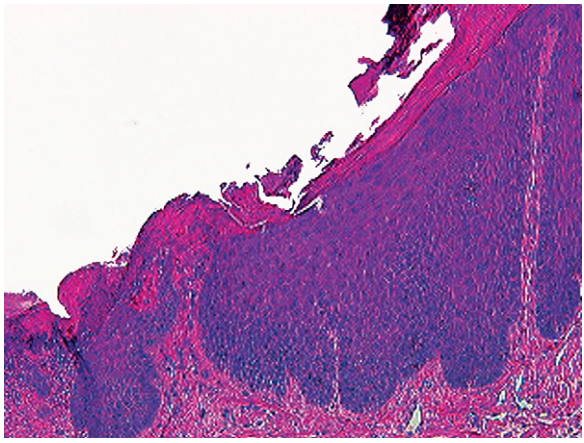

Figure 44-3 Skin biopsy from an acral lick dermatitis lesion; note the marked epidermal hyperplasia. (H&E, ×100.)

13. What considerations should one contemplate when managing a psychocutaneous disorder?

- Identify and treat any primary dermatologic or physiologic diseases
- Identify and correct or eliminate, if possible, all stressors in the environment
- Behavior modification incorporating counterconditioning and densensitization techniques (positive reinforcement of new behaviors while gradually exposing patient to provocative stimuli)
- Identify and treat any secondary complicating dermatoses
- If needed, behavioral pharmacotherapy

14. Describe different classes of behavioral pharmacotherapeutics, specific drugs of each class, drug mechanism of action, and some potential drug side effects of agents used in veterinary psychocutaneous disorders.

See Table 44-2.

Table 44-2 ***Characteristics of Various Pharmacotherapeutic Agents***

DRUG CLASS	SPECIFIC EXAMPLES	MECHANISM OF ACTION	POTENTIAL SIDE EFFECTS
Tricyclic antidepressants	Amitriptyline Doxepin Clomipramine	Block serotonin and norepinephrine presynaptic neurotransmitter receptors in the brain; block muscarinic receptors; amitriptyline and doxepin also block histamine receptors	Tachycardia, prolonged cardiac conduction, hypotension, mydriasis, dry mouth, reduced tear production, urine retention, constipation, sedation, weight gain

Continued

Table 44-2 ***Characteristics of Various Pharmacotherapeutic Agents—Cont'd***

DRUG CLASS	SPECIFIC EXAMPLES	MECHANISM OF ACTION	POTENTIAL SIDE EFFECTS
Selective serotonin reuptake inhibitors	Fluoxetine Paroxetine	Selectively block serotonin presynaptic neurotransmitter receptors in the brain	Anorexia, nausea, diarrhea, sedation, anxiety, agitation, insomnia, xerostomia (cats)
Opioid antagonist	Naltrexone	Endorphin blocker	Relatively free of side effects, possible abdominal cramping, nausea, vomiting, nervousness, rashes, pruritus, hepatotoxicity
Opioid agonist	Hydrocodone	Endorphin substitution	Sedation, constipation, vomiting, antitussive action, dependency
Dopamine antagonist	Haloperidol	Antagonist of dopamine, may also desensitize α-noradrenergic receptors	Hallucinations, limb twitches, ataxia

15. Before administering behavioral pharmacotherapy, what precautions should one consider?

One should become familiar with the route of metabolism and excretion, possible drug interactions, window of therapeutic index, and contraindications before administration of these medications. As a whole, they may potentiate cardiac arrhythmias and seizures, as well as increase hepatic enzymes. In general, most of them have a narrow therapeutic index, and preexisting seizure disorders, cardiac disease, renal disease, and hepatic disease are contraindications. Concurrent administration of tricyclic antidepressant drugs or selective serotonin reuptake inhibitors and monoamine oxidase inhibitors (selegiline) should be avoided. Baseline bloodwork, urinalysis, thyroid function, and possibly electrocardiography are warranted before administration. The use of these medications for psychocutaneous disorders is considered extra-label use.

16. What are the dosages of commonly prescribed behavioral pharmacotherapeutics for psychocutaneous disorders in dogs and cats?

See Table 44-3.

17. Besides treating the psychogenic aspect of acral lick dermatitis, the lesion itself must be treated. What are some therapeutic options?

- Treat any primary dermatologic or physiologic diseases.

Table 44-3 ***Dosages of Commonly Used Pharmacotherapeutic Agents***

DRUG	DOGS*	CATS*
Amitriptyline	1.0-3.0 mg/kg PO q 12 h	0.5-1.0 mg/kg PO q 12-24 h
Doxepin	3.0-5.0 mg/kg PO q 8-12 h 0.5-1.0 mg/kg PO q 12 h for predominantly antihistaminic effects	0.5-1.0 mg/kg PO q 12-24 h
Clomipramine	1.0-3.0 mg/kg PO q 12 h Start at 1.0 mg/kg and increase dose by 1.0 mg/kg q 14 d; use minimum effective dose	0.5 mg/kg PO q 24 h
Fluoxetine	1.0 mg/kg PO q 12-24 h	0.5-1.0 mg/kg PO q 24 h
Paroxetine	1.0 mg/kg PO q 24 h	0.5-1.0 mg/kg PO q 24 h
Naltrexone	2.2 mg/kg PO q 12-24 h	2.2 mg/kg PO q 24 h
Hydrocodone	0.25 mg/kg PO q 8 h	0.25-1.0 mg/kg PO q 12-24 h

*Initial trial period should be at least 3-6 weeks for most drugs. Try to use the lowest effective dose.
PO, Orally.

- *Collars, harnesses, muzzles, and bandages.* Initially, these may be beneficial as adjunctive therapy to prevent self-trauma, but are of no value when used alone.
- *Systemic antibiotics.* Acral lick dermatitis should be regarded as a deep pyoderma. Consequently, oral antibiotics may need to be administered for 6-8 weeks. Ideally, antibiotic selection is based on bacterial culture and sensitivity results.
- *Topical therapy.* Many different topical agents have been advocated. Unfortunately, none of them is totally effective when used alone. Therefore they should be used as adjunctive therapies. Products containing glucocorticoids, nonsteroidal anti-inflammatory drugs, DMSO, analgesics, and antibiotics either individually or in combination have been recommended. These products are usually applied twice daily. Additionally, products that are of poor taste (bitter apple) may be applied to the lesion to negatively reinforce problem behavior.
- *Intralesional injections.* Early small lesions may benefit from intralesional injections of triamcinolone acetonide or methylprednisolone acetate.
- *Surgical excision.* In most cases this is not a viable option due to the size, depth, and location (distal extremity) of the lesion. Other complicating factors such as the need for sutures, postoperative pain, and wound dehiscence secondary to excessive suture tension, infection, and/or problem behavior make this option less than ideal. Occasionally, a full-thickness skin graft/flap may be needed.
- *Surgical CO_2 laser resurfacing.* This surgical procedure has become more popular in recent years. Benefits of laser resurfacing may include less postoperative pain, less postoperative swelling, less postoperative bleeding, vaporization of infected tissue, and perhaps increased wound healing capabilities. Essentially the lesion is ablated down to the level of the surrounding epidermis. Several surgical procedures may need to be performed to achieve this goal. Additional adjunctive therapy is usually warranted.
- *Radiation therapy.* This therapy may only be effective for small and relatively acute lesions.
- *Cryosurgery.* This therapy is reserved for lesions that are extremely large and not amenable to full-thickness skin grafts/flaps. Freezing procedures are usually repeated multiple times.

18. What therapies have proved to be the most beneficial in treating cats with true psychogenic alopecia and dermatitis?

Unfortunately, no therapy has been extremely successful. The most important part of treatment is identifying and correcting or eliminating all possible environmental and social stressors. Overlooking this facet of therapy can ultimately result in complete treatment failure. Tricyclic antidepressants and selective serotonin reuptake inhibitors have been used with varied success. For cats in which the behavior is of recent (<6 months) onset, naltrexone may be tried at 2.5-5.0 mg/cat daily for 7 days then once weekly until clinical signs resolve. If the behavior has been present for > 6 months, haloperidol may be the first drug of choice. However, due to the sometimes severe idiosyncratic adverse side effects, cats should be hospitalized for the first week of treatment. An initial oral dose of 1.0 mg/kg twice daily is given and the cat monitored for ataxia, limb flicks, and hallucinations. If adverse reactions are seen, the dose should be reduced. Treatment should be continued for at least 2 months before evaluating the response to this drug. Up to 50% of cats will be cured after 2-3 months, another 25% may require continued maintenance therapy, and the remaining 25% do not improve.

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45. DISEASES OF THE CLAW AND CLAW BED

John C. Angus, DVM, DACVD

1. Regarding the normal anatomy of the canine and feline claw, what is the ungual crest? What is the corium?

The ungual crest is the crescent-shaped, dorsal process of the distal phalanx (P3). Failure to remove the ungual crest during declaw procedures will result in regrowth of the claw. Injury to this region may result in abnormal claw growth. The corium is a layer of tissue between the overlying claw and the underlying P3. The corium is contiguous with the dermis. The corium and underlying highly vascular periosteum supply blood to the growing claw; this is commonly referred to as the "quick" (Figure 45-1).

2. The hardened claw material is analogous to what structure in the normal skin?

The horny claw material is analogous to the stratum corneum, and is the final product of cornifying epithelial growth from the coronary band and a central dorsal ridge. The structures

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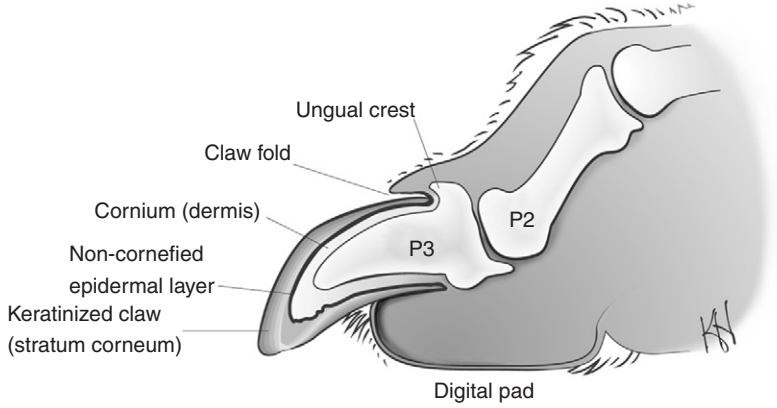

Figure 45-1 Schematic diagram of the normal canine claw.

of the claw, corium and claw plate, are contiguous with the dermis and epidermis of the adjacent skin.

3. What is the most abundant protein in the claw material?
Keratin

4. What is the approximate growth rate of the canine claw?
Information on rate of claw growth in the veterinary literature is limited. Textbook references describe the average rate of claw growth in Beagles younger than 2 years of age to be 1.9 mm per week. This rate declines with age to as slow as 0.8 mm per week. The implication of this information is that recovery from claw abnormalities is prolonged; 10-12 weeks may be needed for a diseased claw to regrow normally following resolution of the primary disorder.

5. What is the claw fold? What is different about the skin in this special area?
The claw fold describes the invagination of skin that covers the junction of cornified claw with soft tissue at the dorsal aspect of the claw. This skin lacks hair follicles.

6. What is the term for sloughing of the claw?
Onycholysis refers to the separation of the cornified claw from underlying corium. Usually this term is used when the claw is still attached proximally (Figure 45-2). When referring to complete sloughing of the claw from the digit, the proper term is onychomadesis.

7. What is the term for abnormal claw formation?
Onychodystrophy (Figure 45-3)

8. What is the term for inflammation of the claw fold?
Paronychia is the correct term. Paronychia may be characterized by swelling of the soft tissue surrounding the claw, or by discharge from underneath the claw fold. In many cases both clinical signs are present.

9. What is the term for claw pain?
Onychalgia

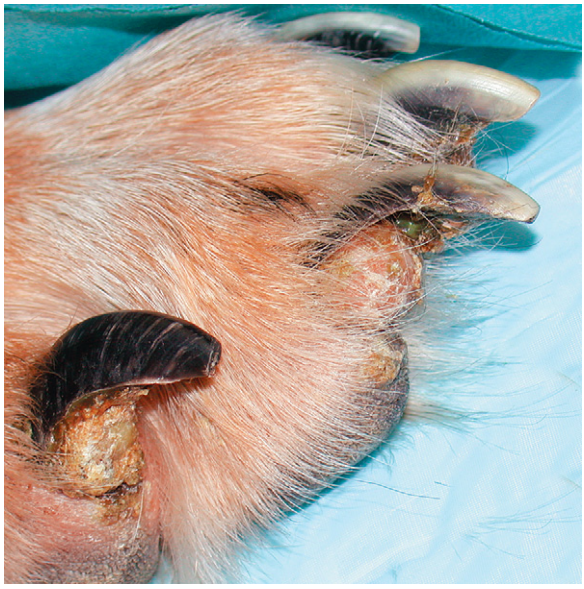

Figure 45-2 Multidigit onycholysis in a dog with pemphigus foliaceus. Note the purulent exudate under the "hollow" claw.

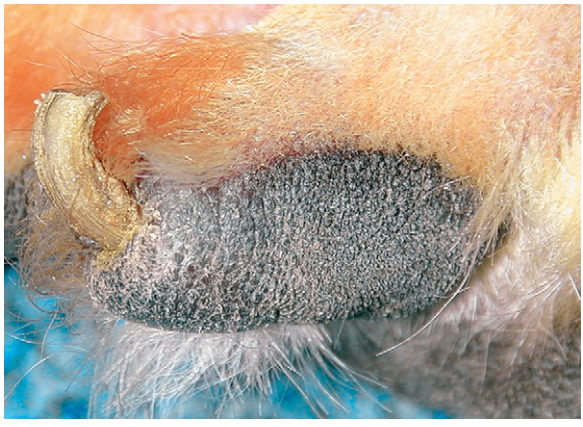

Figure 45-3 Onychodystrophy in a dog with symmetric lupoid onychodystrophy. In this case the soft, brittle claw is also growing in an inappropriate direction. (Courtesy Dr. Keith Hnilica and Dr. Adam Patterson.)

10. What is the term for fungal infection of the claw?
Onychomycosis

11. Several additional terms are used to describe specific abnormalities of claw formation. Define onychogryphosis, onychocryptosis, and onychorrhexis.
- Onychogryphosis: Hypertrophic claws with abnormal curvature
- Onychocryptosis: Ingrown claw. Typically this describes the situation where claws have grown so long and curved that they penetrate the digital paw pad of the same digit.

- Onychorrhexis: Brittle claw; specifically described as spontaneous splitting or fragmenting of a claw on the longitudinal axis of the claw.

12. What physical examination features should be specifically noted when evaluating claw or claw fold diseases?

- Single-digit involvement vs. multiple-digit involvement
- Symmetric vs. asymmetric disease
- Does condition affect only the claw, only the claw fold, or both?
- Presence or absence of regional lymphadenopathy
- Presence or absence of concurrent skin disease
- Presence or absence of concurrent systemic illness

13. Give your top three differential diagnoses for claw or claw fold disease affecting a single digit.

- Bacterial infection
- Trauma
- Neoplasia

14. Formulate a diagnostic plan for evaluation of a dog with pain, swelling, discharge, and loss of claw affecting a single digit.

1. *Cytology from discharge:* Note type of leukocytes present, presence or absence of organisms (bacteria, *Malassezia*, *Blastomyces*, etc.), presence or absence of acantholytic keratinocytes (suggestive of pemphigus foliaceus, although usually have multiple-digit involvement).
2. *Bacterial culture and sensitivity:* Perform if bacteria present on cytology. Since deep infections of the digit and/or osteomyelitis of P3 frequently warrant prolonged periods of antibiotic therapy (16-30 weeks or longer), specific antibiotic selection based on antimicrobial susceptibility testing is preferred to empirical therapy.
3. *Radiograph:* Evaluate radiograph carefully for evidence of bone lysis of P3. Osteomyelitis (bacterial or fungal) or neoplasia may cause lysis. Presence of lysis is indication for amputation of P3 and submission for histopathologic diagnosis.
4. *Biopsy:* Histopathologic diagnosis is indicated for any condition involving bone lysis of P3, suspected neoplasia, or chronic disease that has not responded to appropriate therapy for presumptive diagnosis.

15. Bacterial infections are a common complication of claw or claw fold disease. List the most common causes for bacterial infection of a single digit. What if multiple digits on multiple paws are involved?

Single digit: trauma or neoplasia is the most common primary disease

Multiple digits: systemic immune suppression, such as hypothyroidism, hyperadrenocorticism, feline leukemia virus, or feline immunodeficiency virus; multifocal neoplasia; concurrent immune-mediated disease, such as pemphigus foliaceus; or atopy.

Note: clipping claws too close may embed debris or contaminated material, resulting in a single- or multiple-digit bacterial infection.

16. Purulent exudate from the claw fold may be an indication of infection, but not always. What disease is the most common cause of purulent discharge from multiple claw folds in a cat?

Pemphigus foliaceus (PF)

The index of suspicion for PF should be increased with involvement of the paw pad or concurrent lesions on haired skin; however, purulent claw fold discharge may be the only sign of active disease. Cytologic finding of acantholytic keratinocytes with large numbers of non-degenerate neutrophils supports a diagnosis of PF.

17. What endocrine disorder is associated with symmetric hypertrophy of claws in cats?
Hyperthyroidism

18. Describe your best therapeutic plan for chronic bacterial infection of a single digit.
1. Avulsion of the claw under general anesthesia should be performed if separation is present. Care should be taken to minimize disruption of the underlying corium; injury to the corium may result in abnormal claw shape and integrity.
2. Systemic antibiotic therapy based on culture and susceptibility testing. Selection of an antibiotic with good penetration to bone tissue is ideal, due to the possibility of osteomyelitis of P3.
3. Astringent soaks: Domeboro solution
4. Antiseptic soaks: Chlorhexidine solution
5. Onychectomy (by amputation of P3) is warranted in cases of chronic recurrence, chronic pain, or failure to respond to therapy.

19. After trauma the most common cause of single digit claw disease is neoplasia. Is neoplasia of the digit more likely to be benign or malignant?
Neoplasia of the digits is more likely to be malignant. In a review of 124 cases of digital masses in dogs, 61% were malignant neoplasms, 20% were benign neoplasms, and 19% were pyogranulomatous inflammation. Therefore, of neoplastic lesions of the digit, approximately 75% are malignant.

20. List the three most common types of malignant neoplasia in the claw bed of dogs.
1. Squamous cell carcinoma: 38% of cases
2. Melanoma: 32% of cases
3. Mast cell tumor: 10% of cases

Other, less common tumors reported include nerve sheath tumor, myxosarcoma, atrichial sweat gland adenocarcinoma, fibrosarcoma, lymphosarcoma, leiomyosarcoma, and osteosarcoma.

21. Compare and contrast the clinical features of squamous cell carcinoma of the claw with melanoma in the dog. Include breed predisposition, location of primary tumor, radiographic findings, rates of metastasis, and survival.
See Table 45-1.

Table 45-1 ***Clinical Features of Squamous Cell Carcinoma vs. Melanoma***

FEATURE	SQUAMOUS CELL CARCINOMA	MELANOMA
Breed predisposition	Black Poodles Black Labrador Retrievers	None reported
Location	Two thirds ungual crest One third other location	Not reported
Radiographic findings	Bone lysis of P3 is common	Bone lysis of P3 is uncommon
Metastasis	Uncommon	Common

22. Cats may develop metastatic adenocarcinoma in multiple digits simultaneously. What is the tissue of origin for this particular syndrome? What histopathologic feature may be present that helps the pathologist determine this?
- Pulmonary
- Presence of cilia on neoplastic cells

23. In humans, onychomycosis due to dermatophyte invasion of the keratin claw is one of the most common causes of chronic claw disease (both single or multiple digits). How common is onychomycosis in dogs? In cats? What organisms have been reported?

Onychomycosis is an uncommon cause of claw or claw fold disease

- Dogs: 7 of 196 cases (3.5%); only three cases caused by dermatophyte
- Cats: 3 of 65 cases (4.6%); only one case caused by dermatophyte

Organisms reported: *Trichophyton mentagrophytes* (dog), *Microsporum canis* (cat), *Candida albicans, Malassezia pachydermatis, Sporothrix schenckii, Cryptococcus neoformans, Blastomyces dermatitidis, Coccidioides immitis*

Malassezia species may colonize the claw fold secondary to underlying hypersensitivity disorders, such as atopy or adverse reactions to food; or immune-compromising disorders, such as hypothyroidism. Overgrowth in this area may be characterized by erythema, swelling, pruritus, and dry, yellow-brown exudate. The inflammatory response to the *Malassezia* organisms can vary significantly in the degree of erythema, swelling, and pruritus. Frequently affected dogs exhibit brownish discoloration, or staining, of the keratin claw (Figure 45-4).

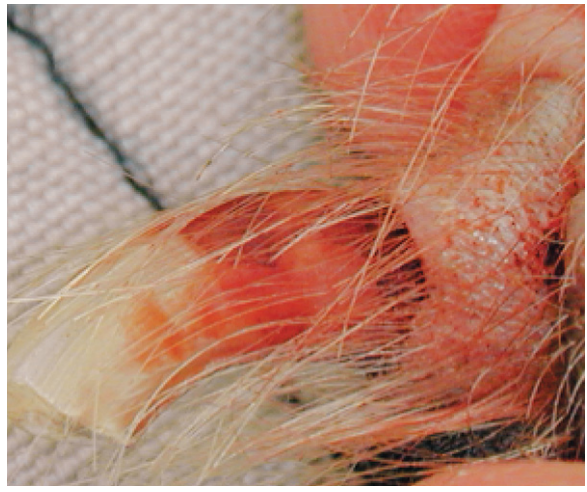

Figure 45-4 Onychomycosis associated with colonization of the claw bed by *Malassezia pachydermatis*. Note the brownish discoloration of the keratin claw. (Courtesy Dr. Adam Patterson.)

24. List 18 differential diagnoses for onychomadesis, onychodystrophy, or onychorrhexis of multiple digits, with or without claw fold involvement.

1. Symmetric lupoid onychodystrophy
2. Systemic lupus erythematosus
3. Pemphigus foliaceus
4. Pemphigus vulgaris
5. Cold agglutinin disease
6. Vasculitis
7. Bullous pemphigoid
8. Epidermolysis bullosa
9. Drug eruption
10. Metastatic pulmonary adenocarcinoma
11. Multifocal squamous cell carcinoma

12. Metabolic epidermal necrosis (necrolytic migratory erythema, superficial necrolytic dermatitis, hepatocutaneous syndrome)
13. Thallotoxicosis
14. Ergotism
15. Severe nutritional deficiency
16. Disseminated intravascular coagulation
17. Zinc-responsive dermatosis
18. Leishmaniasis

25. Describe the clinical features of symmetric lupoid onychodystrophy, include reported age, breed, or sex predispositions; progression of clinical signs; and any potential causes implicated in the pathogenesis of this condition.

Symmetric lupoid onychodystrophy is a condition characterized by spontaneous onychomadesis of most, if not all claws, followed by regrowth of abnormal, misshapen, brittle claws (onychodystrophy). In published case series most animals were 3-8 years of age, although animals as young as 6 months and as old as 10 years have been reported. Most commonly reported breeds are German Shepherds, Rottweilers, Standard or Giant Schnauzers, but other breeds may be affected. Of these breeds, German Shepherds are most consistently represented above reference hospital populations. No gender predilection is reported.

Typical clinical signs of early disease are brownish-red to bluish discoloration of a single claw, attributed to subungual hemorrhage. Onycholysis, separation of claw from corium, and complete onychomadesis follow (Figure 45-5). Swelling of the claw fold, pain, or lameness is variable. After the initial claw sloughs, the condition progresses rapidly, resulting in loss of all claws in 2-9 weeks. A brownish, serosanguineous exudate is reported in some cases. Secondary bacterial infections, characterized by malodorous, purulent discharge, may also occur. In some cases the claw has separated from the corium but remains attached under the claw fold. This situation can be painful for the patient. In some cases therapeutic avulsion of the claws under

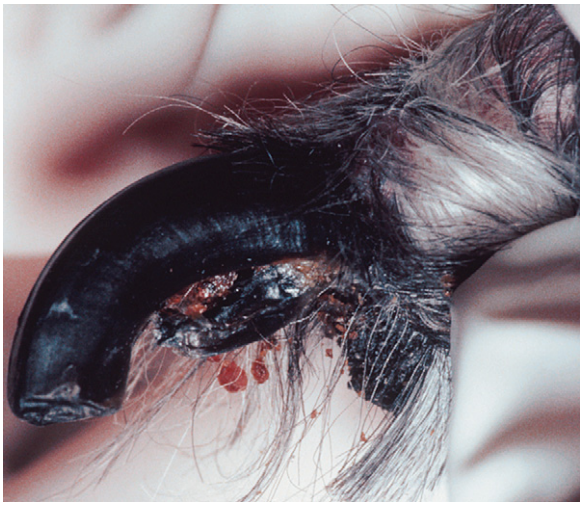

Figure 45-5 Symmetric lupoid onychomadesis/onychodystrophy in a Miniature Schnauzer. Note the brown, serous crust at the point of separation of the keratin claw plate from the underlying corium.

Figure 45-6 Therapeutic avulsion of the claw shown in Figure 45-5.

general anesthesia is necessary to relieve discomfort and remove the dead keratin claw from the claw bed to permit regrowth (Figure 45-6).

Following onychomadesis, claws may grow abnormally; typically affected claws are misshapen, brittle, and dry (see Figure 45-3). Chronic pain may be a characteristic of the abnormal claws in some dogs. Patients are typically free of concurrent dermatologic or systemic disease.

Most cases are idiopathic; however, in a case series four of 24 dogs demonstrated partial or complete remission during elimination diet trial. Two of the four dogs were challenge-fed with the original diet and relapsed; the other two owners were unwilling to perform provocative challenge. This finding suggests adverse food reaction as a potential trigger.

26. What are the histopathologic features of symmetric lupoid onychodystrophy?

- Lymphocytic-plasmacytic, lichenoid dermal infiltrate. Infiltrate is typically cell-rich; however, cell-poor specimens may be obtained from affected individuals.
- Hydropic degeneration of basal keratinocytes
- Individual cell apoptosis in the basal cell layer
- Pigmentary incontinence
- Note: vacuolar changes and subepidermal clefting also may be seen in normal claws.

27. Describe five therapeutic options for treatment of symmetric lupoid onychodystrophy.

1. Essential fatty acid therapy: Dosage is typically based on eicosapentaenoic acid (EPA) content. EPA given orally at approximately 20 mg/kg per day is a commonly used dosage for immune-mediated and inflammatory dermatoses.
2. Tetracycline/niacinamide: Dogs <10 kg receive 250 mg tetracycline and 250 mg niacinamide orally three times daily. Dogs >10 kg receive 500 mg tetracycline and 500 mg niacinamide orally three times daily. If remission is achieved, frequency of medication can be tapered to twice daily then once daily. Anorexia, vomiting, and diarrhea are the most common adverse reactions. Tetracycline/niacinamide should be avoided in dogs with seizure-disorders (unpublished observation).

3. Pentoxifylline: 10 mg/kg orally every 8 to 24 hours. Pentoxifylline is a methylxanthine derivative with immunomodulatory activity: decreased cytokine production and decreased responsiveness of leukocytes. Additionally, pentoxifylline increases deformability of red blood cells. The principal applications of pentoxifylline are in management of vasculitis, peripheral vascular disease, and mild immune-mediated disorders, such as discoid lupus erythematosus and symmetric lupoid onychodystrophy.
4. Prednisone: immune-suppressive doses (2-4 mg/kg per day) then tapered.
5. Onychectomy: This therapy is reserved for cases that have failed medical management and which are characterized by chronic pain.

28. What are the indications for biopsy for claw disease? What tissues must be included for accurate diagnosis? Which digit should be selected in the dog?

Biopsy should be considered for any cases with suspected neoplasia, radiographic evidence of bone lysis, suspected immune-mediated disease, or cases that have failed to respond to appropriate empirical therapy based on presumptive diagnosis.

Biopsy specimens should include the claw fold, claw plate, corium, ungual crest, and all of P3. This specimen ensures adequate evaluation of claw matrix area for evidence of immune-mediated disease, concurrent infection, or neoplastic tissue. Amputation at the articulation of P2 and P3 is the most commonly employed technique. An onychobiopsy without onychectomy technique is described using an 8-mm punch biopsy directed along the lateral aspect of the claw, with the axis of the punch parallel to the axis of the emerging claw. This technique also includes a portion of claw fold, claw plate, corium, ungual crest, and P3.

Biopsy of the most recently affected digit is ideal. Dewclaws are easiest to remove in their entirety. If a suitable dewclaw is not available, the non–weight-bearing second and fifth digits are preferred to the weight-bearing third and fourth digits.

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46. PERIANAL FISTULA DISEASE

Steven L. *Marks*, BVS*c*, MS, MRCVS, DACVIM

1. What is a perianal fistula?

The definition of a fistula is an abnormal passage between two internal organs or leading from an internal organ to the body surface. Perianal fistulas are chronic inflammatory lesions involving the perianal, anal, and perirectal tissues (Figures 46-1 and 46-2).

2. List the historical findings with perianal fistula disease.

The clinical history of dogs with this disease often includes tenesmus, dyschezia, constipation, increased frequency of defecation, perianal licking, self-mutilation, pain in the perianal region, and scooting. Systemic clinical signs such as lethargy, anorexia, and weight loss may also be reported.

3. Describe physical examination findings associated with perianal fistula disease.

The most common physical examination findings include pain associated with manipulation of the perianal or perineal region, and painful ulcerative lesions around the perianal region. These lesions may vary from small superficial lesions to large penetrating lesions. The area is often malodorous and may involve the anal sacs. Rectal examination may indicate thickening and fibrosis of the perirectal tissue.

4. What differential diagnoses should be considered with these clinical signs?

Differential diagnoses for the aforementioned clinical signs include anal squamous cell carcinoma, perianal adenoma, anal sac adenocarcinoma, anal sac abscess, rectal and perianal fistulas.

5. How is the definitive diagnosis made?

The definitive diagnosis is made based on history, physical examination, and histopathology. If the history and physical examination are consistent with perianal fistula disease, then response

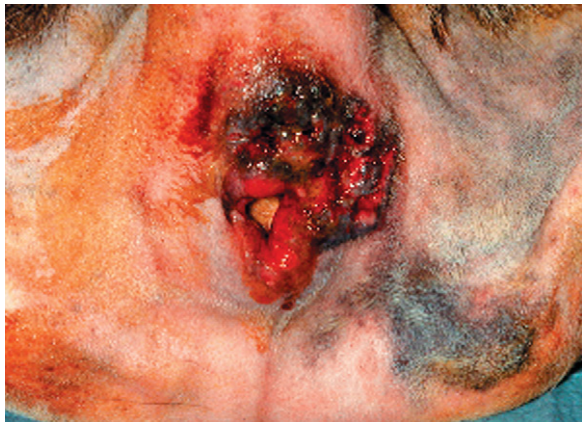

Figure 46-1 Multiple perianal fistulas in a German Shepherd Dog. (Courtesy Dr. Sandra Manfra.)

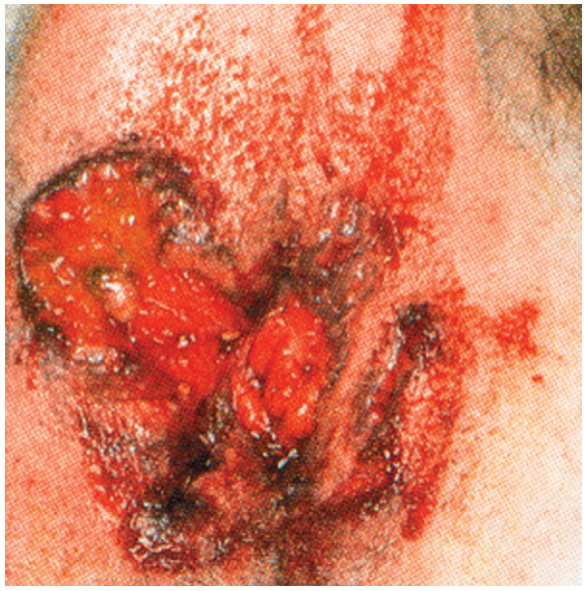

Figure 46-2 Extensively ulcerated perianal fistula disease in a German Shepherd Dog.

to therapy may be supportive of the diagnosis. Histopathologic findings may include hidradenitis, necrotizing pyogranulomatous inflammation of the skin and hair follicles, cellulitis, dilated and inflamed lymphatics, and fibrosis.

6. What is the minimum database when evaluating a patient for perianal fistula disease?

The minimum diagnostic database is always at the discretion of the clinician but in most patients, a complete blood count, serum biochemical analysis, and urinalysis will be beneficial to rule out concurrent disease. Colonoscopy with biopsy will help exclude concurrent colitis.

7. Is this disease reported in the cat?

Idiopathic perianal fistula disease has not been reported in the cat. Other differential diagnoses such as anal sac abscess and neoplasia should be considered.

8. Is there a breed predilection for this disease?

The German Shepherd appears to be over-represented in most clinical reports. Other breeds that have been reported with this disease include the Irish Setter, Labrador Retriever, Old English Sheepdog, and Border Collie as well as mixed-breed dogs.

9. Is there a gender or age predilection for this disease?

There does not appear to be a gender predilection for this disease, although several reports have suggested it may occur more in males than females and more in intact animals. The reported mean age of dogs affected is 5-7 years, although there is a wide age range.

10. Is there a disease corollary in human medicine?

A similar disease that exists in humans is granulomatous enteritis or Crohn's disease. This disease may lead to fistula formation.

11. What is the etiology of perianal fistula disease?

There is currently no known underlying etiology that has been identified for this disease. The current hypothesis is that it is a multifactorial immune-mediated disease process. There is some information to suggest that the German Shepherd is predisposed to this disease due to anatomic variations including a high density of apocrine sweat glands in the cutaneous region surrounding the anal canal. German Shepherds also seem to be predisposed to inflammatory bowel disease and bacterial overgrowth, which may have an immune-mediated component. It has also been suggested that dogs with a broad-based or low carriage tail conformation may be predisposed to this disorder.

12. List the strategies that have been used to medically manage perianal fistulas.

- Cyclosporine and ketoconazole
- Prednisone
- Antimicrobial agents
- Dietary management
- Metronidazole
- Stool softener
- Azathioprine
- Topical tacrolimus

13. List the surgical treatments that have been described for treatment of perianal fistula disease.

- Surgical excision
- CO_2 or yttrium-argon-garnet laser resection
- Cryotherapy
- Chemical cautery
- Tail amputation

14. What possible complications can occur following surgical therapy for perianal fistulas?

- Fecal incontinence
- Anal stenosis
- Flatulence
- Diarrhea
- Constipation

15. What is the current treatment of choice for perianal fistula disease?

For idiopathic cases (having ruled out underlying food allergies and colitis), the suggested therapy at this time is cyclosporine plus ketoconazole. Surgical therapy should only be considered if medical management fails. Cyclosporine is used at a dosage of 2-5 mg/kg orally every 12 hours to achieve a serum trough concentration of 400-600 ng/mL. Ketoconazole is used at a dosage of 12-15 mg/kg orally every 24 hours.

16. What is the mechanism of action of cyclosporine?

Cyclosporine is an immunosuppressive agent that inhibits the production and blunts the response to interleukin-2 (IL-2), IL-6, and gamma interferon by CD4 T lymphocytes.

17. List the side effects and possible complications of cyclosporine therapy.

The side effects of cyclosporine therapy include primarily gastrointestinal signs such as anorexia, vomiting, and diarrhea. Additional side effects occasionally reported in dogs include papillomatosis, gingival hyperplasia, bacteriuria, nephropathy, bacterial skin infections, hirsutism, tremors, bone marrow suppression, and a lymphoplasmacytoid dermatitis.

18. What is the mechanism of action of ketoconazole?

Ketoconazole is an imidazole antimycotic agent that has been used primarily as an antifungal agent in veterinary medicine. It has also been used as an alternative therapy for canine and feline hyperadrenocorticism (Cushing's syndrome) due to its effect on steroid biosynthesis. In combination with cyclosporine, ketoconazole has been used for its inhibitory effect of cytochrome P-450. This allows the effect of cyclosporine to be prolonged and for lower dosages to be used to reach therapeutic concentrations.

19. What are the possible side effects of ketoconazole administration?

The side effects of ketoconazole include anorexia, vomiting, and diarrhea, but these are usually not seen at the dosages recommended for adjunctive use with cyclosporine in treating perianal fistula disease. Hepatotoxicity including cholangiohepatitis and increased liver enzyme activity has been reported as has hepatic necrosis. These phenomena may be dose-related or idiosyncratic.

20. How is cyclosporine therapy monitored?

Cyclosporine therapy is best monitored by following serum concentrations. Although there is some difference of opinion, trough serum concentrations of 400-600 ng/mL seem ideal.

21. Is there an alternative to oral cyclosporine?

Yes, 0.1% tacrolimus ointment (Protopic) is a calicineurin inhibitor that suppresses T-cell activation and cytokine production. Its mechanism of action is similar to that of cyclosporine. Its small molecular weight facilitates penetration into the skin, making it effective for treatment of localized cutaneous lesions.

22. What is the prognosis for perianal fistula disease?

The overall prognosis for perianal fistula disease is guarded. The prognosis improves with response to therapy; however, remission may only be temporary. Financial investment for both medical and surgical treatment of this disease is high.

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47. BLEPHARITIS

Ralph E. H*amor,* DVM, MS, DACVO

1. What is blepharitis?

Blepharitis is defined as inflammation of the eyelid. The inflammation can be focal or diffuse and can involve one, multiple, or all four of the eyelids. Blepharitis can be the result of a primary skin disease or can be secondary to another ocular or systemic disease process. Eyelid inflammation and irritation can also be self-induced if the patient is pruritic. Depending on the

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disease process, the original disease process can be masked or complicated by secondary infection, self-trauma, alopecia, erosion and/or exudates. In chronic cases, the original disease process can be further complicated by secondary cicatricial entropion or ectropion that may lead to ocular disease. Always remember that the eyelids are part of the skin. Therefore, the clinician needs to search for causes of generalized dermatitis and treat as he or she would for the generalized disease process. The primary exception is to be certain that any topical or systemic therapy used is not detrimental to the health of the globe.

2. What are the basic structures of the normal eyelid?

The outer surface is covered with haired skin and the inner surface is covered with conjunctiva. Numerous muscles are present and serve to provide appropriate eyelid movement. Cilia are present in the upper and/or lower eyelid depending on the species. Glands of Moll and Zeis surround the follicle of the cilia or eyelash. A tarsal plate runs parallel to the edge of the eyelid margin, providing structural support to the eyelid margin and the meibomian glands as well as attachment for some of the eyelid musculature.

3. Why are normal eyelid anatomy, physiology, and function so important?

The eyelids, especially the eyelid margin, serve primarily to provide appropriate blinking. Blinking physically protects the globe, spreads the tear film, and provides oxygen as well as other metabolic needs to the cornea.

4. Where do different layers of the tear film come from?

The eyelid provides the inner (from the goblet cells of the conjunctiva) and outer (from the meibomian glands) layers of the tear film. The inner layer aids in the attachment of the tear film to the cornea and the spreading of the tear film over the cornea. The outer layer helps to prevent evaporation of the middle or serous layer of the tear film. The middle layer of the tear film is produced by the orbital lacrimal gland (65-70%) and the gland of the third eyelid (30-35%).

5. Name some common groups of diseases that can cause blepharitis.

- Traumatic
- Bacterial
- Autoimmune
- Allergic
- Mycotic
- Neoplastic
- Parasitic
- Chalazion/hordeolum

6. What is a stye or hordeolum?

A stye is strictly defined as an infection, typically staphylococcal, of the glands of Moll or Zeis. The glands of Moll and Zeis are associated with the hair follicle of the eyelashes. An external hordeolum (stye) is an infection of the glands of Moll or Zeis and an internal hordeolum is an infection of the meibomian glands.

7. How do you treat a stye?

A stye can be treated with supportive therapy including hot compresses and topical antibiotic therapy. If that is unsuccessful, the stye can be lanced from the conjunctival surface of the eyelid. In advanced cases, systemic antibiotic therapy may be indicated.

8. How is a hordeolum different from a chalazion?

A chalazion is a granulomatous inflammation of the meibomian gland, also typically staphylococcal in origin. If the infection breaks out of the gland into the surrounding subcutaneous tissue, it causes a significant granulomatous inflammatory reaction. A chalazion often needs to be treated with surgical removal followed by topical and systemic antibiotic therapy.

Figure 47-1 This photograph shows the proper placement of a muscle hook in the nasal canthus to "unzip" the eyelid margin in a puppy with neonatal ophthalmia.

9. What is ankyloblepharon or neonatal ophthalmia?

Neonatal ophthalmia occurs in young puppies and kittens before the opening of their eyelids. The eyelids are often profoundly swollen and there may be a fair amount of muco-purulent discharge draining from the medial canthus (Figure 47-1). The cause of the syndrome is inoculation of the eyelid with bacteria, or viruses, from the dam's genital tract.

10. How do you treat neonatal ophthalmia and why is it important?

This syndrome needs to be treated early and aggressively because the trapped infection can cause significant damage to the cornea and may even result in blindness secondary to corneal perforation. The best treatment is to manually open the eyelid margins and treat the infection supportively with topical antibiotics (or antiviral agents if a virus is the cause of the infection). The medial canthus of the eyelid margin is not completely sealed in neonates and this is where to begin opening the eyelids. Sometimes the eyelid margins can be opened manually with your fingers. Alternatively, the clinician can use a small blunt instrument like a muscle hook and insert it between the eyelids at the medial canthus and "unzip" the eyelid margin from the medial to lateral canthus.

11. Is trauma a common cause of blepharitis?

Self-trauma can be quite common especially if the patient is pruritic. Significant pruritus and self-trauma may even mask the inciting cause of the blepharitis. An Elizabethan collar can be quite beneficial to keep the patient from rubbing its eyelids and help to determine if the blepharitis is primary or secondary. Primary traumatic blepharitis does occur and usually presents as an acute problem.

12. How do you treat traumatic blepharitis?

Trauma can cause eyelid wounds. Abrasions and superficial wounds can be treated initially by cleansing. Topical triple antibiotic ophthalmic ointment can be used on eyelid wounds, if needed. Deep wounds may also require systemic antibiotics. Full-thickness eyelid wounds usually require surgical as well as medical therapy. Full-thickness wounds should be closed in two layers: absorbable to close the conjunctival layer and nonabsorbable to close the skin. Make sure that absorbable sutures in the conjunctival layer are "buried" within the skin to keep the sutures from

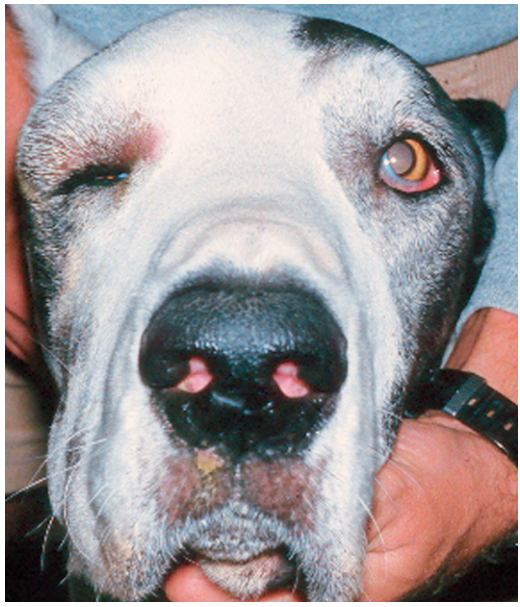

Figure 47-2 This dog has significant blepharoedema secondary to an insect bite.

rubbing on the cornea. A figure-eight or cruciate suture is recommended at the eyelid margin to achieve appropriate closure of the eyelid margin without any knots touching the cornea.

13. Can allergies cause blepharitis?

Yes. Allergic blepharitis can manifest in different ways depending on the cause of the allergic reaction. Insect bites often demonstrate relatively mild signs of erythema and edema but, in more severe cases, can also manifest with significant blepharoedema (Figure 47-2). These cases usually resolve with supportive care (antihistamines and/or corticosteroids). Inhalant, food, or contact allergic blepharitis may also cause significant pruritus of the head and face as well as secondary changes associated with self-trauma. With inhalant and food allergies, the patient usually demonstrates other clinical signs of the allergy along with their ocular signs (i.e., pruritus of the feet, ears, axillae, and inguinal areas). If possible, it is always best to identify and treat the specific allergen to which the patient is reacting. Topical steroids can reduce ocular clinical signs but can also interfere with appropriate diagnosis of the responsible allergen.

14. What types of pemphigus usually involve the eyelids?

While all members of the pemphigus group of vesiculobullous epidermal diseases can involve the eyelid tissue, the facial lesions of pemphigus foliaceus and erythematosus most commonly involve the eyelids. Lesions typically include alopecia, exfoliative crusting, pustular dermatitis, and erosion of the eyelid margin. The disease results from autoantibody production against the intercellular matrix of the epidermis. Diagnosis is by skin biopsy, and treatment for the eyelids is as for the rest of the skin.

15. What are common causes of bacterial blepharitis?

Staphylococcus and *Streptococcus* species are most commonly involved in bacterial blepharitis with *Staphylococcus* being the most common. Acute cases demonstrate erythema, pustules and crusting while more chronic cases may also have ulceration, fibrosis, and alopecia. The

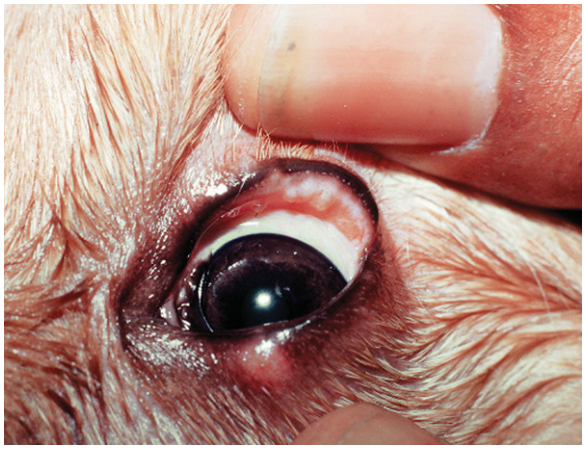

Figure 47-3 The center of the lower lid in this dog has an infected meibomian gland secondary to staphylococcal blepharitis. The upper eyelid is everted to demonstrate what the same lesion looks like from the conjunctival surface.

meibomian glands may be infected and are best visualized by everting the lid margin (Figure 47-3). Chemosis and purulent conjunctivitis can also be seen. As with other areas of the skin, diagnosis is by culture and cytology of a pustule.

Therapy is based on culture and involves systemic antibiotic therapy. Topical antibiotics and antibiotic/corticosteroid combinations may also be indicated if chemosis and conjunctivitis are present but usually are not sufficient on their own. Staphage lysate, staphylococcal bacterins, and/or systemic corticosteroids may also be used to treat advanced, chronic, or nonresponsive cases of staphylococcal blepharitis.

16. What is juvenile pyoderma or juvenile cellulitis?

This syndrome is usually seen in puppies or very young dogs and manifests as generalized pustular dermatitis of the eyelids, face, and muzzle (Figure 47-4). Advanced cases may even

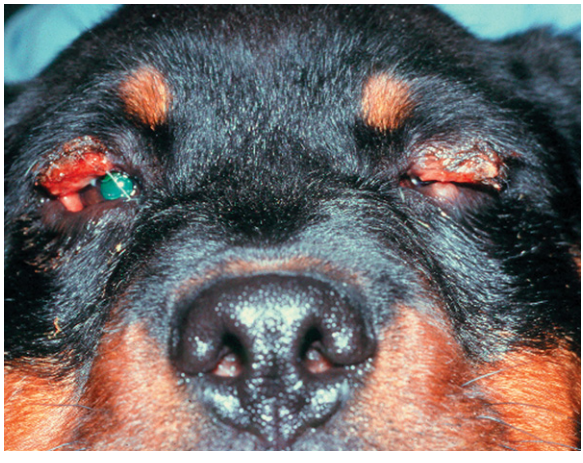

Figure 47-4 This puppy has severe pustular dermatitis of both upper eyelids secondary to juvenile pyoderma.

develop fistulous tracts. Regional lymph nodes are usually enlarged and the patient may be lethargic and febrile. Diagnosis is by clinical signs, cytology, and culture. Therapy involves systemic antibiotic and systemic corticosteroid therapy along with topical therapy. As with staphylococcal blepharitis, topical therapy alone is insufficient. Systemic antibiotics should be continued until all lesions are healed and systemic corticosteroids continued for 1-2 weeks after that.

17. Can a fungus cause blepharitis?

Microsporum spp. *and Trichophyton* spp. are the most common causes of mycotic blepharitis. Affected patients usually demonstrate alopecia, crusting, and scaling. Lesions can be localized or generalized. Diagnosis is usually by cytology and culture. Treatment is as for other areas of the skin, making sure to keep irritating topical antifungal therapeutics out of the eye.

18. Which parasites commonly cause blepharitis?

Many different parasites can cause blepharitis as part of a generalized skin infection. *Sarcoptes scabiei* var. *canis* and *felis* can affect the eyelids as part of a generalized skin disease. Clinical signs include intense pruritus with alopecia, erythema, scaling, and crusting. Self-trauma often causes secondary ulceration. Diagnosis is as with other skin areas: skin scraping and identification of the mite. Systemic therapy is generally preferred for the eyelids as it keeps topical therapies from irritating the eye.

Demodecosis can affect the eyelids as part of a localized or generalized syndrome. In young dogs, the lesions are often restricted to the face (Figure 47-5). Clinical signs include patches of alopecia with mild scaling and erythema. Diagnosis is by deep skin scraping and identification of the mite. Localized infections can be self-limiting especially in very young animals. Again, be sure that any topical therapy will not irritate the eye. Generalized infections usually occur in immunosuppressed patients or patients with a T-cell deficiency. Therapy for the eyelids is as for generalized skin infestation, with systemic therapy (e.g., ivermectin or milbemycin) usually providing the best results.

19. Is eyelid neoplasia common in dogs?

Eyelid neoplasia is not uncommon especially in older dogs. The most common type of

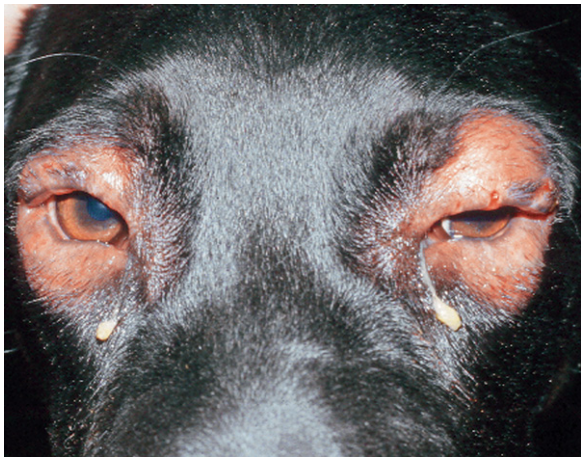

Figure 47-5 This young dog has periocular demodecosis involving both eyes.

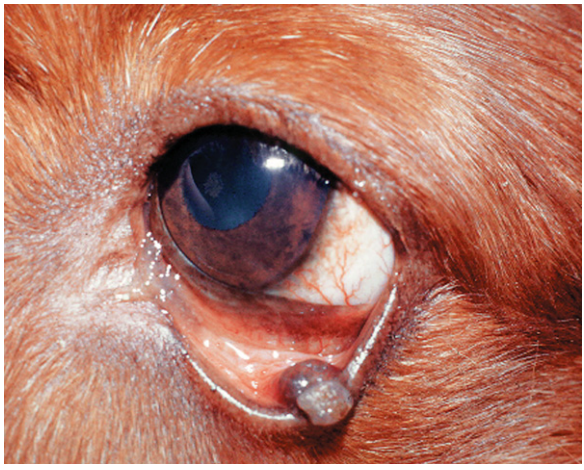

Figure 47-6 The lower eyelid has been everted to demonstrate how a meibomian gland adenoma grows from the meibomian gland.

eyelid neoplasm is a meibomian gland adenoma or adenocarcinoma (Figure 47-6). They usually present as small tan to gray growths protruding from the eyelid margin. If the eyelid margin is everted, the growth can usually be seen coming directly from the meibomian gland. Occasionally, the mass can be large enough to cause mild epiphora and conjunctival irritation. Other common eyelid growths in dogs include papillomas, melanomas, and histiocytomas. In dogs, all of these masses typically demonstrate benign behavior.

20. Do malignant eyelid tumors also occur in dogs?

Malignant eyelid tumors do occur in dogs and most commonly include adenocarcinomas, squamous cell carcinomas, mast cell tumors, and basal cell carcinomas. Depending on the type of tumor and the amount of eyelid that is affected, therapy can include cryoablation, laser ablation, surgery, or radiation therapy. Tumors involving 25% or less of the eyelid margin can often be removed by a wedge resection without damaging eyelid function. Larger tumors usually require more advanced blepharoplastic procedures such as an H-plasty or transpositional flap to allow for adequate removal of the tumor with reasonable eyelid function after surgery.

21. Do cats develop different eyelid neoplasms than dogs?

In cats, eyelid neoplasia is much less common than in dogs and the tumors are much more likely to be malignant (about 75%). One of the most common eyelid neoplasms in cats is squamous cell carcinoma (Figure 47-7). It usually presents as a pink to white proliferative or ulcerated mass. The patient may also demonstrate epiphora and conjunctivitis depending on the size and severity of the mass. In some cases, the tumor can appear to be a chronic, non-healing wound. Diagnosis is by cytology, aspirate, or biopsy, with a biopsy usually providing the most accurate results. Other eyelid neoplasias in cats include basal cell carcinoma, melanoma, mast cell tumor, and fibroma/fibrosarcoma.

22. How do you treat eyelid neoplasia?

Treatment depends on the type of neoplasia. Benign lesions, like meibomian gland adenomas in dogs, can be treated with removal and adjunctive cryotherapy. This can usually be performed under local anesthesia and allows for effective therapy in an older patient. These growths can also

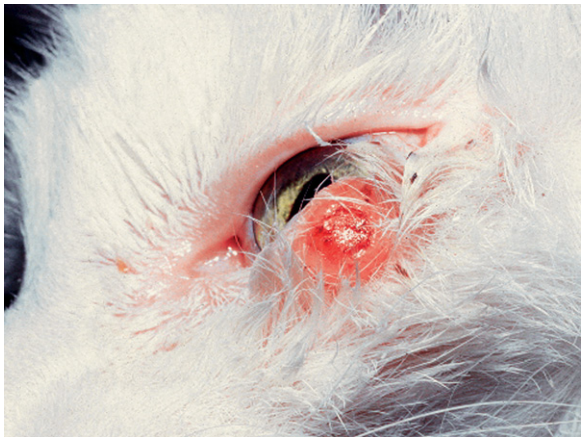

Figure 47-7 This cat has a large squamous cell carcinoma of the lower eyelid.

be removed with a wedge resection of the eyelid margin but this requires general anesthesia and may result in a defect in the eyelid margin.

Therapy for more advanced or malignant neoplasms, like squamous cell carcinoma, must be more aggressive. If possible, surgical excision with 3-cm margins is best. Due to the proximity of the globe, this is usually impossible without also removing the globe and potentially part of the orbit. Therefore, early diagnosis is best if vision is going to be saved. Cryotherapy, laser ablation, and radiation therapy can also be used in a patient with smaller lesions. As with any malignant neoplasm, a full workup including bloodwork, thoracic radiographs, and abdominal ultrasonography is necessary to search for any signs of metastasis.

23. What oral antibiotic has been associated with keratoconjunctivitis sicca (KCS) in dogs?

Oral sulfa drugs have been associated with the development of acute KCS in dogs. The reaction is idiosyncratic and not associated with the overdosage of or extended use of sulfa drugs. If possible, I would avoid the use of oral sulfa drugs especially in dog breeds that are prone to KCS or dogs with low tear production. If sulfa drugs are required, a Schirmer tear test (STT) should be performed before initiating therapy and performed at least weekly during therapy. If the STT is low, another drug should be chosen. If the STT decreases dramatically during therapy (<10 mm/min), the drug should be discontinued and tear replacement therapy begun. If the glandular destruction is not discovered early, then permanent KCS is likely.

24. How do you diagnose uveodermatologic syndrome?

Uveodermatologic syndrome can usually be diagnosed by signalment and clinical signs. Affected dogs are often Arctic Circle breeds but this syndrome can be seen in any dog breed. Affected dogs usually have depigmentation, ulceration, and alopecia of mucocutaneous junctions including eyelid margins, lips, footpads, and scrotum (Figure 47-8). Many patients also exhibit severe uveitis and, potentially, secondary glaucoma. The diagnosis can be confirmed by a skin biopsy that demonstrates diffuse lichenoid interface dermatitis. Therapy includes immunosuppressive drugs including corticosteroids and azathioprine. Therapy often has to be chronic to avoid a relapse.

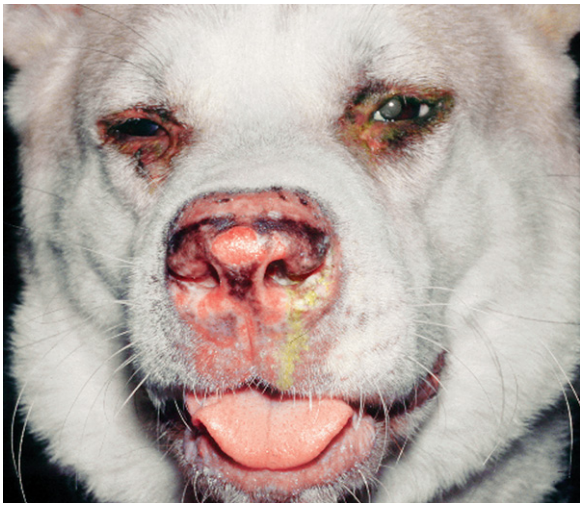

Figure 47-8 Notice the depigmentation and ulceration of the eyelid margins, nose, and mucocutaneous junction of this Akita with uveodermatologic syndrome.

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48. DISORDERS OF PIGMENTATION

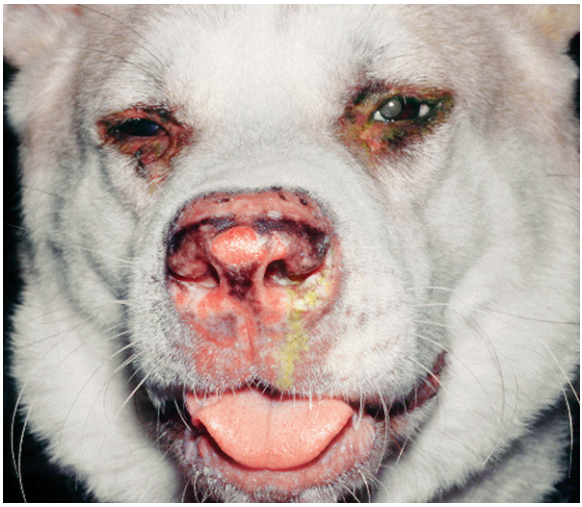
Laura B. Stokking, PhD, DVM
Karen L. Campbell, DVM, MS, DACVIM, DACVD

1. What factors control skin pigmentation?

Ultraviolet and visible light can be absorbed by skin components besides melanin, hemoglobin, or carotenoids. These include keratin, elastin, collagen, lipids, urocanic acids, and nucleic acids.

The color of the skin reflects the combination of multiple pigments: endogenous eumelanin (black, brown) or pheomelanin (yellow, red), oxygenated hemoglobin present in capillaries (red), reduced hemoglobin in venules (blue), exogenous carotenoids (yellows), oxygenated hemoglobin in capillaries, and reduced hemoglobin in venules (blue).

Melanin, produced in melanocytes, makes the most significant contribution to skin color. The color observed in the skin depends not only on the type of pigment produced (eumelanin vs.



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Melanin, produced in melanocytes, makes the most significant contribution to skin color. The color observed in the skin depends not only on the type of pigment produced (eumelanin vs.

pheomelanin), but also on the amount of melanin transferred to keratinocytes or contained in macrophages (melanophages); the number, size, type, and distribution patterns of melanosomes within epidermal layers; and the thickness of various layers of the epidermis as well as the dermis.

2. What is the origin of cutaneous melanocytes?

Most melanocytes originate in the embryologic neural crest. Cells migrate from this site to the uveal tract of the eye (iris, choroid), the stria vascularis of the ear (cochlear and vestibular labyrinth), the leptomeninges of the central nervous system, the hair matrix, mucous membranes, and the dermal-epidermal junction of the skin.

3. What are the differences between eumelanin and pheomelanin?

Eumelanin is produced by the oxidative polymerization of 5,6-dihydroxyindole-2-carboxylic acid, a derivative of tyrosine. It is a solvent-insoluble, brown to black, semiquinone pigment found in ellipsoidal melanosomes. Pheomelanin is an alkali-soluble, sulfur-containing, yellow to red pigment found in spherical melanosomes. This pigment is also derived from tyrosine, but an intermediate synthesis product, dopaquinone, combines with a sulfur-containing amino acid (cysteine or glutathione) to make cysteinyl dopa, which is then oxidatively polymerized to make pheomelanin. Mixtures of eumelanin and pheomelanin are common.

4. Where does pigment synthesis take place? How does pigment get into keratinocytes?

Pigment synthesis occurs within melanosomes. Melanosomes are cytoplasmic organelles formed during melanocytosis. Mature melanosomes migrate to the dendritic processes of melanocytes, where they are phagocytosed by keratinocytes; this process is termed *cytocrinia*.

5. What is an epidermal-melanin unit?

Each epidermal melanocyte secretes melanosomes into a limited number of keratinocytes, forming an epidermal melanin unit. In humans, one melanocyte supplies melanosomes to 36 melanocytes, whereas one melanocyte transfers melanosomes to 10 to 20 keratinocytes in dogs.

6. How does constitutive pigmentation differ from facultative pigmentation?

The amount and to a certain extent, the type, of melanin pigmentation synthesized in accordance with the genetic predisposition of an individual is termed constitutive pigmentation. Facultative pigmentation is inducible melanin pigmentation that reflects an individual's genetic pigment production overlain by hormonal or nutritional effects or responses to ultraviolet radiation.

Several gene loci control pigmentation, influencing the type and proportion of melanin pigment, the size and shape of melanosomes, melanocyte morphology (specifically, dendrite morphology), structure of tyrosinase, and regulation of copper transport (copper is a cofactor in multiple steps in melanin synthesis). Mutations in any of the genes involved in pigment production, melanosome formation or distribution, or melanocyte function or morphology can cause pigmentary abnormalities.

7. List the steps in melanin formation.

See Box 48-1.

8. What factors control pigmentation of the hair?

Hair pigmentation reflects polygenic controls of melanin formation, further influenced by nutritional or hormonal factors. Pigmentation within a single hair can switch from eumelanin to pheomelanin production. In mice, this is controlled by the *agouti* and *extension* gene products.

Interaction of α-melanocyte stimulating hormone (MSH) with the melanocortin 1 receptor (Mc1r), encoded by the *extension* gene, leads to eumelanin production, whereas agouti gene product antagonizes this receptor, leading to pheomelanin production. The agouti protein is

Box 48-1 *Steps in Melanin Formation*

Step 1. Melanoblast migration from the neural crest or optic cup
Step 2. Differentiation of melanoblasts into melanocytes
Step 3. Mitotic division of melanocytes
Step 4. Tyrosinase synthesis
Step 5. Melanosome matrix synthesis
Step 6. Tyrosinase transport
Step 7. Melanosome formation
Step 8. Melanosome melanization
Step 9. Melanosome transfer from melanocyte to keratinocytes
Step 10. Melanosome degradation

expressed from day 4 to day 6 of the hair cycle; the end result is a black hair with a yellow tip. Similar effects probably occur in dogs and cats.

Hair color in cats reflects the influences of at least 15 genes, several with more than two alleles. The natural color of cats is tabby, the expression of which depends on at least three genes. In solid colors, white is dominant, and masks other hair colors. The iris color is usually blue, orange, or heterochromic; cochlear deafness can occur in solid white, blue-eyed cats because of programmed cell death leading to degeneration of the hair cells in the inner ear after birth. Dominant alleles are required on three genes to produce a solid black coat color: *B* (black), *C* (full color expression), and *D* (dense coloration vs. dilute). Red and cream are produced by the orange gene, *O,* which is sex-linked on X. A male with *O* on X will be red, females need to have *O* on both Xs to be red, otherwise will be tortoiseshell. Cream colors reflect the action of the dilute gene on the O locus. This gene leads to changes in the way melanin is distributed within hair shafts. A mutation of the albino gene in Siamese, Himalayan, Balinese, and Burmese cats results in tyrosinase that is inactivated at high temperatures (35-37° C). Pigment is produced in cooler areas of the body (head, tail, extremities), but pigment synthesis is inhibited at higher temperatures (trunk).

9. Do dogs express albinism? What is the difference between albinism and piebaldism?

Albinism in dogs is a genetic absence of tyrosinase, an essential element in melanin synthesis. Melanocyte numbers and morphologies are normal, but melanin is not produced in the skin, hair, or mucous membranes. Unlike type I oculocutaneous albinism in humans, some iris pigment is present in dogs, producing a blue eye color. Inheritance is autosomal recessive. Tyrosinase deficiency in Chow Chows manifests as a transient depigmentation of the tongue, mucous membranes of the mouth, and the hair. Color changes usually reverse within 4 months.

Piebaldism results from absence of melanocytes in patches on the body, leading to white spots or patches. Inheritance is autosomal dominant.

10. What is a lentigo? Describe the clinical presentations of feline lentigo simplex and canine lentigo simplex.

A lentigo is a benign proliferation of melanocytes. Lentigenes in both dogs and cats differ from melanocytoma and malignant melanoma in signalment and lesion distribution, as well as clinical appearance and course. Pigmented epidermal plaques have a rough, irregular topography and are discussed in Chapter 51. The sharp circumscription and smooth texture of lentigenes distinguishes them from acanthosis nigricans and hyperpigmentation secondary to chronic inflammation, both of which have vague, irregular borders and may have rough surfaces. Canine macular melanosis is restricted to the skin of the scrotum, perianal region, groin, and tail. Unlike

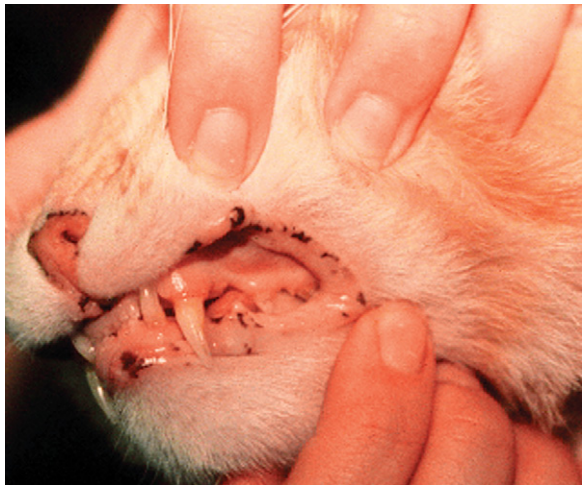

Figure 48-1 A 1-year-old domestic shorthair cat with lentigo simplex.

lentigenes, these macules develop rapidly in intact male dogs and should prompt examination for testicular neoplasia. Histopathologic features will differentiate lentigo simplex from clinically significant diseases.

In feline lentigo simplex, orange, cream, or silver cats develop multiple, darkly pigmented, well-circumscribed macules on the lips, gingiva, eyelids, and nasal planum before the age of 1 year (Figure 48-1). This melanocytic hyperplasia is restricted to the stratum basale of the epidermis. Both size and number of lentigenes typically increase over time until middle age; some macules reach 1 cm in diameter. Lentigenes are asymptomatic; thus, no treatment is required.

Canine lentigo simplex generally affects the ventral abdomen or nipples of older dogs. Numbers of both melanocytes and melanosomes increase to form multiple well-circumscribed macules. Pigment is distributed throughout the epidermis, from the stratum basale to the stratum corneum.

11. What is the pathogenesis of vitiligo? How is it treated?

Vitiligo is the progressive development of depigmentation of the hair (leukotrichia, poliosis), skin (leukoderma), and mucocutaneous tissues; the disease reflects selective destruction of melanocytes. In most individuals, depigmentation is symmetric, but can be patchy or generalized. Asymmetric, unilateral presentations have been reported in humans. Predisposition to vitiligo in humans is polygenic, controlled by at least three to four genes. A genetic predisposition to disease development in dogs is suggested by increased incidence in Rottweilers (Figure 48-2), Doberman Pinschers, Belgian Tervurens, Collies, German Shepherds, and Giant Schnauzers. In cats, female Siamese cats are predisposed. Disease development may reflect an underlying predisposition for disease development. Vitiligo would be phenotypically manifest in individuals in whom an underlying trigger for disease expression occurred. In humans, triggers include a stressful event with vitiligo developing 6 to 12 months following disease onset, melanocytoxic chemicals (e.g., hydroquinone or monobenzone derivatives), and other immune-mediated diseases (e.g., systemic lupus erythematosus, psoriasis, rheumatoid arthritis, polyglandular endocrinopathy, and myasthenia gravis).

Several different hypotheses have been proposed for the pathogenesis of vitiligo. Vitiligo is associated with several immune-mediated disorders; antibodies directed against surface antigens

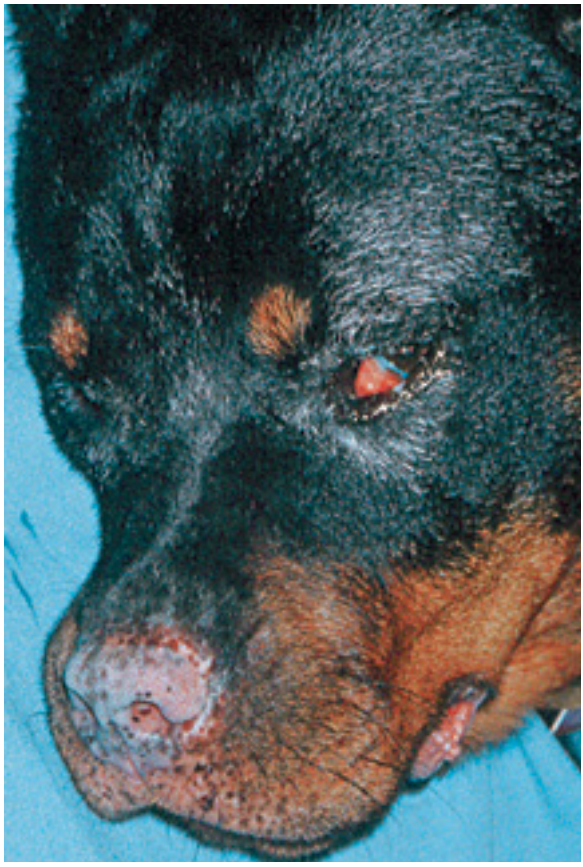

Figure 48-2 Vitiligo affecting the head of a 2-year-old female spayed Rottweiler.

or antigens released by disruption of melanocytes have been identified in humans with vitiligo; the antibodies do not necessarily target tyrosinase. These antibodies lead to melanocyte death in vitro, are rare in individuals without vitiligo, and are sometimes identified in individuals before the onset of clinical signs of vitiligo.

Melanin production generates a plethora of potentially cytotoxic intermediates. Synthesis within melanosomes prevents cell damage under normal circumstances. Release of these compounds or disruption of a melanocyte's mechanisms to protect it from these compounds would lead to pigment cell death. The occurrence of vitiligo in hyperpigmented skin supports this hypothesis.

The neural hypothesis invokes a neurochemical mediator as a trigger to melanocyte destruction. A benefit of this hypothesis is that it would explain segmental, unilateral manifestations of vitiligo that would not be produced from immune-mediated causes.

Some human patients with vitiligo experience psychological distress at the loss of pigmentation. Therapeutic management strategies include repigmentation or depigmentation to make skin color more uniform. As clinical manifestations in dogs are cosmetic, no therapy for vitiligo is required. Nevertheless, the observation of vitiligo in a canine or feline patient should prompt a search for apparent triggers of depigmentation, including immune-mediated diseases

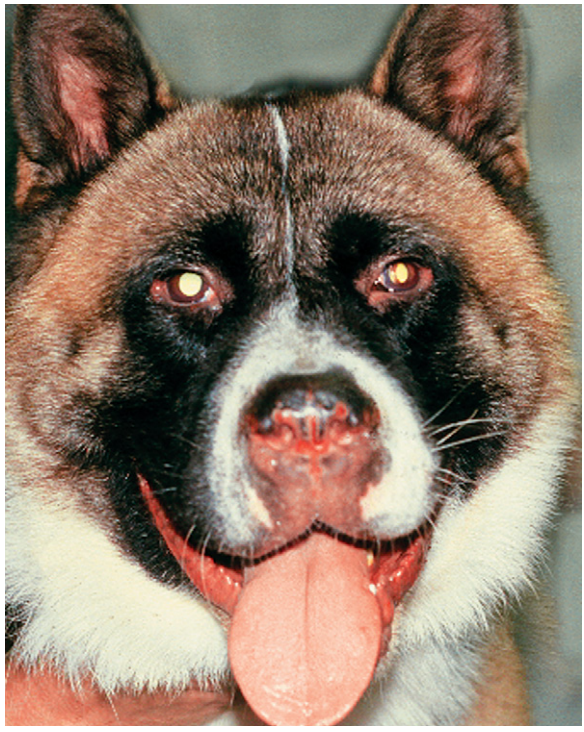

Figure 48-3 Uveodermatologic syndrome in a 2-year-old male castrated Akita; note the depigmentation of skin and hair involving the periocular region and planum nasale.

such as systemic lupus erythematosus or endocrinopathies such as hypothyroidism, diabetes mellitus, or hypoadrenocorticism. Vitiligo can also be a cutaneous manifestation of underlying neoplasia.

12. What is the "Vogt-Koyanagi-Harada syndrome?"

Clinical signs of the Vogt-Koyanagi-Harada syndrome, or uveodermatologic syndrome, include vitiligo, poliosis (leukotrichia), alopecia, acute anterior uveitis (iriditis, choroiditis, cyclitis), dysacusis, or hearing loss; humans also commonly have aseptic meningitis. This constellation of signs results from melanocyte death in the skin and hair matrix, uveal tract, stria vascularis of the ear, and the leptomeninges. Poliosis and cutaneous depigmentation in dogs usually occurs in the eyelids, nasal planum, lips, scrotum, footpads; depigmentation may become generalized (Figures 48-3 and 48-4). Ocular signs are severe; patients may present with acute blindness or chronic uveitis. Affected breeds include the Akita, Samoyed, Golden Retriever, Irish Setter, Siberian Husky, Saint Bernard, Australian Sheepdog, Shetland Sheepdog, and many others. Proposed pathogenesis in humans is the development of cell-mediated or autoimmune attack against melanocytes. Aggressive glucocorticoid or other immunosuppressive therapy is required for ocular manifestations of this disease to prevent blindness. Cutaneous signs are cosmetic.

13. What are the canine breeds affected with color mutant alopecia? How is this disease diagnosed and how are affected dogs managed?

Canine breeds in which color mutant, or color dilute, alopecia has been reported include

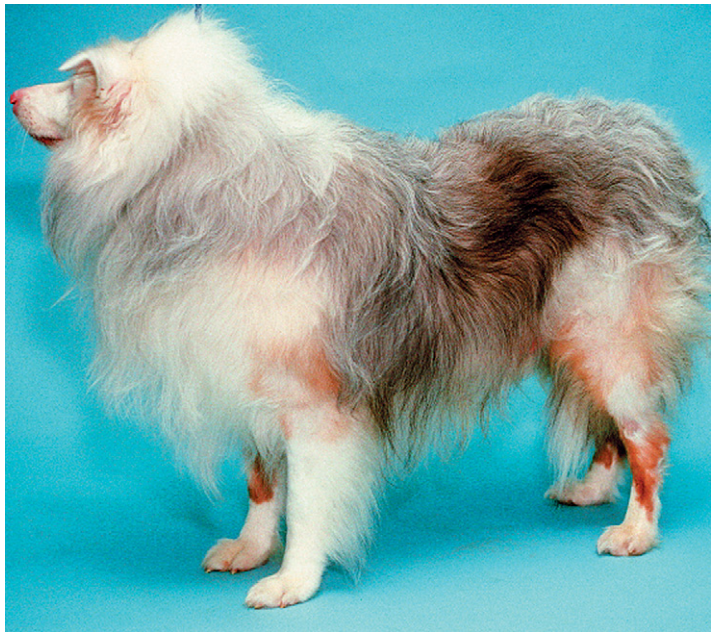

Figure 48-4 Generalized poliosis (leukotrichia) in a Shetland Sheepdog associated with uveodermatologic syndrome.

Doberman Pinschers, Dachshunds, Chow Chows, Great Danes, Whippets, Irish Setters, Italian Greyhounds, Standard Poodles, Miniature Pinschers, Yorkshire and Silky Terriers, Chihuahuas, Boston Terriers, Salukis, Newfoundlands, Shetland Sheepdogs, Schipperkes, Bernese Mountain Dogs, and mixed breeds. Although color dilutions occur in Weimaraners, associated hair loss does not occur.

Hair color in several canine breeds can be modified by the action of a dilution gene at the D locus; other loci may be involved as well. Black is diluted to blue, and brown is diluted to fawn. The genetic mutation affects the storage and transfer of melanosomes; clinical signs appear between the ages of 6 months to 3 years. The result is the production of irregularly shaped macromelanosomes, which are unevenly distributed, or clumped, within the hair shaft. Melanin amounts are actually normal to increased in the color-dilute hairs; their uneven distribution is responsible for the lighter hair color. The disease is diagnosed based on breed, coat color, and finding hair shafts with macromelanosomes and fractured hairs on trichograms or skin biopsy specimens.

Macromelanosomes disrupt the integrity of the hair shaft, with resulting hair breakage and loss. This is exacerbated by rough grooming. Eventually, hair follicles become dilated, cystic, and inactive. Bacterial folliculitis is common. The abnormal distribution and size of melanosomes is visible microscopically and is diagnostic. Therapeutic management relies on slowing hair loss by using only gentle shampoos and minimal brushing. Antibiotics can be used to treat secondary bacterial pyodermas.

14. What clinical abnormalities characterize Chédiak-Higashi syndrome in cats?

Chédiak-Higashi syndrome occurs in blue-smoke Persians with yellow eyes; inheritance is autosomal recessive. Melanosome formation and degradation are abnormal; clumping macro-

melanosomes result. Concurrent clinical signs may reflect abnormal production of other organelles or cell membranes. Granules are enlarged in neutrophils, monocytes, and eosinophils because of defective granule fusion. Leukocytes contain abnormal lysosomes, are fragile, and may rupture spontaneously. Chemotactive responsiveness, intracellular killing, and motility are reduced. The ability of natural killer cells to combat viruses or tumors is greatly reduced. The combination of reduced function of leukocytes, polymorphonuclear cells, and natural killer cells results in profound immune deficiency and an increased susceptibility to infection. Cataract formation follows leukocyte rupture, exacerbating pigment-related photophobia. Abnormal granule formation causes platelet dysfunction despite normal platelet counts; affected cats develop hematomas at injection sites and can die from acute hemorrhage. No treatment is available.

15. What is canine cyclic hematopoiesis? How is it treated?

Canine cyclic hematopoiesis, or gray Collie syndrome, is a lethal autosomal recessive disorder in Collies. Neutrophil and platelet numbers wax and wane in a regular cycle. Every 11 to 12 days, neutrophil numbers drop for a duration of about 3 days. Cell numbers then become elevated for about 7 days. Myeloperoxidase activity is reduced in neutrophils in all phases of the cycle. The defect probably stems from abnormal maturation of neutrophil precursors in the bone marrow. Affected puppies are uniformly silver gray (Figure 48-5), in contrast to the coloration of blue merle Collies. Puppies fail to thrive, healing is delayed, and bouts of lymphadenitis, gastroenteritis, respiratory infections, gingivitis, and arthralgia are frequent. Epistaxis and other bleeding disorders are common.

Antibiotics are used to control recurrent infections. Administration of endotoxin, lithium carbonate and recombinant human colony-stimulating factor can transiently stimulate the bone marrow and stabilize platelet and neutrophil numbers, although the use of these agents is limited by their toxicity and cost. The prognosis is poor; most patients die by the age of 3 years. Bone marrow transplantation can be curative.

Figure 48-5 Gray Collie. This coat color is a marker for cyclic hematopoiesis.

16. Are there any additional genetic causes of pigmentary abnormalities?
Yes, see Table 48-1.

Table 48-1 ***Additional Genetic Causes of Pigmentary Abnormalities***

ABNORMALITY	SPECIES	BREEDS	CUTANEOUS SIGNS	OTHER CLINICAL SIGNS	COMMENTS
Acromelanism	Feline	Siamese Himalayan Balinese Burmese	Hair over cool parts of body (face, extremities, tail) darker than that over warmer areas (trunk)	None	Autosomal recessive
Urticaria pigmentosa	Feline	Sphinx	Pruritic, maculopapular in generalized, bilaterally symmetric distribution; juvenile onset	No systemic involvement	Diffuse infiltration of mast cells into dermis and subcutaneous tissues
Periocular depigmentation	Feline	Siamese	Bilateral periocular depigmentation	Triggered by systemic disease, pregnancy, dietary deficiency	More common in females than in males Resolves within two hair cycles
Aguirre's disease	Feline	Siamese	Unilateral periocular depigmentation	Horner's syndrome, uveitis, or upper respiratory tract infections	
Premature graying	Canine	Golden Retriever German Shepherd Labrador Retriever Irish Setter	Graying of the hair of the muzzle and chin at a young age	Abnormality in mitotic division of melanocytes	Age-associated graying also reflects decreased mitotic division of melanocytes
Idiopathic graying	Canine	Newfoundland	Depigmentation starting on the nose, lips, eyelids; gray roan, rather than uniformly gray Occurs in young dogs, progressive	Etiology undetermined.	Distinguish from premature graying by roan pattern, distribution

Table 48-1 *Additional Genetic Causes of Pigmentary Abnormalities—Cont'd*

ABNORMALITY	SPECIES	BREEDS	CUTANEOUS SIGNS	OTHER CLINICAL SIGNS	COMMENTS
Waardenburg-Klein syndrome	Canine	Bull Terrier Sealyham Terrier Dalmatian	Blue or heterochromic irises, white skin and hair, hearing loss	Defect in migration and differentiation of melanoblasts into melanocytes	No melanocytes present in affected skin; autosomal dominant with incomplete penetrance
Patchy leukotrichia	Canine	Labrador Retriever	Widespread development of patches of light-colored hairs in chocolate or black individuals	Etiology undetermined	Permanent depigmentation of hairs. Transient manifestation reported in one litter of chocolate Labradors

17. What is the pathogenesis of pigmentary changes associated with endocrinopathies?

Hyperpigmentation secondary to endocrinopathy can occur in dogs with hypothyroidism, hyperadrenocorticism, diabetes mellitus, adrenal sex hormone abnormalities, and increased levels of estrogen in patients with Sertoli cell tumors. Melanogenesis is stimulated by the effects of adrenocorticotropic hormone (ACTH) on melanocytes; other hormones may have similar effects. Concurrent cutaneous infection augments endocrine-associated hyperpigmentation. Endocrine-associated alopecia contributes to facultative hyperpigmentation stimulated by ultraviolet light.

18. What diseases cause nasal depigmentation?

- Vitiligo
- Uveodermatologic syndrome
- Drug reaction
- Squamous cell carcinoma
- Epitheliotropic T-cell lymphoma
- Nasal solar dermatitis
- Immune-mediated diseases (systemic or discoid lupus erythematosus, pemphigus foliaceus or erythematosus)
- Increased licking or nasal discharge
- Breed-related seasonal changes–"Dudley nose" and "snow nose"

19. What is the difference between "Dudley nose" and "snow nose"?

Dudley nose is a progressive condition and is probably a form of vitiligo. It occurs in Afghan Hounds, Doberman Pinschers, white German Shepherds, Golden Retrievers, Irish Setters, and Pointers. Complete depigmentation of the nasal planum is the only clinical sign. Spontaneous remission and repigmentation has occurred.

In contrast, "snow nose" is a cyclic hypopigmentation of the nasal planum of Bernese Mountain Dogs, Golden Retrievers, Labrador Retrievers, and Siberian Huskies that occurs during the winter months.

20. Describe the process of taking nasal biopsies.

Nasal biopsies should be taken under general anesthesia; the nasal planum is sensitive and highly vascular. Areas of partial depigmentation or hypopigmentation characterized by gray coloration with a loss of the normal cobblestone texture should be biopsied. Ulcerated, scarred, or completely depigmented sites should be avoided.

21. What is acanthosis nigricans?

Acanthosis nigricans is characterized by bilateral hyperpigmentation and lichenification of the axillary skin. Prevalence is highest in Dachshunds (Figure 48-6). A similar condition is also observed in other breeds, usually secondary to a cutaneous infection, intertriginous friction, underlying atopy or adverse reaction to food, or endocrinopathy. Successful therapeutic management depends on identification and treatment of any underlying predisposing or perpetuating causes. Antiseborrheic shampoos or topical and systemic glucocorticoids can be palliative.

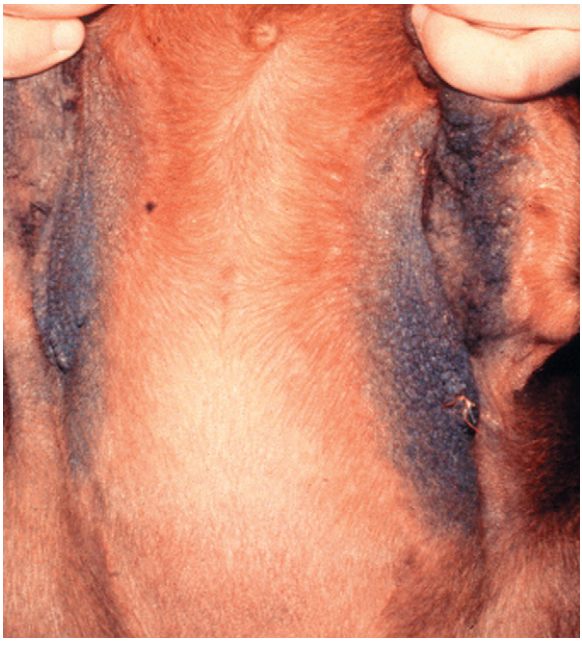

Figure 48-6 Acanthosis nigricans in a 3-year-old female spayed Miniature Dachshund.

22. What causes hyperpigmentation after skin infections or hair loss?

Postinflammatory hyperpigmentation reflects increases in cytokine amounts and activity following infection or inflammation. Several cytokines, among them arachidonic acid, prostaglandin (PG) E_2, and PGD_2, increase melanocyte proliferation. Melanocyte dendricity is enhanced by PGE_2, leukotriene (LT) C_4, LTD_4, and thromboxane 3 (TX_3). Arachidonic acid, TX_3, LTD_4, and LTC_4 enhance the activity of tyrosinase. Melanocyte production is stimulated by LTD_4. Hypopigmentation is possible if interleukin (IL)-1, IL-6, or tumor necrosis factor predominate;

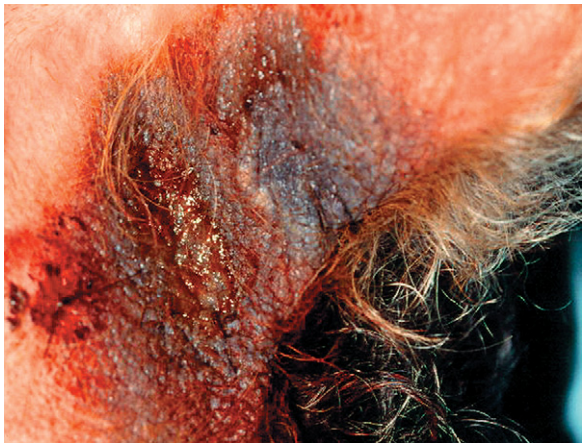

Figure 48-7 Postinflammatory alopecia in the axilla of a West Highland White Terrier with chronic allergies and *Malassezia* dermatitis.

these cytokines inhibit melanogenesis. Thus, postinflammatory hyperpigmentation or hypopigmentation reflects the cytokine environment.

Postinflammatory hyperpigmentation is quite common (Figure 48-7). Its appearance is similar to that of endocrine-associated hyperpigmentation. Both are diffuse, reticular, and poorly circumscribed. Clinical history, cytology, and diagnostic tests for endocrinopathy will differentiate the disorders, although they are not mutually exclusive. Hyperpigmentation in a hypothyroid dog with bacterial pyoderma or *Malassezia* probably reflects postinflammatory as well as endocrine-related effects.

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49. DISEASES OF THE EAR

John C. Angus, DVM, DACVD

1. **The gross anatomy of the ear can be divided into five structural components; name the five components and briefly describe anatomic features and boundaries of each** (Figure 49-1).

Pinna

The pinna, or auricle, together with the acoustic meatus, forms the external ear. In dogs there is considerable variation in the shape and carriage of the pinna as the result of selective breeding for appearance and functional characteristics. Generally, the pinna is a funnel-shaped appendage that serves to focus sound vibrations toward the external canal. The pinna consists of a broad, leaf-shaped extension of auricular cartilage called the scapha. This sheet of cartilage is covered on both sides by normal dermis and epidermis. At the proximal region of the pinna, the cartilage begins to scroll into a concave shape that is continuous with the vertical ear canal. The transition

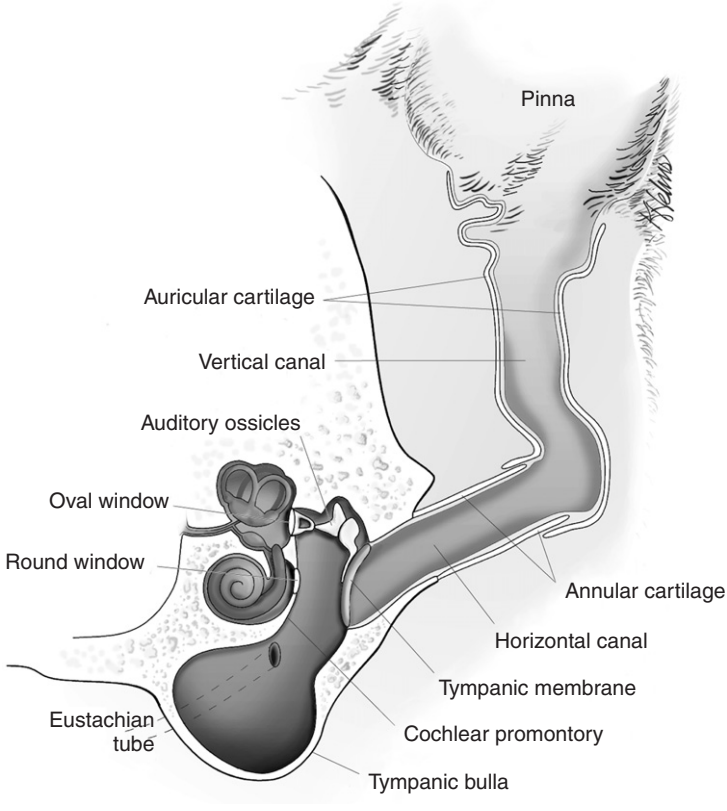

Figure 49-1 Schematic drawing of components of the canine ear.

from pinna to vertical ear canal occurs at the level of the anthelix, a cartilage prominence on the medial side of the canal, and the tragus, a prominence on the lateral side of the canal.

External Ear Canal

The external canal, also known as the external acoustic meatus, is an epithelial-lined, cartilage tube that conducts sound vibrations to the tympanic membrane. Two telescoping cartilage tubes define the canal; the proximal end of the scrolled auricular cartilage telescopes over the narrower annular cartilage. The annular cartilage is attached at the distal end to the auricular cartilage and at the proximal end to the skull by ligaments. The dimension of the canal varies from 5 to 10 cm in length and from 4 to 5 mm in diameter. In the dog and cat the canal contains an approximately 75-degree bend, which redirects the lumen horizontally and medially; this bend divides the "vertical canal" from the "horizontal canal." The horizontal canal terminates at the tympanic membrane. The tympanic membrane is recessed within the skull; therefore, the most proximal portion of the horizontal canal is actually encompassed by bone rather than cartilage.

Tympanic Membrane

The tympanic membrane (tympanum, eardrum) is a semitransparent membrane that separates the external acoustic meatus from the tympanic cavity. In dogs, the tympanum is positioned at an angle of up to 45 degrees to the long axis of the horizontal canal, such that the dorsal aspect is closer in view than the ventral portion. In cats, the membrane is perpendicular to the axis of the canal.

Middle Ear

The middle ear consists of the air-filled tympanic cavity, auditory ossicles, auditory (eustachian) tube and associated nerves. The tympanic cavity is located completely within the skull and is lined by ciliated, respiratory epithelium. This gourd-shaped cavity can be divided into three anatomic compartments: (1) the narrow cavity, located dorsal to the tympanic membrane, contains the auditory ossicles, the oval window, and the round window; (2) the middle portion lies just ventral to the round window and is defined by the tympanic membrane on one side and the bony protuberance of the cochlear promontory; and (3) the large, ovoid tympanic bulla, which is ventral to the cochlear promontory and opening of the auditory tube.

Inner Ear

The endolymph- and perilymph-filled inner ear is separated from the middle ear by two membrane-covered openings (the round and oval windows). This bony labyrinth contains the cochlea, vestibule, and semicircular canals.

2. Describe the muscles, sensory and motor innervation, and vasculature associated with the canine pinna.

Ear movement is achieved by three sets of muscles located rostral, ventral, and caudal to the pinna. Afferent branches of the trigeminal, facial, vagus, and second cervical nerve supply sensory innervation; motor function is supplied by the facial nerve. Branches of the external carotid and maxillary arteries provide a generous blood supply to the pinna. The majority of blood arrives on the convex surface via the caudal auricular artery, which divides into three branches: lateral, intermediate, and medial. The concave surface receives blood from arterioles that traverse numerous small holes in the auricular cartilage or that pass around the helical margins. Venous drainage of the pinna occurs via the internal maxillary vein.

3. Describe the epithelial lining of the external ear canal (external auditory meatus).

The external canal is lined by normal stratified epidermis and dermis similar to normal skin elsewhere on the body. The dermis contains hair follicles, sebaceous glands, and modified

apocrine glands, known as ceruminous glands. In general the hair follicles and adnexal units are smaller and less dense than their counterparts elsewhere. Follicular units are present along the entire length of the canal, all the way to the junction with the tympanic membrane.

4. What glandular tissue produces cerumen?

Cerumen is formed by a combination of secretions from both the sebaceous and ceruminous glands. Sebaceous secretions are thicker and contain primarily neutral lipids, while ceruminous glands produce a thinner secretion containing phospholipids and mucopolysaccharides.

5. Name three beneficial functions of cerumen.

1. The cerumen coating the external canal protects the epithelial lining and the tympanic membrane by trapping debris, parasites, and microorganisms.
2. Cerumen also contains immunoglobulins (IgA, IgG, and IgM) contributing to passive local immunity. IgG is the predominant class found in normal and diseased ears; a substantial increase in cerumen IgG occurs during otitis externa.
3. Cerumen covering keeps the tympanum moist and pliable by protecting this thin membrane from desiccation.

6. How are debris and cerumen eliminated from the normal ear canal?

The stratified squamous epithelium lining the external canal slowly migrates laterally from the deep canal to the opening of the ear canal. The keratinized stratum corneum, cerumen, and any trapped debris from the canal is dispersed onto the pinna, where it can fall away harmlessly. This centripetal migration originates from the germinal epithelium located on the tympanic membrane.

The process of epithelial migration is a vital protective feature for normal otic health. Failure of epithelial migration due to rupture of the tympanic membrane or chronic inflammation, injury, or scarring of the epithelial lining results in chronic accumulation of debris, cerumen, and desquamated keratinocytes. Disruption of epithelial migration is a key concept in understanding progression of chronic otitis.

7. The tympanic membrane can be divided into two discrete regions, the *pars flaccida* and the *pars tensa*. Compare the otoscopic appearance and functional significance of each region.

The pars flaccida is a small, opaque, highly vascular bed of tissue located at the dorsal aspect of the tympanum. This tissue becomes edematous in response to inflammation and appears engorged in many patients with atopic otitis externa. The pars flaccida provides the blood supply for the pars tensa (Figure 49-2).

The pars tensa is the thin, translucent membrane that stretches across the opening to the tympanic cavity. The membrane is attached to a fibrocartilaginous ring, which is attached to the osseous ring arising directly from the skull. The manubrium of the malleus (the first of the auditory ossicles) is embedded in the tough fibrous middle layer of the pars tensa; this structure is visible on otoscopy as a white, hooked, finger-like projection coming down from the dorsal junction with the pars flaccida, pointing rostrally. Small blood vessels and striations in the pars tensa can be seen radiating from the manubrium (Figure 49-3). This region is also the location for the germinal epithelium, from which perforations will heal. Damage to the manubrium may result in permanent rupture of the tympanic membrane. The pars tensa acts to transmit sound vibrations funneled by the pinna and the external canal to the auditory ossicles.

8. On histologic cross-section, the pars tensa has four distinct layers. What are the four layers? What are the unique features of these layers?

Starting from the external aspect the first layer encountered is a thin, epidermis-like, stratified squamous epithelium, which is only a few layers thick. This layer is continuous with the epithelial lining of the external canal.

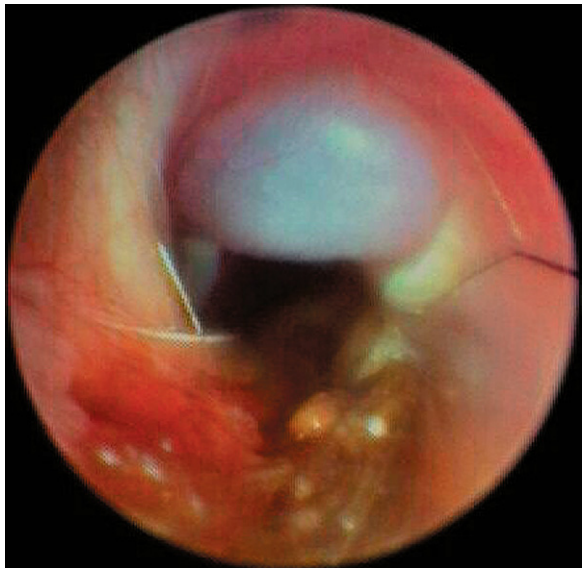

Figure 49-2 Video-otoscopic view of engorged pars flaccida in a dog. The pars tensa is not visible in this photograph because of shadowing from the pars flaccida and the 45-degree angle away from canal.

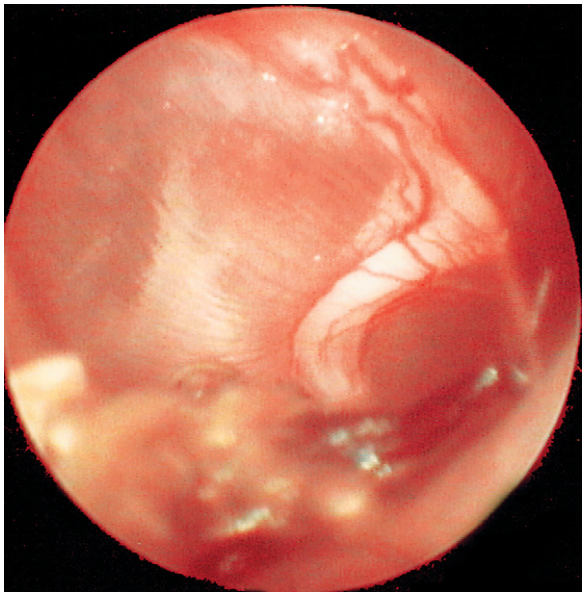

Figure 49-3 Video-otoscopic view of normal pars tensa in a dog. Note the clearly visible manubrium of the malleus, fine vasculature of the germinal epithelium, and striations in the membrane. The cochlear promontory is visible through the tympanum.

Next is a layer of fibroblasts, fine nerves, and blood vessels analogous to and continuous with the dermis. The principal difference between this layer of the pars tensa and normal dermis is the absence of hair follicles and glandular structures.

The third and thickest layer consists of dense fibers connecting to the fibrocartilaginous ring supporting the pars tensa. The manubrium of the malleus is embedded here. The arrangement of these fibers optimizes transmission of vibrations.

The deepest layer is continuous with the respiratory mucosal epithelium that lines the middle ear. This portion consists of a single layer of respiratory epithelium overlying a thin lamina propria and contains no goblet cells or cilia. The epithelium is more squamous centrally, becoming more cuboidal as it radiates outward, until it becomes columnar at the margins with the normal mucosa.

9. Name the three auditory ossicles found within the tympanic cavity.

The auditory ossicles are the malleus, incus, and stapes. Distally the manubrium of the malleus is embedded in the pars tensa and proximally it articulates with the incus. The incus, in turn, articulates with the stapes, which is attached to the oval (vestibular) window. The tensor tympani is a muscular attachment to the ossicles that contracts in response to sudden, intense sound vibrations.

10. There are four openings into the bony chamber of the tympanic cavity. What are they and where do they lead?

1. The junction of the tympanic cavity with the external ear canal is the largest of the four openings and is covered by the tympanic membrane.
2. The oval (vestibular) window is a membrane-covered opening separating the air-filled tympanic cavity from the inner ear. Vibrations of the stapes are transmitted across this membrane to the endolymph of the vestibule.
3. The round (cochlear) window is located ventral to the oval window, just dorsal to the cochlear promontory (across from the tympanic membrane). Energy from vibrations is dissipated across this membrane from the inner ear into the tympanic bulla.
4. The opening from the auditory tube is not covered by a membrane. This tube connects the tympanic cavity with the nasopharynx, permitting movement of air.

11. What anatomic difference between dogs and cats increases the risk of iatrogenic Horner's syndrome following ear flushing and bulla osteotomy in the cat?

In the feline tympanic cavity there is a bony septum that separates the dorsal chambers from the larger ventral chamber. There are prominent postganglionic sympathetic nerve fibers running in the epithelium near this septum. Overaggressive ear flushing or intentional disruption of the septum during bulla osteotomy may damage these nerve fibers, resulting in Horner's syndrome (myosis, ptosis, and prolapse of the third eyelid). In most cases, this is a temporary phenomenon.

12. How common is otitis externa in small animal practice?

Otitis externa is one of the most common conditions seen in small animal practice. An estimated 5-20% of canine patients and 2-6% of feline patients experience clinically significant otitis externa during their lifetime. A precise estimate of prevalence is difficult to determine due to variable expressions of severity and difficulty defining diagnostic criteria. The primary reason for the challenge of defining diagnostic criteria is that otitis externa is a clinical sign rather than a primary disease. Just as coughing can be a clinical sign of heart disease, tracheal collapse, neoplasia, pneumonia, etc., otitis externa is a clinical manifestation of many diverse underlying conditions.

13. In the conceptual approach to the pathogenesis of ear disease, proposed by August (1988), there are three general categories: predisposing conditions, primary causes, and perpetuating factors. Define each category and give examples for each.

Predisposing conditions *alone do not cause ear disease*, but rather may make affected individuals *more susceptible* to developing otitis externa or more likely to have more severe disease when afflicted by primary causes.

Primary causes are conditions that *directly result in the development of clinical disease* in otherwise normal individuals

Perpetuating factors are conditions that result from the primary causes or complications of active ear disease that *once established can maintain, worsen, or prevent resolution* even after the primary cause has been resolved.

See Table 49-1 for examples of each category. Figure 49-4 illustrates severe proliferative changes of the external ear canal.

Table 49-1 ***Examples of Conditions Affecting Otic Health in Dogs and Cats***

PREDISPOSING CONDITIONS	PRIMARY CAUSES	PERPETUATING FACTORS
Conformation	Parasites	Bacteria
Stenotic canals	Foreign objects	Yeast
Pendulous pinna	Hypersensitivity disorders	Progressive pathologic changes
Excessive hair	Keratinization disorders	Failure of epithelial migration
Increased moisture	Endocrinopathies	Edema
Swimming	Immune-mediated skin disease	Glandular hyperplasia
Cleaning with water	Neoplasia	Folding
Inappropriate treatment	Trauma	Stenosis
Irritants	Viral	Fibrosis
Overaggressive hair plucking	Miscellaneous conditions	Ossification
Trauma from cotton swabs		Otitis media
Immune suppression from systemic disease or therapy		Cholesteatoma

14. Explain how a low burden of *Otodectes cynotis* (two to three mites) could result in severe bilateral disease in a canine or feline patient.

Several studies have shown that *O. cynotis* can induce both type I and type III hypersensitivity reactions in veterinary patients. Type I hypersensitivity reactions result from antigen specific IgE-mediated mast cell degranulation; vasoactive peptides released from mast cell granules result in edema and inflammation of the external ear canal. Type III, or Arthus-type, reactions occur when mite antigen and host antibody form immune complexes in the dermal vessels or along the epidermal-dermal junction. Immune complex deposition triggers activation of the complement cascade. The subsequent cytokine- and cell-mediated immune response results in intense local inflammation, pruritus, and pain. Even a very low number of mites can trigger these reactions (Figure 49-5).

15. How might *Otodectes cynotis* infections cause ongoing disease even after adult mites within the ear canal are eliminated?

Treatment Failure or Reinfestation

A common problem with *O. cynotis* is inadequate treatment of all stages, all locations, and

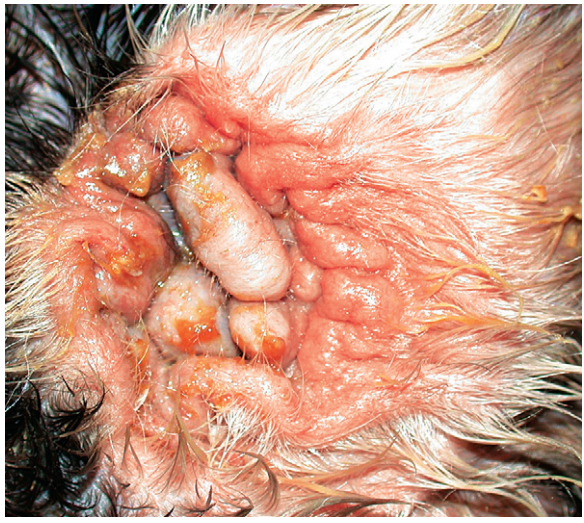

Figure 49-4 Proliferative otitis externa in a dog as a result of underlying atopy.

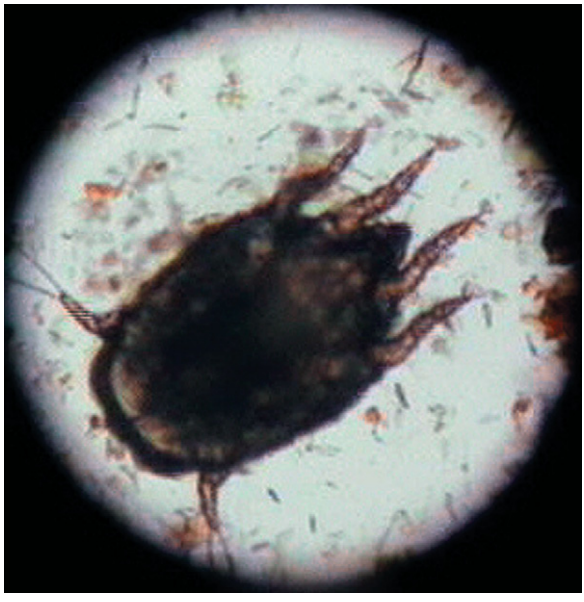

Figure 49-5 Photomicrograph of adult *Otodectes cynotis*.

all in-contact animals. Larval and adult stages are readily susceptible to most short-acting, topical products (pyrethrins, organophosphates, or occlusive "smothering" agents); however, these agents are not ovicidal, and therefore, reinfestation may occur from newly hatched eggs. Adult mites feed primarily on the epidermal debris and fluids of the external ear canal, but the mites may migrate elsewhere on the host body, most commonly the dorsal neck and tail head. Local treatments of the ear canal should be combined with an effective topical spray, foam, bath, or dip

to ensure elimination of mites from the skin. *O. cynotis* is not a species-specific parasite and is highly contagious between animals. Because clinical signs are variable between individuals, all dogs and cats in regular contact with the affected individual must be treated, even if they are asymptomatic. Failure to recognize and treat asymptomatic carriers will reliably result in recurrent clinical signs in the primary patient.

Loss of Epithelial Migration

Recurrent or severe inflammation may cause extensive damage to the epithelium of the external ear canal, resulting in disruption of orderly epithelial migration. Instead of centripetal migration out of the ear the desquamating keratinocytes slough into the central canal lumen. Even after effective treatment for the ear mites, there can be ongoing failure of the normal clearance mechanism. Debris consisting of keratin, cerumen, hair, and trapped material accumulate on the ventral floor of the horizontal canal, forming a ceruminolith. Ceruminoliths and diffuse debris act as a foreign obstruction or serve as a focus for bacterial and yeast overgrowth. Other changes associated with chronic otitis externa, such as stenosis, fibrosis, and mineralization, may permanently alter the external canal, perpetuating clinical disease in the absence of the primary cause.

Otitis Media

During the primary infestation, secondary bacterial infection of the external canal may weaken the tympanic membrane's normal barrier function, permitting infection to extend to the tympanic cavity. After resolution of the primary infestation, failure to recognize and manage otitis media results in recurrent bacterial infection and perpetuation of clinical signs of otitis externa.

16. What is the most common ear mite of rabbits?

Psoroptes cuniculi

17. What primary conditions result in abnormal or excessive accumulation of cerumen within the external ear canal?

- Hypersensitivity reactions
- Primary keratinization defects
- Hypothyroidism
- Sex-hormone imbalance
- *Otodectes cynotis*

18. Discuss the role of atopy in the pathogenesis of otitis externa.

An estimated 10% of the canine population is affected by atopic dermatitis; 40-80% of these animals exhibit otitis externa as part of their clinical disease. In 3-5% of animals with atopy, otitis externa is the only clinical sign. The precise mechanisms for development of atopy are not completely understood, but involve both genetic susceptibility and environmental factors, which result in an adverse immunologic response to otherwise harmless environmental allergens. In the ear canal, early pathologic changes include alteration of epidermal barrier function, changes in cerumen composition, and narrowing of the canal lumen due to dermal edema and glandular hyperplasia. Loss of barrier function increases penetration of microorganism antigens and exotoxins exacerbating local inflammation, while narrowing of the canal and occlusion with ceruminous debris provides a better environment for microorganism overgrowth. This cycle amplifies both primary atopic disease and secondary infection, resulting in progressive worsening of clinical otitis externa. Secondary infections can perpetuate signs year-round even if the initial allergen trigger is seasonal. In some cases, chronic allergen, bacterial, and yeast stimulation results in severe proliferative changes, fibrosis, and ossification. These ultimately lead to permanent stenosis of the canal lumen.

19. In addition to atopy, what other hypersensitivity reactions are considered primary causes for otitis externa?

Although the immunologic mechanisms are not well understood, adverse food reactions

(food allergies or food intolerance) can result in similar clinical presentations to that seen in atopic patients. In these cases, the antigenic trigger is dietary rather than environmental. Food reactions are less common in the general population than atopy, but because ear disease is seen in 80% of dogs and cats with food reactions, it is considered a common primary cause of chronic otitis and should never be overlooked in the diagnostic approach to patients with clinically significant otitis externa.

Contact hypersensitivities are type IV (delayed) hypersensitivity reactions to topically applied substances. In the case of otitis, contact reactions are rare. When present, reactions are most commonly associated with topically applied medications used to treat otitis externa secondary to other disease. A typical history is either a good initial response to therapy followed by progressive worsening of signs, or resolution of a previous episode followed by treatment failure when used on subsequent episodes. The owner or veterinarian may also notice extension of inflammation to involve the pinna or other areas the medication is used. Neomycin is the most commonly recognized cause of contact dermatitis, but other materials may also trigger reactions, including silver sulfadiazine, other antibiotics, propylene glycol, plant extracts, topical anesthetics, and topical insecticides. Definitive diagnosis can only be made by resolution with discontinuation of the suspected agent and recurrence following provocative challenge. True contact hypersensitivity and contact irritant reactions are difficult to differentiate, but both should respond to removal of the inciting medication.

20. Name a viral cause of otitis media in dogs.

Otitis media and otitis externa have been associated with the canine distemper virus. The virus targets rapidly dividing epithelium of the gastrointestinal and respiratory tract. Ascending secondary bacterial infection from the nasopharynx or primary viral infection of the respiratory epithelium lining the tympanic cavity could result in clinical otitis media. Immune suppression and debilitation of the patient may also contribute to disease.

21. What are nasopharyngeal polyps and how do they develop?

Nasopharyngeal polyps are an uncommon disorder in cats characterized by the development of a fleshy benign mass of fibrous connective tissue most often covered by ciliated respiratory epithelium. Most often polyps originate from the lining of the tympanic cavity, but may also develop from the lining of the eustachian tube or the nasopharynx. The etiopathogenesis of polyps is not known. Investigators speculate that polyps most likely result from inflammation or injury to the mucosal surface by ascending viral upper respiratory infection, *O. synotis* extending from the external canal, or other inflammatory trigger. Benign inflammatory polyps originating from the tympanic cavity may also occur in dogs.

22. Describe the clinical presentation of nasopharyngeal polyps in the cat.

Polyps are most commonly observed in young cats; there is no reported gender or breed predilection. If the polyp extends from the middle ear into the nasopharynx, affected cats commonly present for chronic signs of upper respiratory disease, including nasal discharge, sneezing, and stertorous respirations. Other presenting complaints include dysphagia and recurrent bouts of gagging. In some patients the polyp ruptures the tympanic membrane and protrudes into the external canal (Figure 49-6). These cases present for unilateral otitis externa characterized by excessive purulent or hemorrhagic otic discharge and frequent head shaking. Rarely patients present with Horner's syndrome or clinical signs of otitis interna (nystagmus, head-tilt, ataxia, deafness).

23. How are nasopharyngeal polyps treated in cats? What potential complications should be discussed before treatment?

The location of the polyp and extent of involvement should be determined by otoscopy and oropharyngeal examination. Visualization of a polyp in the oropharynx can be performed under

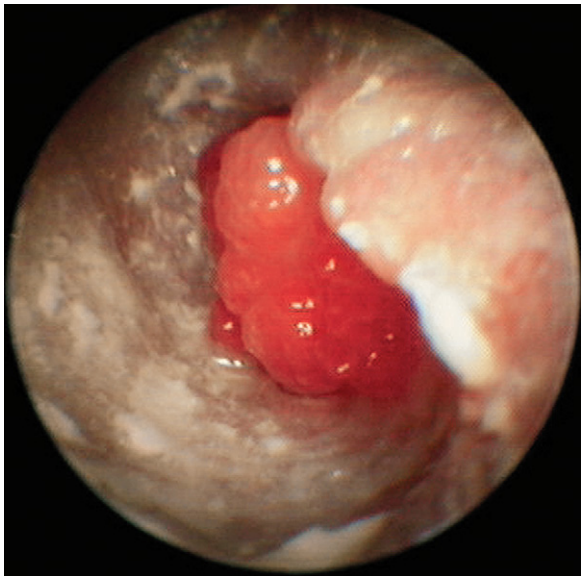

Figure 49-6 Video-otoscopic view of nasopharyngeal polyp in a cat.

anesthesia by gently retracting the soft palate with an atraumatic hook or tissue forceps. In some cases radiographic imaging or computed tomography is necessary before surgery to determine which bulla is involved. Ventral bulla osteotomy with curettage of the epithelial lining is the best method for long-term management, because regrowth occurs frequently following removal by traction alone.

The most common complication is damage to the postganglionic sympathetic fibers running in the epithelial lining of the tympanic cavity (see Question 11) during curettage of the bulla, affecting approximately 80-95% of surgical patients. The resultant Horner's syndrome is usually temporary. In one study, 19 of 22 cats with this complication returned to normal in less than 1 month; 2 cases resolved in 2 months and 18 months; one case was lost to follow-up. Regrowth of the polyp is another troublesome complication, which may occur in up to 50% of cats that do not receive a bulla osteotomy at the time of removal. Recurrence decreases to approximately 5% in cats with bulla osteotomy. Other potential complications include damage to the auditory ossicles, vestibular dysfunction, deafness, and injury to the hypoglossal nerve, facial nerve, or vascular structures in the soft tissue adjacent to the bulla during the approach.

24. What is the most common malignant neoplasm associated with otitis externa in dogs and cats? Describe the biologic behavior of the tumor.

Ceruminous gland adenocarcinoma is the most common malignancy of the external ear canal in both species (Figure 49-7). Patients typically present for unilateral otitis externa with purulent or hemorrhagic discharge. Secondary bacterial infections are common. In some cases, tumors arise in patients suffering from long-standing bilateral otitis externa from other causes, suggesting that chronic inflammation and cerumen gland hyperplasia are risk factors for malignant transformation. Most tumors appear as irregular, friable, ulcerative masses, arising from either the vertical or horizontal ear canal; however, malignant tumors may also mimic the smooth, nodular appearance of the more common, benign masses such as polyps or ceruminous gland adenomas (Figure 49-8).

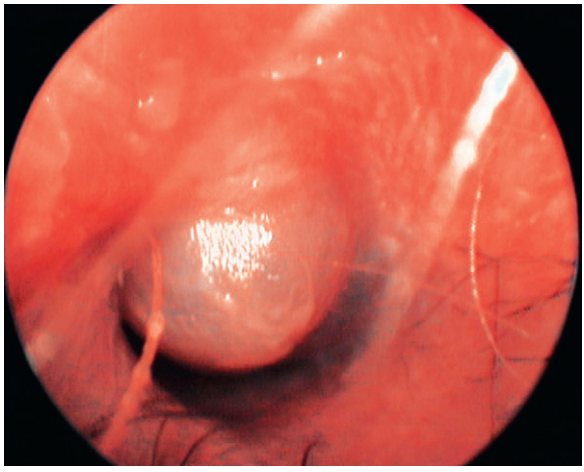

Figure 49-7 Video-otoscopic view of ceruminous gland adenocarcinoma in a dog.

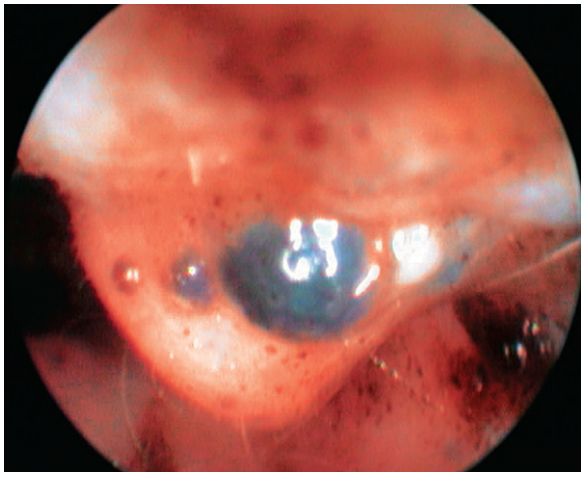

Figure 49-8 Video-otoscopic view of ceruminous gland adenoma in a cat.

Ceruminous gland adenocarcinoma tends to be locally invasive. Fortunately, in most cases, the auricular cartilage acts as a temporary physical barrier, permitting surgical intervention and complete excision by total ear canal ablation with lateral bulla osteotomy (TECA/LBO). Without treatment, the tumor will eventually breach the auricular cartilage and extend into the parotid region. Extension of the mass into the parotid region is a poor prognostic indicator because complete surgical excision is unlikely

In one study of 22 cats with ceruminous gland adenocarcinoma, patients with TECA/LBO had a 42-month median disease-free interval and a 75% survival at 1 year. Only 25% of these cats

had recurrence of disease. In contrast, cats with lateral ear canal resection alone had a recurrence rate of 66.7% and only 33.3% survival at 1 year; the median disease-free interval was 10 months. This study clearly elucidates the advantages of aggressive surgical intervention in the management of ear canal tumors.

Veterinarians and owners should also be aware that metastasis can occur to regional lymph nodes, lungs, and viscera; however, reports of the frequency of metastatic disease vary significantly.

25. List the other benign and malignant neoplastic conditions of the ear that occur in dogs and cats.

In general, masses in cats are more frequently malignant than benign, and masses in dogs are more frequently benign than malignant. However, clinical decisions should be made based on histopathologic diagnosis in all cases (Table 49-2).

Table 49-2 ***Benign and Malignant Ear Conditions in Dogs and Cats***

	BENIGN	MALIGNANT
Dog	Fibrous polyp	Ceruminous gland adenocarcinoma
	Papilloma	Squamous cell carcinoma
	Sebaceous gland adenoma	Round cell tumor
	Basal cell tumor	Malignant melanoma
	Ceruminous gland adenoma	Hemangiosarcoma
	Histiocytoma	Mast cell tumor
	Plasmacytoma	Fibrosarcoma
		Carcinoma of undetermined origin
		Sarcoma of undetermined origin
Cat	Nasopharyngeal polyp	Ceruminous gland adenocarcinoma
	Ceruminous gland adenoma	Squamous cell carcinoma
	Papilloma	Sebaceous gland adenocarcinoma
		Carcinoma of undetermined origin

26. Describe the role of bacteria in the pathogenesis of otitis externa.

Bacteria are rarely a primary cause of otitis externa. In most cases, bacteria contribute to clinical disease following overgrowth and infection secondary to the primary cause. Normal bacteria are present in small numbers throughout the external canal. Primary diseases result in changes in the bacterial microenvironment favorable to overgrowth of native flora or colonization by opportunistic organisms. Once established, bacteria and bacterial products perpetuate inflammation in the ear, either exacerbating the primary disease or maintaining clinical signs even after the underlying condition is resolved. Treatment of only the bacterial infection will result in recurrence of clinical signs if the primary disease is not managed; similarly focusing on only the primary disease without attention to the bacterial component may result in treatment failure (Figures 49-9 and 49-10).

27. What bacterial organisms are most commonly isolated from the ear canal of normal dogs and dogs with active otitis externa or media?

Mixed infections with multiple different isolates are commonly observed in clinical cases (Table 49-3). In one study of 22 dogs with otitis media the average number of isolates per case was 2.4 from the horizontal ear canal and 2.0 from the middle ear. As many as five different organisms were isolated from some patients.

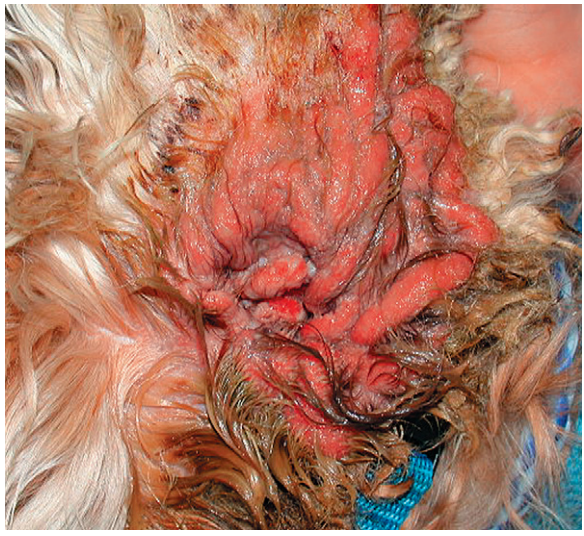

Figure 49-9 Severe purulent otitis externa in a dog.

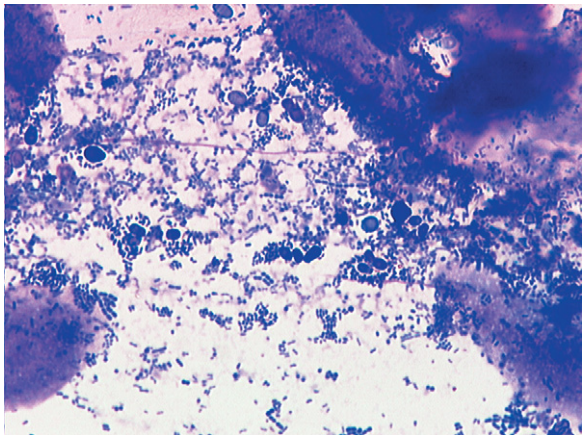

Figure 49-10 Photomicrograph of mixed bacteria seen on cytologic preparation from the external ear canal of a dog (Wright's stain).

28. Is a culture/susceptibility sample taken from the external ear canal likely to be a satisfactory predictor of species and antimicrobial susceptibility of organisms present in the tympanic cavity of a dog with otitis media/externa?

No, both species and susceptibility to antimicrobial drugs may vary significantly between cultures taken from the horizontal ear canal and the middle ear in the same patient. In fact, differences between the two locations are so common (89.5% of cases) that difference rather than similarity should be considered the norm. Likewise, isolates from one ear canal are frequently different from isolates from the other ear canal in the same patient. Because culture from the horizontal canal does not predict the species or antimicrobial susceptibility for the middle ear,

Table 49-3 *Isolates from Ear Swab Specimens*

ISOLATE	NORMAL EAR CANAL (%)	OTITIS EXTERNA (%)	OTITIS MEDIA (%)
Staphylococcus spp.	15-48	30-80	37-54
Pseudomonas spp.	2-4	4-35	35-37
Streptococcus spp.	Not reported	4-30	18-26
Proteus spp.	0-2	4-21	13-17
Escherichia coli	Not reported	3-14	5-9
Corynebacteria spp.	Not reported	1-4	2-13

rational antibiotic selection should be based on culture specimens obtained from tympanic cavity via myringotomy or bulla osteotomy.

29. Explain the role of yeast in clinical ear disease.

Malassezia pachydermatis and other *Malassezia* species are common inhabitants of normal external ear canals (Figure 49-11). The pathogenesis of yeast overgrowth and infection is similar to that of bacterial otitis externa; colonization and overpopulation occurs following alteration of the microenvironment secondary to underlying primary disease. Once established, *Malassezia* organisms stimulate an inflammatory response, which worsens or perpetuates clinical disease.

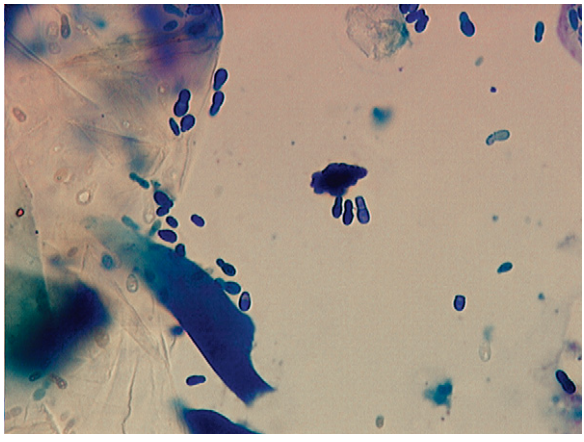

Figure 49-11 Photomicrograph of *Malassezia* spp. seen on cytologic preparation from the external ear canal of a dog (Wright's stain).

Malassezia spp. can be isolated from the horizontal canal of dogs in 65-80% of chronic cases of otitis externa, and from the tympanic cavity of dogs in 35% of otitis media cases. Although yeast and bacterial overgrowth frequently occur simultaneously, *Malassezia* alone may be the sole organism present in clinically significant otitis externa or otitis media.

30. What is the likely pathogenesis of otitis media in a dog? How does this differ from otitis media in humans?

In the majority of canine cases, otitis media is believed to result from direct extension of

otitis externa through a compromised tympanic membrane. Rarely is infection thought to occur by hematogenous route or extension from the nasopharynx.

In sharp contrast, otitis media in humans is most commonly the result of viral respiratory disease, extending to the tympanic cavity via the eustachian tube. Primary or secondary bacterial infection occurs by the same route.

31. How common is otitis media in dogs with clinical signs of otitis externa?

Otitis media may be present in 16% of acute cases and 52-83% of cases with recurrent or continuous clinical signs of otitis externa for longer than 6 months. In one study, the tympanum appeared to be intact in 71% of cases with otitis media, illustrating the important point that observation of an intact membrane does not rule out concurrent otitis media. Otitis media should be considered likely in any case of otitis externa persisting for 6 months or longer.

32. Describe four findings commonly present on cytologic evaluation of otitis externa and the significance of each finding.

1. Yeast: *Malassezia pachydermatis* is a normal inhabitant in the external canal, but overgrowth is a frequent response to primary otitis externa. Presence of large numbers of yeast warrants the addition of topical or systemic antifungal medication.
2. Bacteria: Gram-positive coccoid bacteria are normal inhabitants in the external canal, but act as a perpetuating factor in cases of overgrowth or secondary infection. While Gram-negative rods may be found in a small percentage of normal ear canals, they are more frequently associated with pathologic conditions. Identification of Gram-negative organisms in abundance indicates the need for topical or systemic antibiotic therapy.
3. Parasites: presence of any parasite is considered pathologic and requires treatment.
4. Leukocytes: White blood cells (WBCs) are not present in normal external ear canals and are less frequently found in ceruminous otitis with bacterial or yeast overgrowth. The finding of WBCs on ear cytologic studies may indicate a true infection rather than simple overgrowth, particularly if intracellular or phagocytized bacteria are seen. Thus, the finding of leukocytes on cytologic specimens indicates the need for systemic therapy in addition to topical therapy.

33. Describe the goals of ear flushing.

- Removal of debris
- Improves visualization of canal and tympanic membrane (diagnostic goal)
- Decreases organic material that provides ideal microenvironment for bacteria and yeast
- Enhances efficacy of some topical antimicrobials. Debris decreases contact, physically or by dilution, and may inactivate some antibiotics, such as polymyxin and aminoglycosides.
- Better drainage and ventilation
- Direct antimicrobial activity of flushing agent
- Astringent action displaces water after swimming or bathing, which could predispose patients to bacterial or yeast overgrowth.

34. What are the characteristics of an ideal ear-cleansing agent?

- Effective at removing tenacious, waxy debris
- Non-irritating to epithelial lining of external and middle ear
- Non-toxic to inner ear (cochlea and vestibular apparatus)
- Leaves no residue
- Leaves the canal dry
- Directly inhibits or kills microorganisms
- Acts synergistically with, or at least does not antagonize, other otic medications
- Inexpensive enough for owners and veterinarians to use liberally

35. Discuss the advantages and disadvantages of available antiseptic cleansing agents.

Using an antiseptic cleaner has several advantages, including direct inhibition of microorganisms, synergism with topical antibiotics (TrisEDTA), and prolonged duration of action (acidifying agents). However, there are potential disadvantages, such as irritation of tissues (povidone-iodine, ethanol, isopropyl alcohol, and weak acids), ototoxicity (chlorhexidine, benzalkonium chloride, povidone-iodine), and potential inhibition of antibiotics (aminoglycosides and fluoroquinolones in low pH). Knowledge of the specific properties of individual ingredients should be applied to rational selection of appropriate ear cleaning products.

The largest group of antiseptic cleaning agents focuses on acidifying the ear canal. Examples of acidifying agents include acetic acid, boric acid, malic acid, lactic acid, salicylic acid, and benzoic acid. Many commercially available solutions contain two or more different acids. The general concept of these agents is that *Malassezia* spp. and most bacterial isolates do not thrive in acidic conditions. Large, rapid changes in pH may be directly fungicidal and bactericidal for some isolates. In other cases, organisms are weakened or have decreased reproduction. However, most of the common organisms found in normal and infected ears can thrive at a wide range of pH if they are allowed to acclimate to pH changes gradually. Because it is unlikely that 100% of organisms are eliminated during initial treatment; theoretically, the remaining organisms can adapt to new pH environment with repeated therapy over a long time. In addition, two common classes of topical antibiotics, aminoglycosides and fluoroquinolones, have decreased efficacy in an acidic environment. However, because topical application of antibiotics frequently exceeds minimum inhibitory concentrations, the altered function in acidic environment may not be clinically relevant. Acidifying agents are used routinely as the preferred agent for most cases of *Malassezia* otitis and susceptible bacterial infections.

Chlorhexidine has activity against yeast and bacteria and these organisms do not develop resistance to chlorhexidine over time. However, chlorhexidine can be toxic to cochlear and vestibular hair cells. Experimental studies have failed to induce ototoxicity in normal dogs, but deafness is reported in clinical cases of otitis externa/media. In most cases loss of function is immediate. Additionally, chlorhexidine can cause fibrosis and ossification of the tympanic bullae if left in the middle ear for prolonged periods. Consequently, the U.S. Food and Drug Administration has eliminated chlorhexidine from human otic preparations, and veterinarians should use available products with caution if the tympanic membrane is ruptured or if patency is not known.

TrisEDTA is an antiseptic solution that works at an alkaline pH; and therefore may be an appropriate selection when therapy includes topical aminoglycoside or fluoroquinolone antibiotics. TrisEDTA is a chelating agent that binds the divalent cations (magnesium and calcium) in the cell membrane of bacteria. This effect compromises the barrier function of the cell wall, increasing permeability to intracellular antibiotics (e.g., tetracycline, chloramphenicol, aminoglycosides, and fluoroquinolones), while acting synergistically with antibiotics that target the bacterial cell wall (e.g., penicillins and cephalosporins). TrisEDTA also inactivates P-glycoprotein pumps in the cell wall of gram-negative bacteria, a mechanism for antibiotic resistance to fluoroquinolones. Consequently the principal use of TrisEDTA is in combination therapy with systemic and topical antibiotics during the management of resistant bacterial infections.

36. What role do ceruminolytic agents have in the management of otitis externa?

Ceruminolytic cleansers are typically detergents or surfactants designed to break up and remove waxy, hydrophobic debris. Impacted cerumen may occlude the deep canal, resisting flushing, or liquid cerumen and purulent exudates may cling tenaciously to the canal and tympanum, resisting removal by flushing or curette. Examples of commonly used ceruminolytics include squalene, propylene glycol, dioctyl sodium sulfosuccinate (DSS), and toluene. While ceruminolytic agents are useful for removing debris, caution must be exercised when the tympanic membrane is compromised. Except for squalene, all ceruminolytic agents are potentially ototoxic or may result in severe inflammation of the respiratory epithelium lining the tympanic cavity. Potent detergents left in the middle ear can be tremendously damaging. When performing an ear

cleaning under general anesthesia, ceruminolytics can be used first to remove tenacious debris, followed by thorough rinsing to remove any remaining detergent. In general, potent agents should be used only in the veterinarian's office if the tympanum is compromised or its condition is unknown. If ceruminolytics are sent home, the owners should be instructed to follow ceruminolytic treatment by flushing with copious amounts of a second less-toxic flushing agent.

37. List the clinical indications for otoscopy and deep ear cleaning under full anesthesia.

- Suspected foreign objects
- Severe acute otitis
- Purulent otitis
- Vestibular symptoms
- Horner's syndrome
- Chronic or recurrent otitis
- Suspected otitis media

38. What precautions should always be taken during ear flushing of an anesthetized patient?

Always check the endotracheal tube for a functional cuff. If the tympanic membrane is ruptured, fluid from the flush, mixed with bacteria and debris, may pass into the nasopharynx via the eustachian tube. Without a good seal around the endotracheal tube the fluid could cause a chemical pneumonitis or bacterial pneumonia. Note: Deeply sedated patients may lose the gag reflex. For this reason, full anesthesia and a controlled airway are preferred to sedation during ear cleaning procedures.

Liberally apply sterile eye lubricant to protect the cornea from fluid run-off from the flush procedure. Ceruminolytic and acidifying agents could irritate the cornea or cause an iatrogenic corneal ulcer. This also helps avoid accidental exposure to *Pseudomonas* spp. and other bacteria.

39. What are the potential complications of overaggressive or inattentive ear flushing under anesthesia?

- Rupture of tympanum and subsequent otitis media
- Excessive pain
- Horner's syndrome. Cats are especially prone to this complication (see Question 11)
- Vestibular signs (head tilt, nystagmus, and ataxia)
- Deafness (idiosyncratic ototoxicity)
- Bacterial otitis interna via damage to the oval or round windows
- Iatrogenic pneumonia (see Question 38)
- Iatrogenic corneal abrasion, ulceration, or infection (see Question 38)

40. List common classes of topical therapeutic agents and examples of each class.

Most commercial veterinary otic preparations are combinations of an antibiotic, antifungal agent, and glucocorticoids (Table 49-4). For select antibiotics, off-label usage of ophthalmic drops in the external ear canal is necessary when no otic preparation is available.

Table 49-4 ***Commonly Used Treatments***

CLASS	EXAMPLES
Antibacterial	Gentamicin, neomycin, polymyxin B, enrofloxacin, ciprofloxacin, chloramphenicol, ticarcillin, tobramycin, silver sulfadiazine
Antifungal	Thiabendazole, nystatin, clotrimazole, miconazole, silver sulfadiazine
Antiinflammatory	Hydrocortisone, prednisone, dexamethasone, triamcinolone, fluocinolone, betamethasone
Parasiticidal	Pyrethrins, organophosphates, thiabendazole, ivermectin, milbemycin, selamectin (applied transcutaneously, not directly to ear canal)
Anesthetic	Tetracaine, benzocaine, proparacaine

41. What are some special considerations when selecting an aminoglycoside for topical therapy?

- Inactivated by large amounts of organic debris → Avoid in cases with copious ceruminous or purulent exudate.
- Decreased efficacy in acidic conditions → Use in combination with TrisEDTA solution (pH = 8.0) rather than acidifying ear flush solutions.
- May be ototoxic → Use with caution in animals with compromised tympanic membranes, or avoid entirely.
- Neomycin is a potential contact sensitizing agent and may result in local contact dermatitis → Switch to different product if initial improvement gives way to worsening inflammation.

42. What guidelines should be followed when applying topical glucocorticoids?

Glucocorticoids are an important component of therapy for acute otitis and for maintenance therapy for chronic otitis externa. Milder anti-inflammatory actions of hydrocortisone may be appropriate for symptomatic management of patients with otic pruritus and minimal physical changes. More potent glucocorticoids, such as betamethasone, triamcinolone, and fluocinolone, should be used in severely affected patients. The immediate benefits are associated with decreased edema, decreased cerumen production, decreased purulent exudate, and decreased pain or pruritus. Longer courses of therapy are required to decrease proliferative changes in the external canal. All potent topical glucocorticoids will absorb systemically, resulting in elevations in liver enzyme levels and suppression of the hypothalamic-pituitary-adrenal axis. Therefore use should be limited to short courses whenever possible. In general, use of topical therapy should follow the same guidelines as oral or injectable glucocorticoids: avoid prolonged courses, switch to alternate-day protocols, use with caution in patients sensitive to glucocorticoid effects such as patients with diabetes mellitus, demodicosis, or history of calcium oxalate uroliths.

43. Discuss miticidal therapy for management of *Otodectes cynotis*.

There are numerous agents, routes, and protocols for treatment of ear mites in dogs and cats. Regardless of which method is selected, in order to be effective, therapy should: (1) treat all in-contact animals regardless of clinical signs, (2) take into account adult mites traveling on haired skin outside the ear canal, and (3) continue beyond the length of the full life-cycle (approximately 21 days). *O. cynotis* is a relatively easy to kill parasite; treatment failure generally results from failure to identify and manage sources of reinfestation.

44. Define ototoxicity and discuss this complication to otic therapy.

Ototoxicity refers to damage to cochlear or vestibular functions as the direct result of therapeutic agents, either systemic or topical. Loss of function may be unilateral, bilateral, partial, temporary or permanent. Aminoglycosides, the most commonly implicated ototoxic agent, are directly toxic to hair cells of the cochlea and vestibular apparatus, resulting in either deafness or vestibular signs. In experimental studies of normal dogs, aminoglycoside infused directly into the middle ear failed to reliably produce ototoxic reactions, leading to speculation that inflammation may affect permeability of the round or oval windows. In clinical practice, ototoxic reactions to topical therapy appear to be unpredictable and idiosyncratic. Aminoglycoside agents and other known ototoxic preparations are frequently used in cases with known or undiagnosed ruptures of the tympanic membrane, without causing deafness or vestibular dysfunction; in other cases ototoxicity may become manifest after a single application in dogs with mild disease and apparently intact membranes. Toxicity to hair cells is known to be dependent on concentration of aminoglycosides in the perilymph of the inner ear. Explanations for the observation of variable toxicity may include individual differences in sensitivity to aminoglycosides or variation in diffusion, metabolism, or elimination of the agent from the inner ear. Nevertheless, practitioners should remain cautious in all cases of known or suspected compromise of the tympanic membrane.

45. What is the role of systemic antibiotics in treatment of otitis externa?

Systemic antibiotics are appropriate for patients with suspected or proven otitis media, severe acute suppurative otitis externa, or chronic otitis with extension into para-aural soft-tissue. Antibiotic therapy should be continued for at least one week beyond clinical resolution of bacterial infection; 6-12 weeks of continuous therapy is commonly required. Because of difficulty reaching target organisms in the canal lumen and the tympanic cavity, antibiotics should be given at the high end of the dosage range. In general, antibiotic selection, dosage, frequency, and duration that would be appropriate for management of osteomyelitis would be appropriate for management of otitis media.

Because of the frequency of mixed infections and the presence of organisms with unpredictable susceptibility patterns, whenever possible antibiotic selection should be based on antimicrobial susceptibility results obtained from cultures of the middle ear. Cultures obtained from the external ear canal are less valuable, as substantial differences in the species and susceptibility patterns may exist between isolates from the external canal and isolates from the tympanic cavity. See Table 49-5 for reported antibiotic susceptibility patterns of the two most common bacterial isolates from otitis externa.

Table 49-5 ***Percentage of Common Isolates Susceptible to Routinely Available Oral Antibiotics***

ORGANISM	50%	50-90%	>90%
S. intermedius	Ampicillin Penicillin Trimethoprim-sulfadiazine	Cephalothin Clindamycin Enrofloxacin Erythromycin Tetracycline	Amoxicillin–clavulanic acid Chloramphenicol
Pseudomonas spp.	Enrofloxacin	None	None

46. Should systemic glucocorticoids be used to manage inflammation localized to the external ear canal?

Mild inflammatory or infectious conditions do not require systemic therapy and can be treated with topical glucocorticoids in combination with other appropriate therapies. However,

Table 49-6 ***Proposed Benefits of Systemic Glucocorticoid Therapy***

ACTION	RESULT	BENEFIT
Inhibition of vasodilation and capillary leakage	Reverse tissue edema	More open canal Reduction of pain
Suppression of cerumen gland activity	Less cerumen production Decreased hyperplasia	Less organic debris More open canal
Inhibition of leukocyte recruitment	Fewer neutrophils and eosinophils in tissue and canal lumen	Reduction of pain Less organic debris Decrease tissue damage by excess inflammatory mediators
Inhibition of tissue proliferation	Less epidermal hyperplasia Less fibrosis	Reversal of chronic proliferative changes

systemic glucocorticoids have a vital role in successful management of severe acute otitis externa and chronic proliferative otitis externa. In severe cases, the canal lumen may be completely occluded by edema, preventing diagnostic otoscopy or therapeutic flushing even under anesthesia. Prescribing relatively high doses of prednisone (1.1-2.2 mg/kg orally every 24 hours) for 3-5 days will reverse edema, open the canal, and greatly enhance the value of the procedure postponed to a later date. For owners attempting to clean painful ears at home the immediate benefits of glucocorticoids are reduction of pain, opening of the canal, and reduction of purulent and ceruminous debris. Higher doses and longer therapy may be necessary to reverse chronic proliferative changes, such as epidermal proliferation and glandular hyperplasia. Glucocorticoids will not reverse permanent changes such as calcification and long-standing fibrosis.

Glucocorticoids have numerous benefits that contribute to immediate and long-term improvement in patient condition, but should never be used to relieve symptoms at the expense of diagnosis and treatment of primary conditions. See Table 49-6.

47. Compare and contrast the indications, goals, and common complications of lateral ear canal resection and total ear canal ablation.

See Table 49-7.

Table 49-7 *Resection vs. Ablation*

	LATERAL EAR CANAL RESECTION	TOTAL EAR CANAL ABLATION
Indications	Anatomic deformity or obstructive changes to the vertical canal Benign neoplasia of the vertical canal	Irreversible changes to the horizontal canal Neoplasia
Goals	Improved ventilation Improved drainage of exudates Facilitate cleaning and topical therapy	Alleviate chronic pain Eliminate nidus of chronic infection Adequate margins for neoplasia of ear canal
Complications	Fails to resolve clinical signs Progressive changes involve horizontal canal	Change in appearance in breeds with erect pinnae Loss of hearing Facial nerve dysfunction Vestibular dysfunction Draining fistula

48. What factors affect postoperative complications of surgical procedures?

The most common reason for complications is the failure to identify and treat the primary cause of the disease. Lateral ear canal resection does not treat atopy, food allergy, hypothyroidism, etc., and therefore should not substitute for proper diagnosis and management of otitis externa.

Chronicity and severity may play a role in recovery, especially if inflammation, proliferation, and dystrophic calcification entrap the facial nerve running near the junction of the external canal and tympanic cavity.

Surgical technique is the most important factor in determining outcome. Poor attention to detail and rough handling of tissues may worsen facial nerve and vestibular complications. Contamination of surrounding tissue by debris may result in spread of bacterial infection. The frustrating complication of a draining fistula is most often associated with incomplete removal of secretory epithelium of the horizontal canal and tympanic cavity, rather than with inability to resolve infection.

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Section IX
Tumors of the Skin

50. NON-NEOPLASTIC TUMORS

Thomas O. *Manning*, DVM, MS, DACVD
Brett C. *Wood*, DVM

1. What is a cyst?
- A cyst is a nodule that contains semisolid material (Figure 50-1).
- A cyst is a saclike structure with an epidermal lining or the cells of the structure from which it developed (Figure 50-2)
- A cyst is non-neoplastic.

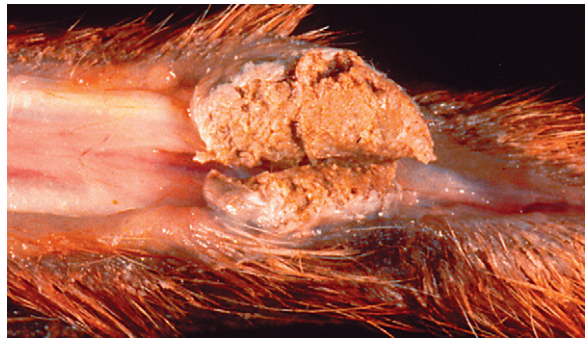

Figure 50-1 Epidermal cyst on the ventral tail of a dog.

2. What is an infundibular (epidermal/epidermoid) cyst?
- This type is a simple cyst lined by stratified squamous epithelium.
- All four layers of the normal epidermis are present including the granular cell layer.

3. How does an infundibular cyst clinically present itself?
- A cyst is usually present within the dermis; however, large cysts may extend into the panniculus.
- Cysts are solitary or multiple. They are usually unilocular.
- The cornified cells that occupy the cyst are found as basketweave (loose) or compact (tight) orthokeratotic cells.
- The cyst must be entirely removed because rupture will evoke a granulomatous reaction to the keratin; incomplete removal is the usual cause of a postsurgical recurrence.

4. How do endogenous "foreign" bodies cause granulomas?

Endogenous substances produce a granulomatous reaction whenever there is exposure to tissues that normally enclose them. An example of this is when an epidermal cyst wall ruptures

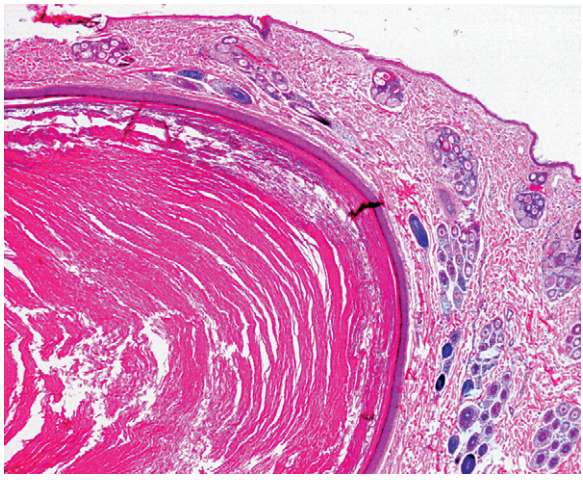

Figure 50-2 Photomicrograph of a follicular cyst in canine skin. (H&E, ×100.)

and its keratin contents come in contact with the dermis. The most common cause of foreign body reactions in the dog is rupture of hair follicles.

5. **What is an isthmus cyst?**
   - An isthmus cyst is lined by cells that resemble the middle area of an anagen hair follicle or the lower segments of a catagen hair follicle.
   - An isthmus cyst is lined by stratified squamous keratinizing epithelium, without a granular cell layer.
   - The cyst contents are typically less eosinophilic and not as compacted (laminar) as those of an infundibular cyst.

6. **What type of epidermal cells makes up the cyst lining of a panfollicular (trichoepitheliomatous) cyst?**
   - The wall is made up of stratified epithelium with foci similar to infundibular and isthmus cysts.
   - However, a third type of cell lining the wall consists of primitive, small basophilic cells that demonstrate abrupt keratinization. Intracytoplasmic trichohyalin granules can be found between zones of infundibular and matrical keratinization.
   - These cells may develop into trichoepitheliomas.

7. **What is matrical keratinization?**
   Anatomic tissue of origin from which a structure develops, that is, hair matrix, claw matrix, hair follicle isthmus.

8. **What are dermoid cysts?**
   Dermoid cysts are congenital dermal and/or subcutaneous cysts lined by epidermis with mature dermal and appendage (follicular, glandular, etc.), structures in the cyst wall.
   In human medicine dermoid cysts are also known as pilonidal cysts.

9. **Where are dermoid cysts most commonly found in animals?**
   Dorsal midline of young animals.

10. What other condition has been associated with dermoid cysts in Rhodesian Ridgebacks?

The cystic lesions commonly extend to the level of the subarachnoid space and thus predispose the dogs to meningitis.

Dermoid cysts in Rhodesian Ridgebacks should be evaluated with contrast radiography (fistulography and/or myelography) to assess for communication with the subarachnoid space. If there is communication noted, then surgical excision should be considered and in most cases is curative.

11. Are dermoid cysts as common as follicular cysts?

Dermoid cysts are rarely observed in dogs and cats. They are developmental anomalies and are often congenital and hereditary. Most commonly reported in:

- Boxers
- Kerry Blue Terriers
- Rhodesian Ridgebacks

12. Dermoid cysts are inherited abnormality in which of the following breeds?

(a) Rhodesian Ridgeback
(b) German Shepherd
(c) Weimaraner
(d) Rottweiler

Correct answer is (a) Rhodesian Ridgeback

13. What are sebaceous duct cysts?

Cysts located in the dermis. The cyst wall is made up of basaloid cells and squamous cells (sebaceous duct). The inner lining of the cyst is brightly eosinophilic and corrugated. Around the cyst are hyperplastic sebaceous glands.

14. What are apocrine cyst(s)/apocrine cystomatosis?

- Solitary or multiple cysts that are filled with clear secretion.
- The cyst is lined with a single layer of apocrine secretory epithelium. This epithelium may demonstrate function (decapitation), however, these cells often become nonfunctional due to pressure atrophy.
- Multiple cysts at multiple sites are called apocrine cystomatosis.
- Clinically these cysts often have a "blue" color (Figures 50-3 to 50-5).

Figure 50-3 Apocrine cysts and calcinosis cutis in a English Bulldog with hyperadrenocorticism.

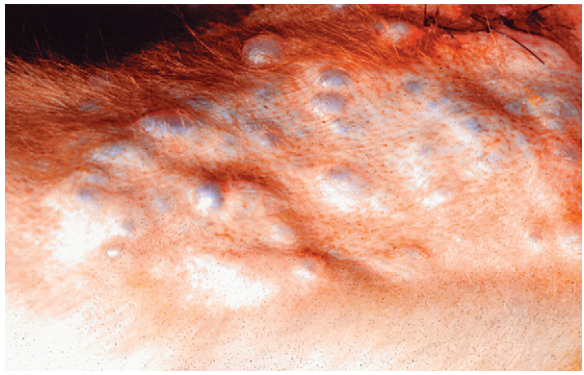

Figure 50-4 Apocrine cystomatosis in a dog.

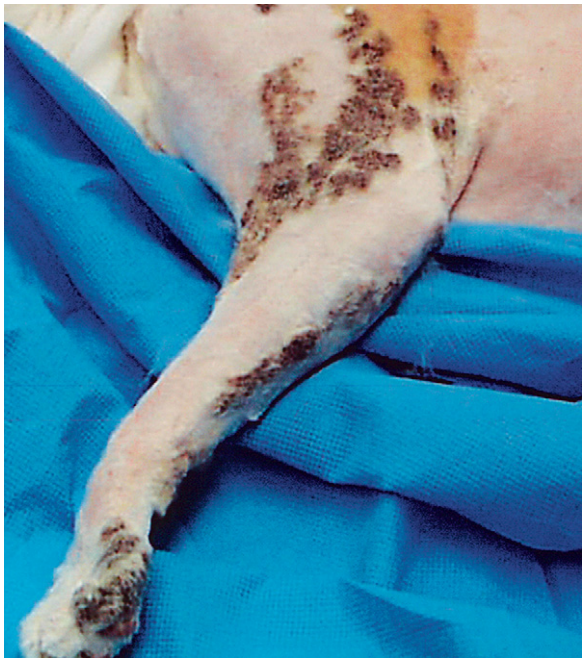

Figure 50-5 Apocrine papillary cystadenomas on the shoulder and foreleg of a domestic shorthaired cat.

15. What type of structure is found surrounding a subungual epithelial inclusion cyst?

The subungual epithelial inclusion cyst is identical to the infundibular cyst, but is surrounded by the bone of the third phalanx.

16. Rupture of a subungual epithelial inclusion cyst evokes a granulomatous response. What important differential diagnoses should be on your list of masses associated with the digit?

- Melanoma
- Squamous cell carcinoma
- Foreign body reaction
- Deep bacterial/fungal infection and the like

17. What is the most common matrical or tissue matrix source of cutaneous cysts in the dog?

The majority of cutaneous cysts in the dog and cat are follicular in origin and may be further categorized by the level of the follicle from which they develop.

- Infundibular: common (dog), uncommon (cat)
- Isthmus: catagen (trichilemmal) – common (dog), uncommon (cat)
- Matrical: uncommon (dog), rare (cat)
- Hybrid: uncommon (dog), uncommon (cat)

18. Where do follicular cysts most commonly occur?

- Head
- Neck
- Trunk
- Proximal limbs

19. What breeds of dog may be predisposed to follicular cysts?

- Boxers
- Doberman Pinschers
- Shih Tzus
- Miniature Schnauzers

20. What is the most common location of multiple congenital follicular cysts?

- Dorsal midline of young dogs
- Thought to be associated with trauma, fibrosis, and obstruction of affected follicle openings.
- Pressure points (especially elbows)

21. What is an epitrichial cyst?

Apocrine sweat gland cyst.

22. Where do Persian and Himalayan cats commonly get apocrine gland cysts?

- Multiple apocrine gland cysts occur on the eyelids of these breeds of cats.
- Both eyelids are usually involved in affected cats.
- The medial canthus may also be involved.

23. How common are sebaceous gland cysts in the dog and cat?

These are rare in dogs and cats.

24. What is a hamartoma?

- A mass of disorganized but mature specialized cells or tissue
- Cells/tissue are indigenous to the particular site where they were found.
- However, the mass is an abnormal amount of tissue.

25. Why do we use the term hamartoma?

Hamartoma is the preferred term to describe these lesions, rather than the more common term *nevus*.

We hope to avoid possible confusion with the melanocytic cells that make up the pigmented lesions referred to as nevi in man.

26. When are hamartomas recognized as clinical entities?

- Hamartomas are congenital.
- Many are not clinically diagnosed until later in life.

27. How are hamartomas classified in veterinary literature?

Scott DW, Miller WH, Griffin CE: *Muller & Kirk's small animal dermatology*, ed 6. Philadelphia, 2000, WB Saunders:

- Collagenous nevi
- Organoid nevi
- Epidermal nevi
- Hair follicle nevi

- Vascular nevi
- Sebaceous gland nevi
- Epitrichial (apocrine) sweat gland nevi
- Comedo nevi
- Pacinian corpuscle nevi
- Melanocytic nevi

Goldschmidt MH, Dunstan RW, Stannard AA, von Tscharner C, et al: Histological classification of epithelial and melanocytic tumors of the skin of domestic animals, AFIP, Am Reg Pathol WHO (Series 2), vol 3, Washington, DC, 1998:

- Epidermal hamartoma (pigmented epidermal nevus)
- Follicular hamartoma
- Sebaceous hamartoma
- Apocrine hamartoma
- Fibroadnexal hamartoma (adnexal nevus, focal adnexal dysplasia, folliculosebaceous hamartoma)

28. Is there a form of multiple collagenous hamartomas in the dog that is associated with renal disease and neoplasia?

- Yes, in German Shepherd Dogs (Figure 50-6)
- Syndrome is referred to as nodular dermatofibromas and includes multiple, spontaneous, symmetrically distributed collagenous hamartomas that often develop in dogs between the ages of 3 and 7 years old.
- The lesions most frequently develop on the head, neck, and extremities.
- Affected German Shepherd Dogs virtually always develop bilateral renal disease that may be polycystic kidneys or renal cystadenocarcinomas.
- Intact females consistently develop multiple uterine leiomyomas.
- Syndrome is autosomal dominant in inheritance.

29. In what other breeds has this disorder been reported?

- Golden Retrievers
- Boxers
- German Shepherd Dog crosses
- Mixed breeds

30. Is adnexal dysplasia identical to organoid hamartomas?

- These two conditions may or may not be identical.
- Adnexal hamartomas are usually not inflamed, and the hyperplastic adnexal structures maintain a normal anatomic orientation.
- Focal adnexal dysplasia is usually inflamed with fibrosis and is characterized by a bizarre configuration of the adnexal structures (Figure 50-7).
- These lesions are generally solitary, firm, and well circumscribed.
- The distal limbs (pressure points and digits) are most commonly affected.
- Affected dogs are usually middle age or older.
- No gender predilection
- Doberman Pinschers and Labrador Retrievers are predisposed.

31. Are all hamartomas nodular?

No. Epidermal and organoid hamartomas may be linear. They may follow Blaschko's lines, which are the pattern of lines separating skin surface areas supplied by individual peripheral nerves.

32. What is a melanocytic hamartoma ("melanocytic nevus")?

The term "melanocytic nevus" has been adapted for use in veterinary medicine; however, most of these lesions are acquired and should be called "melanocytomas." Congenital melanocytic hamartomas are rarely recognized in animals.

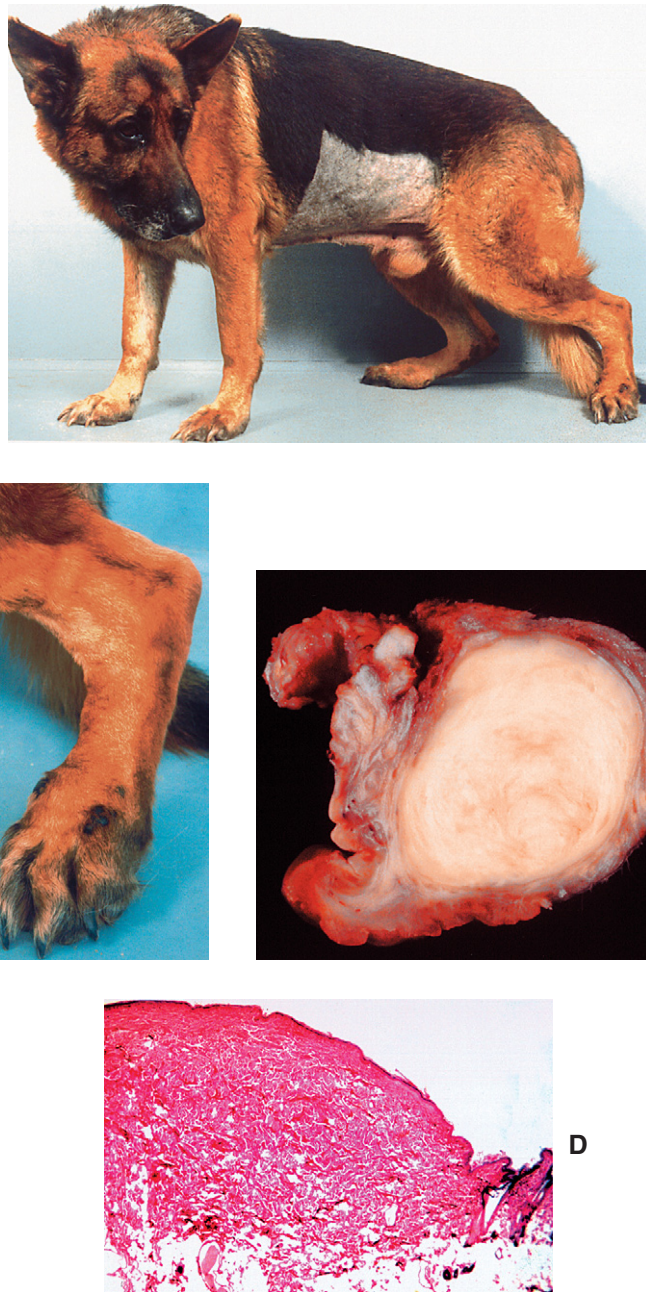

Figure 50-6 **A,** German Shepherd Dog with nodular dermatofibrosis associated with a renal cyst adenocarcinoma. **B,** Closeup of the lesions of nodular dermatofibrosis on the rear leg. **C,** Section through one of the lesions of nodular dermatofibrosis. **D,** Photomicrograph of nodular dermatofibrosis. (H&E, ×100.)

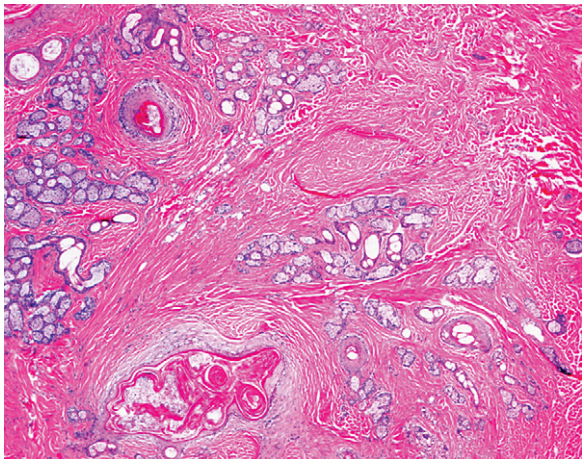

Figure 50-7 Photomicrograph of adnexal dysplasia in canine skin. (H&E, ×100.)

33. Name four tumors or tumor-like lesions that are cystic and may have central pores.
- Intracutaneous cornifying epithelioma (ICE, also termed "infundibular keratinizing acanthoma" and "keratoacanthoma")
- Pilomatrixoma
- Trichofolliculoma
- Dilated pore of Winer

34. What are other tumor-like lesions (keratoses) that have been found or reported in veterinary medicine ?
- Squamous papilloma
- Pressure point comedones
- Cutaneous horn
- Warty dyskeratoma
- Sebaceous hyperplasia (senile nodular sebaceous hyperplasia)
- Fibroepithelial "polyp" (cutaneous tag, skin tag, acrochordon)
- Fibropruritic nodule
- Acral lick granuloma

35. How should cutaneous horns be managed?
- Excise with wide surgical margins
- Submit the cutaneous horn for histologic examination. Some cutaneous horns grow from a malignant neoplasia base, for example, squamous cell carcinoma.

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51. EPITHELIAL NEOPLASMS

Laura B. Stokking, PhD, DVM

1. What cell types are involved in epidermal neoplasia?

- Keratinocytes
- Melanocytes
- Langerhans cells
- Merkel's cells

These are the four main cell types normally found in the epidermis. This chapter focuses on tumors of Merkel's cells and keratinocytes. Melanocytic neoplasms are presented in Chapter 56 and tumors derived from Langerhans cells are discussed in Chapter 55.

2. What are Merkel's cells? What neoplasms arise from these cells?

Merkel's cells are neuroendocrine dendritic cells that act as slow-reacting mechanoreceptors and also function in cutaneous circulation, sweat production, keratinocyte proliferation, and the hair cycle. Merkel's cells lie either immediately below or within the basal cell layer of follicular epithelium and tylotrich pads; the cells have desmosomal connections with adjacent keratinocytes. Merkel's cells are distinguished morphologically from other cutaneous cells by the presence of a large cytoplasmic vacuole that displaces the nucleus. In humans, Merkel cell carcinoma is a rare, biologically aggressive tumor. Local recurrence and distant metastases are common despite *en bloc* surgical excision and concurrent radiation therapy. Cutaneous neuroendocrine tumors in dogs and cats probably arise from Merkel's cells. These neoplasms are rare and develop either within the dermis or the epidermis. Most canine cutaneous neuroendocrine tumors are malignant and readily metastasize; however, benign neoplasms for which radical surgical excision is curative do occur. In contrast, most feline cutaneous neuroendocrine tumors are benign, although a malignant Merkel cell tumor has been reported in an aged Maine Coon Cat. Differential diagnoses in all species include basal cell neoplasms, histiocytoma, plasmacytoma, amelanotic melanoma, and epitheliotropic lymphoma.

3. How does ultraviolet radiation lead to epidermal neoplasia?

Ultraviolet (UV) radiation can cause epidermal neoplasia by several direct and indirect mechanisms, including inhibition of DNA repair mechanisms by the formation of pyrimidine dimers, production of free radicals, purine photoproducts, stimulation of enzymes that act in tumor promotion, inflammation, immunosuppression, stimulation of angiogenesis and growth factor production, or co-factor with other types of radiation, viruses, or chemicals. Dimer-related mutations in the *p53* tumor suppression gene facilitate the development of squamous cell carcinoma (SCC) and basal cell carcinoma (BCC) in humans. In humans, development of actinic keratoses, SCC, and melanoma is associated with long-term exposure to UV radiation, whereas the development of basal cell carcinoma (BCC) results from episodes of intense exposure, such as blistering sunburn. Although the most reactive wavelengths are within the UVB band (290-320 nm), radiation within the UVA range (320-400 nm) is also carcinogenic.

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4. What is actinic keratosis? What are the differential diagnoses for these lesions?

Keratosis is a proliferation of reactive keratinocytes; actinic keratosis results from reactions to ultraviolet radiation. Actinic keratosis occurs in sun-exposed areas of glabrous or thinly haired, unpigmented skin. The lesions are singular or multiple and can vary in appearance from slightly erythematous patches of scale to thickened, keratotic, erythematous to pigmented plaques up to several centimeters in diameter. Microscopically, the epidermis is hyperplastic and dysplastic, with a loss of orderly keratinocyte maturation and normal stratification. Abnormal cells do not extend below the basement membrane; dermal invasion signifies progression to SCC. In humans, approximately 12% to 13% of untreated solar keratoses progress to SCC.

Middle-aged to older, light-colored dogs and cats with a propensity to sunbathe develop actinic keratosis most commonly. Canine breeds at particular risk include American Staffordshire Terriers, Beagles, Basset Hounds, and Whippets. No gender predilection has been demonstrated. Normal window glass does not protect against ultraviolet radiation, thus indoor cats that sunbathe are also at risk.

Differential diagnoses in dogs include solar-induced SCC, discoid lupus erythematosus (DLE), cutaneous hemangiomas or hemangiosarcomas, and superficial or deep bacterial folliculitis and furunculosis. Differential diagnoses in cats include solar-induced SCC, DLE, and pemphigus foliaceus.

5. What are risk factors for SCC?

SCC makes up about 15% of feline and 5% of canine cutaneous neoplasia. Older animals are at increased risk; the mean age in felines is 12 years and in canines is 8 years, although tumors can occur in cats as young as 1 year of age. As in humans, SCC in dogs and cats is associated with solar exposure and may progress from actinic keratoses; risk factors for actinic keratoses therefore also predispose to SCC. SCCs commonly occur in sun-exposed sites, including the eyelids, nares, and pinnae of white-faced cats, and the nailbeds, ventral abdomen, scrotum, nose, and legs of shorthaired, light-colored dogs. The incidence of SCC in white cats is reported to be 13.4 times that in nonwhite cats. As in humans, incidence is higher in geographic locations that receive long durations of intense solar radiation. Indoor cats are not protected from solar exposure: window glass is not an effective filter against ultraviolet radiation. Association with *p53* gene mutation has been identified in feline SCC. Solar-induced SCC is most common in light-colored or thinly haired areas of Beagles, Basset Hounds, American Staffordshire Terriers, Dalmatians, and Bull Terriers. Genetic predisposition is a risk factor in certain canine breeds. SCC unrelated to solar exposure has an increased incidence in the Scottish Terrier, Pekingese, Boxer, Poodle, and Norwegian Elkhound. Subungual SCC is prevalent in black Labrador Retrievers, black Standard Poodles, Bouvier des Flandres, Giant Schnauzers, and Dachshunds. About 75% of subungual SCC occurs in large dogs; approximately 66% of cases develop in black-coated dogs such as Standard Poodles or Labrador Retrievers. Viral infection can be a factor in the development of SCC; several different papillomaviruses in dogs (Table 51-1) and the recently identified feline papillomavirus

Table 51-1 ***Summary of Canine Papillomas***

TYPE	CLINICAL FEATURES	HISTOPATHOLOGIC FEATURES	ETIOLOGY
Canine oral papillomatosis (exophytic papilloma)	Single or multiple papillated masses on face and/or oral mucosa, occasionally other sites	Projections or fronds of heavily keratinized squamous epithelium; may contain giant keratohyalin	Canine oral papillomavirus (COPV)

Table 51-1 ***Summary of Canine Papillomas—Cont'd***

TYPE	CLINICAL FEATURES	HISTOPATHOLOGIC FEATURES	ETIOLOGY
	Typically <1 cm in diameter Generally regress spontaneously	granules and koilocytes; intranuclear inclusions	
Verruca plana	Flat warts Papules to plaques on face and/or oral mucosa, generally <0.5 cm in diameter	Keratohyalin granules, koilocytes, intranuclear inclusions	May represent regression of exophytic papillomas
Cutaneous papilloma	Older male dogs, Cocker Spaniels, Kerry Blue Terriers Typically <0.5 cm in diameter Smooth to papillomatous, pedunculated		Papillomavirus positive
Cutaneous inverted papilloma	Multiple, raised, firm masses with a central pore, usually on ventral abdomen, <2 cm diameter	Flask-shaped core of keratin opening to umbilicated surface, poorly defined intranuclear inclusions	Papillomavirus positive (not COPV)
Footpad papillomas	Generally present on multiple footpads, paws; hyperkeratotic		Undetermined
Pigmented epidermal plaques (PEP)	Darkly pigmented, multiple, hyperkeratotic, papillomatous, waxy macules, papules, plaques; on head, neck, trunk, and limbs Typically progressive	Exophytic; abundant, enlarged keratohyalin granules, intranuclear inclusion bodies	Genetic predisposition (Pugs, Miniature Schnauzers, Chinese Shar Peis) Association with immuno-suppression, papillomavirus positive (not COPV)
Pigmented papules	Round to coalescing, pigmented papules ≤2 mm; ventral abdomen	Endophytic, keratohyaline granules rare, intracytoplasmic and intranuclear inclusion bodies	Papillomavirus positive (not COPV, not PEP)

are associated with malignant transformation to SCC. The link between SCC and feline leukemia virus (FeLV) or feline immunodeficiency virus (FIV) is not clear; approximately 25% of FIV-positive cats in a California study developed SCC. Chronic lesions, including otitis externa, burns, scars, follicular cysts, and poorly controlled nasal lesions in dogs with DLE can progress to SCC. Chemical carcinogens, such as arsenic, hydrocarbon, psoralens, nitrogen mustard, lead to SCC in mice and humans, so are probable predisposing factors in feline and canine SCC as well.

6. How is SCC diagnosed?

Accurate diagnosis of SCC requires histopathology. Differential diagnoses include those listed for actinic keratosis, along with other infectious or inflammatory dermatoses (Question 7). Distinction between actinic keratosis and SCC requires microscopic examination to detect cytologic characteristics of malignancy and abnormalities of tissue architecture, such as invasion of neoplastic cells beneath the basement membrane into the underlying dermis.

7. What are differential diagnoses for well-circumscribed ulcerative dermatosis of the skin and mucocutaneous junctions of the face of a cat?

- Hypersensitivity: indolent ulcer, contact
- Neoplasia: squamous cell carcinoma, mast cell tumor, epitheliotropic cutaneous lymphoma
- Infectious causes of ulcerative stomatitis and cheilitis:
  - Viral: FeLV, FIV, feline pox virus, feline herpes virus-1, calicivirus
  - Bacterial infections
  - Fungal infections: candidiasis, systemic mycoses
- Metabolic disease: uremia
- Immune-mediated disease: pemphigus vulgaris, systemic lupus erythematosus, drug reactions
- Thermal or electrical burns
- Periodontal disease
- Idiopathic plasmacytic stomatitis

8. What ancillary diagnostic tests should be performed in cases of SCC?

SCC is slow to metastasize, but typically occurs in middle-aged or older animals. Ancillary tests to evaluate the patient's general health and suitability for therapy should therefore include thoracic radiographs (three views), a complete blood count, general chemistry panel with electrolytes, and urinalysis. Thyroxine levels should be measured in cats. In cases with deep tissue invasion, a biopsy of draining lymph nodes should be performed. Radiographs should be taken to detect bony involvement in digital lesions.

9. What is the clinical course of SCC in dogs and cats?

SCC lesions may be proliferative, producing plaques or exuberant cauliflower-like masses, or erosive, characterized by shallow crusts to deep ulcers. Erosions are more common in cats than in dogs. Early lesions may simply be erythematous or hyperplastic crusts and may wax and wane in response to solar exposure. Ulcerative lesions can progress to destroy substantial amounts of adjacent and underlying tissues. Although solar-induced SCC is locally invasive, it tends to metastasize slowly. Digital lesions, however, are characterized by a more aggressive biological behavior and can produce bony lysis of the third phalanx. Subungual tumors can be singular or multiple.

10. How are the stages of squamous cell carcinoma defined?

See Table 51-2.

11. What are the most common sites of squamous cell carcinoma in dogs and cats?

When all cases of canine SCC are considered, the nailbed is the most commonly affected site. Solar-induced SCC in both species obviously arises in sun-exposed sites. Dogs that sunbathe

Table 51-2 *Staging of Squamous Cell Carcinoma*

STAGE	DIAMETER	DEPTH
Tis		In situ (is), does not extend beneath basement membrane zone
T1	<2 cm	Superficial (restricted to epidermis)
T2	2-5 cm	Minimal dermal invasion
T3	>5 cm	Invasion of subcutaneous tissues
T4	Any diameter	Invasion of deep tissues (muscle, cartilage, bone)

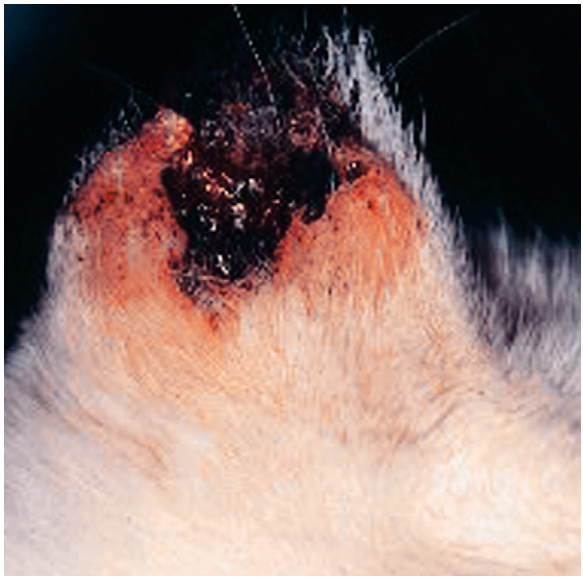

Figure 51-1 Squamous cell carcinoma on the ear of a cat. (Courtesy Dr. Karen Campbell.)

on their backs develop SCC on their ventral abdomen, groin, and medial thighs. Lesions are most common on the nose, eyelids, and pinnae of cats (Figure 51-1).

12. How is SCC treated?

Therapy depends on the nature of the skin and the size, shape, and location of the tumor.

Surgical excision is considered the treatment of choice. Pinnectomies and removal of the nasal planum are often required in feline cases and result in median disease-free intervals of up to 20 months. Laser ablation may be a useful alternative to surgical excision when lesions are widespread; it allows rapid removal of multiple masses and causes less tissue destruction than surgical excision. Cryosurgery using liquid nitrogen requires multiple treatments and does not achieve the median disease-free interval of conventional surgery.

Where available, concurrent radiation therapy is recommended. Several protocols have proven to be effective. Superficial lesions can be treated with strontium-90 plesiotherapy using handheld devices. Orthovoltage radiation (200-300 kV) delivers the maximum dose at the skin surface and is commonly used to treat cutaneous neoplasia. Electron radiotherapy has replaced

orthovoltage radiation in human medicine, but is not yet available for veterinary patients. Megavoltage radiation (>1 MV) is not substantially better than orthovoltage therapy for cutaneous lesions. Adverse effects of radiation therapy include cutaneous reactions ranging from erythema and scaling to ulceration, crusting, and necrosis; local immunosuppression; and damage to associated structures near the irradiated site. The risk of adverse effects is increased in FIV-positive patients.

Photodynamic therapy can be effective for in situ tumors as well as those in stages T1 and T2. A photosensitizing agent is administered systemically; compounds such ethyl–Nile blue sulfur are taken up preferentially by neoplastic tissues. The modality is therefore nondestructive to adjacent tissues. The tissues are irradiated using light whose wavelength is absorbed by the photosensitizing agent; the result is production of cytotoxic free radicals within the neoplastic tissue. Multiple lesions can be treated simultaneously, the therapy can be given in conjunction with other modalities, and treatment can be repeated. Therapy is limited to approximately the upper centimeter of tissue if surface radiation is used as a light source because of the penetration depth of the wavelength absorbed by the sensitizer. This can be circumvented by placement of intralesional fiberoptics. The best responses have been reported in lesions less than 0.5 cm in diameter. This modality has been effective in treating early cases of invasive SCC in cats. Acute hepatic necrosis resulted from the use of earlier photosensitizers, such as phthalocyanine dye. Ethyl–Nile blue sulfur is cleared rapidly. Adverse effects include photosensitization for up to 4-6 weeks, facial edema, and erythema. The lesions may be painful when neoplastic tissues necrose and slough. Current research in photodynamic therapy involves development of new photosensitizers to improve energy delivery.

Interferon (IFN)-α has both antiviral and antitumor properties and thus can be useful as an adjunct to therapy for SCC that has developed secondary to papillomavirus (PV) infection. Low-dose oral IFN-α has proved effective in prevention and therapy for viral diseases in several species. When administered orally, IFN-α binds to cell receptors associated with mucosal lymphoid tissue. Both local and systemic immunity are stimulated, additional IFN-α along with IFN-β is produced, and a systemic Th_1 immune response is the result. Topical imiquimod is an alternative. This imidazoquinoline amine has antiviral and antitumor effects caused by the induction of several cytokines that stimulate both innate and cell-mediated immunity, including IFN-α. In humans, topical application of imiquimod at a concentration of 5% (Aldara) has led to remission in patients with Bowen's disease, PV infections, and SCC.

Oral and topical retinoid therapy has produced disappointing results in cases of SCC in cats and dogs. Cell-mediated immunity is depressed by at least one member of the group, etretinate, thus retinoids could potentially enhance the progression and development of PV-associated lesions.

Results of systemic chemotherapy have been disappointing. Agents used with limited success include bleomycin, bleomycin with doxorubicin, doxorubicin, and carboplatin in feline SCC. Systemic cisplatin and 5-fluorouracil (5-FU) can be used to treat SCC in dogs, but should not be used in cats: cisplatin can produce fatal pulmonary edema and 5-FU is neurotoxic in cats. Intralesional chemotherapy (cisplatin and 5-FU) in a viscous gel has been used to treat both actinic-induced SCC and non-solar-associated SCC in dogs and in actinic SCC in cats and has shown favorable responses.

13. What is Bowen's disease?

Bowen's disease in humans is a form of SCC characterized by multifocal hyperkeratotic plaques and crusts. The lesions are referred to as "in situ" because neoplastic cells do not penetrate the basement membrane. Sun-exposed skin is typically affected in humans. In cats, multicentric squamous cell carcinoma in situ has been considered an analogue to human Bowen's disease. Unlike the human form of the disease, the feline disease is not associated with solar exposure; development of multicentric squamous cell carcinoma in cats has been linked to infection by feline papillomavirus. Dysplastic cells are confined to epidermal and follicular epithelium and do not penetrate the basement membrane of the epidermis. Bowen's disease

occurs predominantly in middle-aged to older cats. Ages of affected individuals range from 2 months to 20 years, with a mean of approximately 11.5-12 years. No predilections for sex or coat color have been observed. The thickened and dysplastic epidermal and follicular infundibular epithelium may be elevated, papillated, or form plaques. Crusts may form over ulcerated areas, which may bleed and become painful when crusts are removed. Affected areas can be present for months to years before diagnosis. Lesions are typically multifocal; over 30 tumors may be present on a single individual, and plaques may coalesce. An irregular, but distinct, margin surrounds the hyperkeratotic plaques and crusts, which may be pruritic. The lesions can originate in haired or glabrous skin and may become partially alopecic. The most common sites are the head, neck, shoulders, thoracic limbs, and digits; less common sites include ventral abdomen, thighs, and oral mucosae.

14. How is feline Bowen's disease treated?

The preferred treatment for Bowen's disease in humans is surgical excision with wide margins; other modalities include cryosurgery, laser surgery, electrodesiccation, radiation therapy, and 5-FU, which is neurotoxic in cats. Because lesions are typically multiple in cats, surgical excision is not always appropriate. Laser ablation may be palliative. Poor responses have been reported for feline cases treated with alkylating agents, antibiotics, retinoids, and corticosteroids. Photodynamic therapy has been used successfully in both human and feline Bowen's disease. One disadvantage of photodynamic therapy in the treatment of feline Bowen's disease, however, is that lesions commonly occur in pigmented tissues. Melanin absorbs light, thus preventing activation of the photosensitizer. Because of the association with PV, IFN-α might prove useful.

15. What are the different types of basal cell tumors in cats and dogs?

In veterinary medicine, the term "basal cell tumor" has been used to refer to several canine and feline neoplasms that develop from both epidermal and adnexal basal epithelial cells. Current preference restricts the term to the basal cell neoplasms of cats that lack adnexal features (feline benign basal cell tumor). The tumors of low-grade malignancy that develop from pluripotential epithelial cells in the basal layers of both the epidermis and adnexae are basal cell carcinomas.

Benign basal cell tumors of cats are uncommon, singular, conical masses up to 2 cm in diameter. As these tumors can sometimes contain melanin, they may appear lightly to moderately pigmented. The overlying epidermis is usually hairless and can ulcerate. Liquefactive necrosis of the center of the tumor may make it appear cystic. These tumors are most common in Persian, Siamese, and Himalayan cat breeds. Surgical excision is curative; observation without treatment is an alternative. Differential diagnoses include basal cell carcinoma and its various adnexal differentiates and trabecular trichoblastoma.

Basal cell carcinomas are considered the most common feline cutaneous neoplasm. They can originate in basal cells in the epidermis, hair follicles, sebaceous glands, and sweat glands. Siamese cats appear predisposed. These tumors are most common in middle-aged to older cats, with no gender predilection. Biologic behavior is usually benign; malignant variants rarely metastasize. The tumors are most commonly found on the head or neck. The tumors are typically small, firm, circumscribed, and elevated. They may be pigmented, cystic, and/or lobulated. Surgical excision is usually curative. Many tumors contain melanin. Cytology reveals basal cells, several of which show evidence of mitosis. Despite a high mitotic index, however, basal cell carcinomas are not biologically aggressive and rarely metastasize in any species. Basal cell carcinomas in dogs and cats can have a variety of subtypes, depending on the degree to which the basal cells present have matured or differentiated. These can have features of follicular or other adnexal cells. Differential diagnoses include melanocytomas or malignant melanomas, apocrine sweat gland tumors, sebaceous adenomas or adenocarcinomas, mast cell tumors, and other tumors of hair follicles or adnexa.

Basal cell carcinomas are not common in dogs. A genetic predisposition is suggested from its increased prevalence in Poodles, Siberian Huskies, Kerry Blue Terriers, Shetland Sheepdogs,

Cocker Spaniels, and English Springer Spaniels. Tumors develop on the thorax, head, and neck of middle-aged to older dogs. No gender predilection has been determined. Clinical appearance is similar to that of basal cell carcinomas in cats.

Causes of basal cell carcinoma in dogs and cats are unclear. In humans, UV light plays a role, as discussed previously. Papillomavirus has been detected in some human basal cell carcinomas, but not in canine or feline tumors. A genetic etiology is evidenced by the increased frequency of tumors in some breeds of dogs and cats. The biologic behavior of BCC in humans as been linked to alterations in the expression of some components of the basement membrane, including bullous pemphigoid antigen, epiligrin, and some integrins ($\alpha 6$ and $\beta 4$). These alterations could lead to structural defects in the lamina lucida and the hemidesmosome-anchoring fibril complex that permit tumor invasion and metastasis.

16. What are the different types of papillomas in dogs?

Dogs can develop a variety of different papillomas (Figure 51-2); the best described types are compared in Table 51-1. Although at least three distinct viruses have been detected, clarification of the role of individual viruses in canine papillomas awaits further genetic sequencing and cloning.

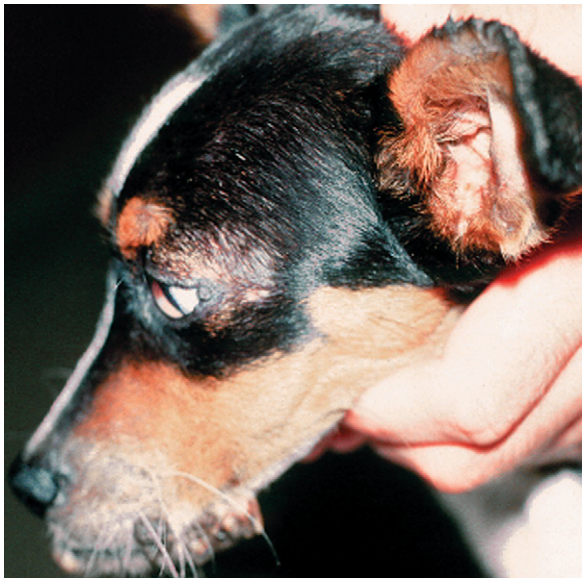

Figure 51-2 Papillomas associated with oral papillomavirus infection in a 9-week-old mixed-breed puppy. (Courtesy Dr. Karen Campbell.)

17. What is a pigmented epidermal plaque?

Lesions formerly called pigmented epidermal nevi are now referred to as pigmented epidermal plaques. Affected dogs have a widespread distribution of heavily pigmented, hyperplastic, cutaneous macules, papules, and plaques. A genetic predisposition is indicated by increased prevalence in Miniature Schnauzers, Pugs, and Chinese Shar Peis; single cases have been reported in other breeds as well (Figure 51-3). A papillomavirus distinct from the virus that causes canine oral papillomatosis has been demonstrated in plaques from several affected individuals. Acquired or congenital immunodeficiency may also play a role, possibly by facilitating

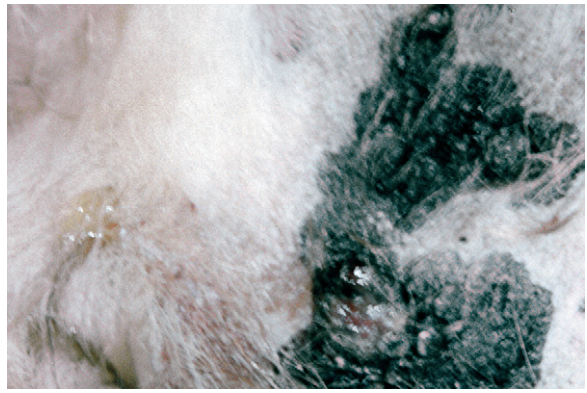

Figure 51-3 Pigmented epidermal plaques on the ventral abdomen of a Pomeranian. (Courtesy Dr. Karen Campbell.)

viral progression, as in the human analogue, epidermodysplasia verruciformis. Therapy involves identification and management of any underlying immunodeficiency and antiviral therapy using IFN-α or imiquimod. Laser ablation is more appropriate than surgical excision for generalized lesions that fail to resolve with antiviral therapy. A biopsy should be performed on ulcerated or erythematous plaques to rule out neoplastic transformation to SCC.

18. What is the link between papillomavirus and cancer in dogs and cats?

The association between PV infection and the development of neoplasia has been documented in several species. In cats, PV infection can lead to multicentric squamous cell carcinoma in situ. Mechanisms of neoplastic transformation by PVs include interference with the functions of *p53* gene products, leading to decreased tumor suppression. Retinoblastoma (Rb) protein is another suppressor of tumor growth. Papillomavirus can bind to Rb protein, which accelerates its degradation, thereby facilitating cellular proliferation. Certain human PVs can also inhibit regulation of the cell cycle by a negative-feedback, cyclin-dependent kinase.

19. How are papillomas treated in dogs and cats?

Therapy depends on the type of papilloma. Oral papillomas, resulting from canine oral papillomavirus, commonly regress on their own. Nonspecific immunostimulants, such as low-dose oral interferon-α, can hasten remission. Solitary papillomas, such as cutaneous inverted papillomas or footpad papillomas, can either be surgically excised or observed without treatment. More widespread papillomatoses, such as feline papillomas and pigmented epidermal plaques or epidermal papules in dogs, are not amenable to surgical excision. Multiple lesions can be ablated using a CO_2 laser. The possibility of a predisposing underlying immunodeficiency should be investigated and treated if identified. As with other viral-induced papillomas, interferon-α should be considered as an adjunct to therapy. The topical antiviral immunostimulant imiquimod is an alternative to systemic cytokine therapy.

20. What is a cutaneous horn? What causes their formation?

Cutaneous horns are uncommon, solitary or multiple proliferations of basal cells that mature to produce excess amounts of keratin, forming conical structures that can be several centimeters long. In humans, cutaneous horns develop as a reaction pattern in seborrheic keratosis, basal cell epithelioma, and SCC. In dogs and cats, associations have been reported between cutaneous horns and actinic keratoses or SCC, BCC, dilated pores, infundibular keratinizing acanthoma,

keratinous cysts, and papillomas. Multiple cutaneous horns have been reported on multiple footpads of FeLV-positive cats. Horns on the footpads of FeLV-negative cats occur as well, but are restricted to subungual sites. Although cutaneous horns are themselves benign, excisional biopsy is recommended to determine their underlying cause.

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52. TUMORS OF ADNEXAL ORIGIN

Thomas O. Manning, DVM, MS, DACVD
Brett C. Wood, DVM

1. **Skin neoplasms (dog and cat) are accountable for the following approximate percentage of all neoplasms:**
   Dog (skin neoplasms) = 30% of total neoplasms
   Cat (skin neoplasms) = 20% of total neoplasms
   The incidence of skin neoplasia is approximately six times greater in the dog than in the cat.

keratinous cysts, and papillomas. Multiple cutaneous horns have been reported on multiple footpads of FeLV-positive cats. Horns on the footpads of FeLV-negative cats occur as well, but are restricted to subungual sites. Although cutaneous horns are themselves benign, excisional biopsy is recommended to determine their underlying cause.

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   Dog (skin neoplasms) = 30% of total neoplasms
   Cat (skin neoplasms) = 20% of total neoplasms
   The incidence of skin neoplasia is approximately six times greater in the dog than in the cat.

2. **How are these skin neoplasms categorized (tissue of origin) in the dog and cat, and what is the general prevalence of each type?**
   Dog: 55% mesenchymal, 40% epithelial, 5% melanocytic
   Cat: 50% epithelial, 48% mesenchymal, 25% melanocytic

3. **What are major characteristics of malignant neoplasia involving the skin or subcutaneous tissue?**
   - Sudden onset
   - Rapid growth
   - Ulceration, irritation
   - Infiltrative growth
   - Recurrence
   - Metastasis

   The most important criterion of malignancy is metastasis.

4. **What is the key to appropriate management and accurate prognosis of cutaneous neoplasms?**
   Specific diagnosis, *which can only be achieved with surgical cutaneous biopsy sample, histologic evaluation, and proper clinical staging when appropriate.*

5. **Is exfoliative cytology (aspiration and/or impression smears) accurate in all cases of dermal neoplasia?**
   - Exfoliative cytology techniques (aspiration and impression) are easy, rapid, and may provide valuable information concerning cell type and differentiation in some instances of dermal neoplasia (mast cell tumor, melanocytic tumors).
   - *However*, exfoliative cytologic examination is inferior to and cannot substitute for histopathologic diagnosis for most cases.

   "A lump is a lump, until examined histologically."

6. **List some of the reasons for the growing importance of special stains (cytokeratins) and immunohistochemical stains.**
   - These stains may help separate the more anaplastic tumors into specific categories.
   - Predict future malignancy
   - By more accurate diagnosis, treatment can be more specific

7. **What is an intracutaneous cornifying epithelioma (ICE) (keratoacanthoma, infundibular keratinizing acanthoma)?**
   - An uncommon, benign skin tumor seen in dogs
   - Unsubstantiated reports in cats
   - Occurs in dogs younger than 5 years of age
   - Clinically may have a "rabbit's foot" appearance

8. **What forms does ICE occur in and in what breeds is it seen?**

Solitary	**Generalized**
Collie	Norwegian Elkhound
Lhasa Apso	Keeshond
Yorkshire Terrier	German Shepherd Dog
	Old English Sheepdog

9. **What are the treatment modalities available for both types of ICE?**
   Solitary
   - Surgical excision using conventional methods
   - Radiation therapy or laser therapy
   - Cryotherapy is also useful for single, smaller lesions

Multiple

- Cryotherapy for a small number of multiple lesions
- ICE therapy with vitamin A–related synthetic retinoids (isotretinoin, etretinate, or acretinoin) has been used with some success.
- CO_2 laser ablation

10. Surveys of hair follicle neoplasia in dogs and cats indicate that these neoplasms account for _____ % of skin tumors?

Dogs = 5%
Cats = 1%

11. What are neoplasms arising from the region of the hair follicle in the dog and cat?

- Tricholemmoma
- Trichoblastoma
- Trichoepithelioma
- Pilomatrixoma

12. With the reclassification of so-called basal cell tumors (see previous chapters), it seems that the majority of previous reports of these neoplasms would currently be classified as what type of neoplasia?

Trichoblastoma; therefore, neoplasms of the hair follicle are much more common than recognized in earlier veterinary literature.

13. What are the characteristics of trichoblastomas?

- Common
- Usually benign
- Derived from primitive hair germ cells
- Poodle, Cocker Spaniel breeds are predisposed
- Solitary, dome shaped firm, 1-2 cm diameter
- Occur most commonly on the head, neck, or base of the ear

14. What are the characteristics of trichoepitheliomas?

- Usually solitary (Figure 52-1)
- Rarely invasive or metastatic (Figure 52-2)
- Dorsal lumbar, lateral thoracic, and extremities are common sites.
- Basset Hounds, Cocker and English Springer Spaniels, German Shepherd Dogs, Golden Retrievers, Miniature Schnauzers, and Standard Poodles are predisposed.

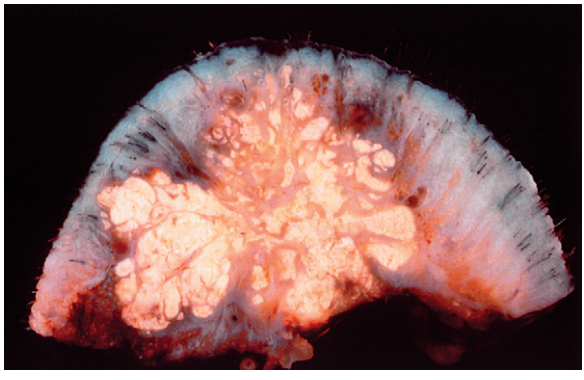

Figure 52-1 Cross-section of canine trichoepithelioma.

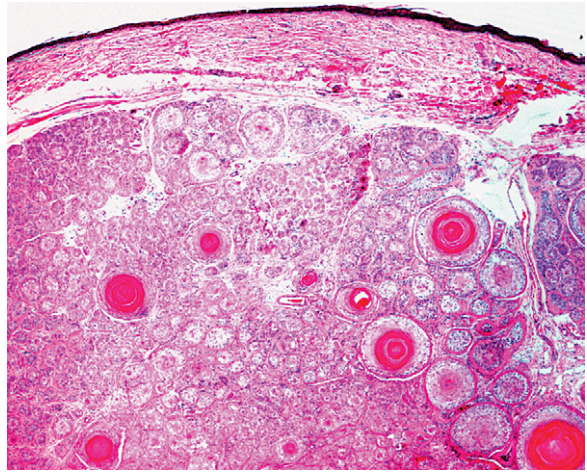

Figure 52-2 Photomicrograph of canine trichoepithelioma (H&E ×100).

15. What are the characteristics of pilomatrixomas?
- Uncommon in dogs, rare in cats
- Predilection for neck, shoulders, lateral thorax, and back

16. Breeds predisposed to pilomatrixoma are:
- Kerry Blue Terrier
- Poodle
- Old English Sheepdog

17. On cutting into a cutaneous neoplasm, it is found to be very firm, and the central core shows areas of calcification. This is suggestive of which of the following tumors?
(a) Trichoepithelioma
(b) Pilomatrixoma
(c) ICE
(d) Epidermal inclusion cyst
(e) *Corynebacterium* spp. infection
Correct answer is (b) Pilomatrixoma

18. Incidence of sebaceous gland tumors, growths arising from sebocytes, is _____ in dogs and _____ in cats.
- Common in the dog, representing from 6-21% of all canine skin tumors
- Uncommon in the cat

19. What are the breeds most commonly affected with sebaceous gland tumors?
- Beagle
- Cocker Spaniel
- Poodle
- Dachshund
- Miniature Schnauzer

20. What is the percent occurrence of the different sebaceous gland tumors and their breed associations (see previous question) and site predilections (if any)?
- Nodular sebaceous hyperplasia: 53%
- Sebaceous epithelioma: 37%, Shih Tzu, Lhasa Apso, Malamute, Siberian Husky, Irish Setter

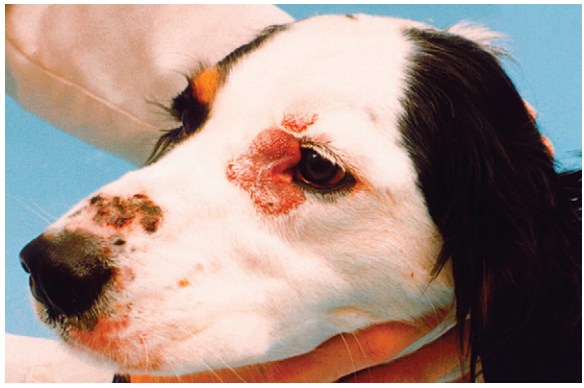

Figure 52-3 Sebaceous gland hyperplasia involving the medial canthus of an English Setter.

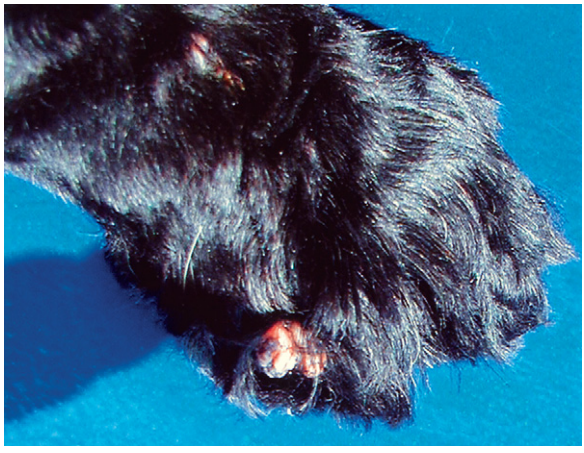

Figure 52-4 Nodule consisting of sebaceous gland hyperplasia on the paw of a Cocker Spaniel.

- Sebaceous adenoma: 8%, Poodle, eyelid and limbs (Figure 52-3)
- Sebaceous carcinoma: 2%, Cocker Spaniel, head and limbs (Figure 52-4)

21. What happens to nodular sebaceous hyperplasia (is there a progression to neoplasia)?

Eighty-one percent of sebaceous epitheliomas and 54% of sebaceous adenomas had areas of sebaceous hyperplasia peripheral to and often mixing into neoplastic areas.

These findings suggest that sebaceous hyperplasia may be a precursor to sebaceous epitheliomas and adenomas.

22. Which of the following statements is most correct regarding sebaceous gland tumors in the dog?

(a) All sebaceous glands are malignant
(b) Show no age or breed predilection; majority of tumors are malignant
(c) Mostly in older, giant breed dogs; majority of tumors are benign
(d) Mostly in older small breed dogs; majority of tumors are benign

Correct answer is (d)

23. Which of the following statements regarding perianal (hepatoid) gland tumors is correct?

(a) Malignant, most commonly arise in the perianal areas of older male dogs
(b) Benign, most commonly arise in the perianal areas of older male dogs
(c) Malignant, most commonly arise in the perianal areas of older female dogs
(d) Benign, most commonly arise in the perianal areas of older female dogs

Correct answer is (b)

24. Perianal (hepatoid) glandular tissue may be found on the dog around the:

(a) Anus
(b) Prepuce
(c) Dorsal area of the tail
(d) Skin of the lumbar and sacral areas
(e) All of the above

Correct answer is (e)

25. What are therapeutic choices when treating perianal (hepatoid) gland adenomas?

(a) Castration is probably the single best initial choice. Tumors may regress spontaneously over the 1- to 2-month postoperative period or reduce greatly in size, making surgical removal easier.
(b) Cryosurgery is used primarily for tumors that are less than 1-2 cm in diameter.
(c) Systemic administration of long-acting estrogenic compounds has been used before surgical debulking, but chronic use runs a substantial risk of bone marrow suppression.
(d) External beam radiation therapy has been reported in the treatment of benign and malignant perianal/anal tumors but is used as more of a last resort due to increased cost and possible morbidity associated with procedure.

26. Is there a gender predilection for perianal gland adenomas and adenocarcinomas in the dog?

Perianal gland adenomas are nine times more common in male than in female dogs (Figure 52-5).

Perianal gland adenocarcinomas occur with equal frequency in both sexes (Figure 52-6).

27. How do circumanal gland (apocrine) carcinomas differ in their disease progression compared to perianal gland adenomas?

- Grow more rapidly
- Grow larger
- Ulcerate

28. Are there prognostic indicators for dogs with perianal tumors?

Yes, Tumor Size

- Dogs with lesions greater than 5 cm. have an 11-fold higher risk of dying of tumor-related causes; in particular, metastasis to sacral and sublumbar lymph nodes.
- Metastasis occurs in approximately 30% of cases.

29. How common are apocrine gland neoplasms of the dog and cat?

- Primary apocrine gland neoplasia is rare in dogs (approximately 2% of all skin tumors)
- More common in cats than sebaceous gland tumors.
- Adenocarcinomas are more common than adenomas (50-90% malignant).
- There are two modified apocrine gland tumors, ceruminous gland tumors of the ear and apocrine gland tumors of the anal sac, that are more commonly seen in the veterinary patient.

30. What clinical features are consistently helpful in differentiating histologically benign from histologically malignant tumors?

- There are no clinical features that help.

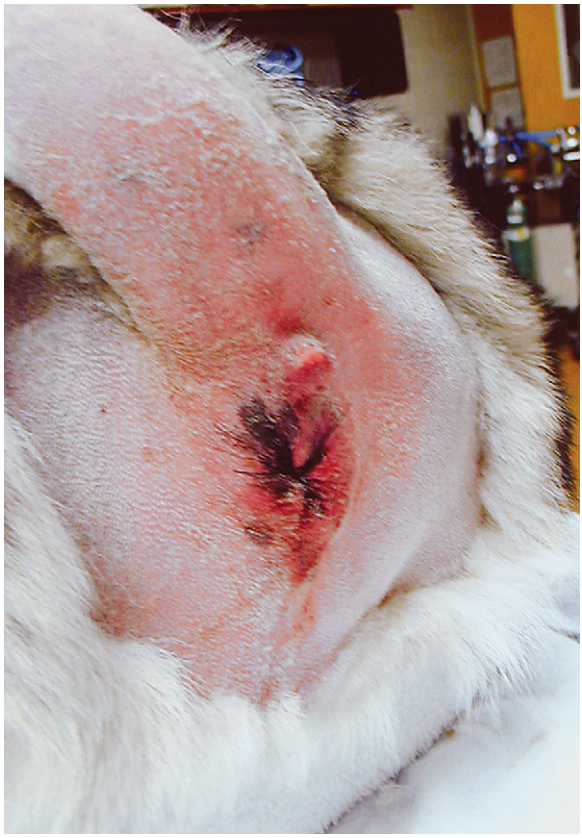

Figure 52-5 Perianal adenoma in an intact male dog.

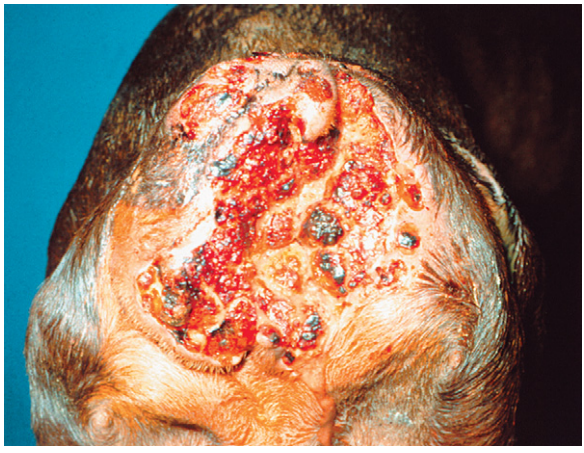

Figure 52-6 Perianal adenocarcinoma in an intact female dog.

- Therefore, another reason for excisional biopsies with wide surgical margins.
- Unfortunately a common area on which adnexal tumors grow are the limbs; therefore making complete surgical removal a more difficult, sometimes impossible procedure. Tissue flap/plastic procedures, radiation, or limb amputation would then be considered.
- However, incisional biopsy before aggressive surgery or adjunctive procedures is always recommended.

31. What are some special stains that can sometimes differentiate apocrine (epitrichial) adenomas from adenocarcinomas?

- Apocrine sweat gland (epitrichial) tumors are positive for cytokeratins.
- Carcinomas, not adenomas, are positive for carcinoembryonic antigen (secretory cell) and vimentin (myoepithelial cell).

32. What are the most common neoplasms of the ear canal?

- Inflammatory polyps
- Papillomas
- Basal cell tumors
- Ceruminous gland adenomas (Figure 52-7)

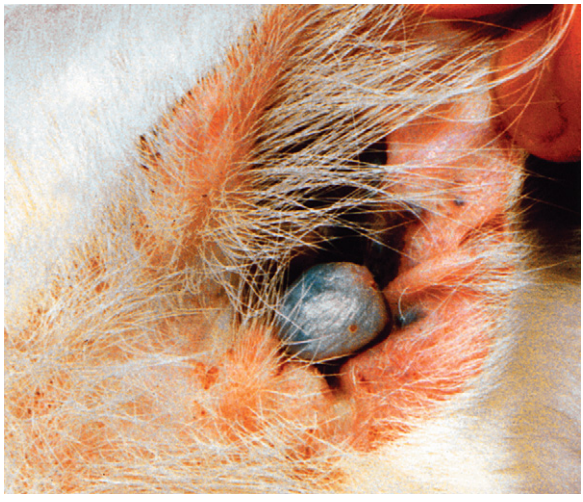

Figure 52-7 Ceruminous gland adenoma (1 cm diameter) and ceruminous cysts (1 mm diameter) in the external ear canal of a cat.

- Common malignant tumors found in the ear canal include ceruminous gland adenocarcinoma, squamous cell carcinoma, and carcinoma of undetermined origin.

33. What are the most common ear pinnal neoplasms?

DOG	**CAT**
Sebaceous gland tumors	Squamous cell carcinoma
Histiocytoma	Basal cell tumor
Mast cell tumor	Hemangiosarcoma
Melanocytic neoplasms	

34. Are ceruminal gland tumors usually benign?
- Dog: ceruminal gland tumors are typically benign
- Cat: ceruminal gland tumors are malignant in 50% of cases

35. What are common clinical observations in animals with ear canal tumors?
- Older animals
- Unilateral involvement only
- Head scratching/head-shaking behavior
- Frequent secondary bacterial/yeast infections with no history of problems
- Aural discharge and/or intermittent hemorrhage from affected ear
- Occasionally cause bulging, ulceration/draining mass below ear in the parotid region of the skull
- Neurologic signs (peripheral vestibular disease, facial nerve paresis, Horner's syndrome) are noted in approximately 10% of dogs and approximately 25% of cats with ear canal tumors.

36. What does proper clinical staging of an ear canal–based tumor include?
- Minimum database (complete blood cell count, serum biochemistry, urinalysis)
- Thoracic radiography
- Fine needle aspirate or excisional biopsy of local lymph nodes
- Radiologic study of the skull: computed tomography of the ear canal and tympanic bullae is recommended due to improved ability to evaluate soft tissue and bony changes and evidence of local extension. Skull radiographs may be used to evaluate primarily for evidence of bony changes and superimposition of anatomic structures may occur.
- Incisional biopsy may be recommended in cases of suspected neoplasia if owners are considering adjunctive therapies instead of primary surgical excision.

37. What is the only effective therapy for an ear canal–based ceruminal tumor?
- Complete surgical excision, usually by lateral ear resection or total ear canal ablation (TECA)
- The best results are achieved with TECA and lateral bulla osteotomy.
- The approximate recurrence rate for ceruminous gland tumors after lateral ear resection is 70%.

38. What is the most common signalment for anal sac gland tumors (apocrine)?
Older female dogs, often associated with hypercalcemia of malignancy (PTHrP).

39. In a female dog, which of the following tumors is most likely to show metastasis to regional lymph nodes?
(a) Anal gland tumor
(b) Squamous cell carcinoma
(c) Papilloma
(d) Intracutaneous cornifying epithelioma
Correct answer is (a)

40. What are common clinical signs noted in animals afflicted with anal sac adenocarcinoma?
- Palpable rectal mass noted in the region of the anal sac
- Perineal swelling
- Tenesmus
- Constipation/obstipation
- Change in the shape of stool
- Polyuria/polydipsia (associated with hypercalcemia)

41. What does the recommended clinical staging of an anal sac tumor include?

- Minimum database (complete blood cell count, serum chemistry, urinalysis)
- Thoracic radiography (low yield procedure)
- Abdominal imaging to evaluate regional lymph nodes
- In general, ultrasonography of the abdomen is considered superior to caudal abdominal radiography for examination of regional lymphadenomegaly.
- Rectal examination
- Exfoliative cytology of this region is usually unrewarding in differentiation between benign and malignant processes in this region.

42. What is the general prognosis for animals with anal sac apocrine gland adenocarcinoma?

- In general, the prognosis is poor; mean survival times for females is approximately 12 months with local recurrence occurring in approximately 50% of operated cases.
- Metastasis and hypercalcemia are both considered poor prognostic indicators (approximate 6-month survival vs 12-month survival times).

43. What are adjunctive therapies for anal sac adenocarcinoma?

External beam radiation has been offered as a monotherapy or as adjunctive therapy in cases of incomplete resection with variable results. The efficacy for this tumor is unknown, but in most cases chemotherapeutic agents have not been useful as an adjunctive therapy. One study revealed partial remission in approximately 30% of dogs using the platinum compounds.

44. Eccrine (atrichial) sweat gland tumors of the dog and cat:

- May be benign or malignant in the dog
- Almost always malignant in the cat
- Are restricted to locations on the paw pads or digits

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53. MESENCHYMAL NEOPLASMS AFFECTING THE SKIN AND SUBCUTANEOUS TISSUES IN THE DOG AND CAT

Timothy M. Fan, DVM, DACVIM

1. What types of tumors may arise from the skin and subcutaneous tissues in dogs and cats?

All cell types that compose the skin and subcutaneous tissues possess the potential to undergo malignant transformation. Tumors affecting the skin and subcutis may arise from melanin-producing cells, cells of epithelial origin, and cells of mesenchymal origin. Mesenchymal tumors involving the subcutis are referred to as soft tissue sarcomas. Based on histologic morphology, soft tissue sarcomas may be described as being well, intermediate, or poorly differentiated. Soft tissue sarcomas may arise from several tissue types including fibrous connective, neuronal, synovial, adipose, fascial, and neovascular tissues. The resulting neoplasms possess variable biologic behavior, with some tumors adopting a benign phenotype, with others being capable of early and aggressive metastasis (Table 53-1).

Table 53-1 ***Soft Tissue Sarcomas: Tissue of Origin, Biologic Phenotype, and Metastatic Potential***

TISSUE OF ORIGIN	BIOLOGIC PHENOTYPE		METASTATIC POTENTIAL
	Benign	***Malignant***	
Fibrous tissue	Fibroma	Fibrosarcoma	Low
Myxomatous tissue	Myxoma	Myxosarcoma	Low-Intermediate
Blood vessel pericyte	Hemangiopericytoma		Low
Lymphatic vessel	Lymphangioma	Lymphangiosarcoma	Intermediate
Blood vessel	Hemangioma	Hemangiosarcoma	Low-High
Adipose tissue	Lipoma	Liposarcoma	Intermediate
Nerve		Neurofibrosarcoma	Low
Smooth muscle	Leiomyoma	Leiomyosarcoma	Low
Synovial cell	Synovioma	Synovial cell sarcoma	Intermediate
Skeletal muscle	Rhabdomyoma	Rhabdomyosarcoma	Intermediate

Adapted from Withrow SJ, MacEwen GE: *Small animal clinical oncology*, ed 3. Philadelphia, 2001, WB Saunders, p 284.

2. What are some general characteristics of soft tissue sarcomas?

Soft tissue sarcomas are raised, fleshy masses arising from the subcutaneous tissues. Tumors can vary in size and physical appearance, as well as involve different anatomic sites (Figures 53-1 and 53-2). Tumors may be freely movable upon manipulation; however, more infiltrative lesions can become solidly adhered to deeper structures. When surgically excised, soft tissue sarcomas appear to be pseudoencapsulated. However, microscopically these tumors frequently have satellite neoplastic cells peripheral to the primary lesion. Furthermore, neoplastic cells can infiltrate along fascial planes, sometimes making complete surgical resection difficult. Incomplete surgical resection of soft tissue sarcomas commonly results in a high rate of local tumor regrowth. Benign

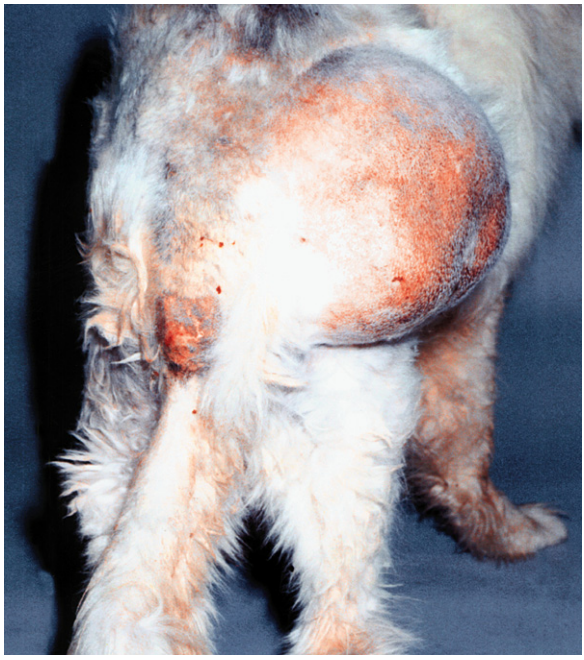

Figure 53-1 A dog with a large, unresectable soft tissue sarcoma involving the right proximal hind leg.

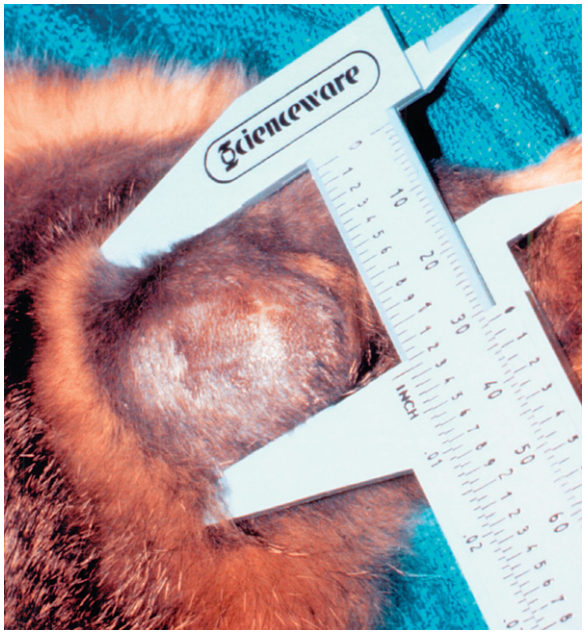

Figure 53-2 A cat with a vaccine-associated sarcoma arising from the subcutaneous tissue of the right lateral hind leg.

soft tissue sarcomas are not metastatic and if anatomically feasible, complete surgical resection may be curative. Malignant soft tissue sarcomas are locally invasive, and some tumors possess high metastatic potential. Approximately 25% of all malignant soft tissue sarcomas are capable of metastasis, primarily by hematogenous routes.

3. How frequently do soft tissue sarcomas affect the dog and cat?

Soft tissue sarcomas make up a minority of neoplasms affecting the subcutis of the dog and cat. For canines, approximately 15% of all subcutaneous tumors may be categorized as soft tissue sarcomas. In felines the incidence of soft tissue sarcomas is only 7% of all subcutaneous neoplasms. Despite the relatively low incidence of soft tissue sarcomas that affect the dog and cat, because of their invasive properties these tumors contribute significantly to patient morbidity and mortality.

4. Are there known causative factors for the development of soft tissue sarcomas in the dog and cat?

In the dog, the development of soft tissue sarcomas has been associated with exposure to physical carcinogens. Physical carcinogenesis may result in neoplasia formation by either directly inducing DNA damage or promoting cellular proliferation subsequent to chronic inflammation. Exposure to ionizing radiation can damage DNA, which may result in the development of soft tissue sarcomas. Additionally, chronic inflammation secondary to parasitic migration, foreign bodies, and metal implants has been reported to induce malignant transformation of bone and associated soft tissue structures. Despite the recognition of physical carcinogens as a potential risk factor, the etiology of soft tissue sarcoma development remains largely unknown in dogs. Similarly in felines, only a few causes responsible for the development of soft tissue sarcomas have been identified. Combined retroviral infections with feline sarcoma virus and feline leukemia virus have been demonstrated to cause the spontaneous development of multiple soft tissue sarcomas in cats. The administration of injections, vaccine and non-vaccine, have been incriminated with the development of vaccine-associated soft tissue sarcomas in cats.

5. How may soft tissue sarcomas be diagnosed?

When compared to round cell or epithelial neoplasms, mesenchymal tumors do not exfoliate well. Because mesenchymal cells tend to adhere tightly with one another, cytologic evaluation of suspect soft tissue sarcomas by fine-needle aspiration can be non-diagnostic or unreliable. Sampling of tumor tissue via a biopsy for histologic evaluation is considered the most reliable means for arriving at a definitive diagnosis. If the cancerous population is well differentiated, identifying the exact cell of origin is possible. In some cases where soft tissue sarcomas are poorly differentiated, routine histologic examination may not provide adequate information to determine if the cancerous cells are mesenchymal, hematopoietic, or epithelial in origin. In these circumstances, suspect mesenchymal tumors may be further characterized by the application of antibodies specific for mesenchymal markers. Common immunohistochemical stains applied to suspect mesenchymal tumors include vimentin, desmin, and actin. Undifferentiated mesenchymal cancers may be diagnosed by the presence of the intermediate filament, vimentin. Additionally, skeletal and smooth muscles contain the intermediate filaments actin and desmin, allowing for the identification of poorly differentiated smooth muscle tumors (leiomyoma/leiomyosarcoma) and striated muscle tumors (rhabdomyoma/rhabdomyosarcoma).

6. What factors may be useful for predicting soft tissue sarcoma metastatic potential?

Predicting the metastatic potential of soft tissue sarcomas can be difficult. Several factors including tumor type and histologic grade are believed to be helpful in accurately predicting biologic behavior. Although all malignant soft tissue sarcomas are capable of distant hematogenous metastasis, certain tumor types have been reported to possess higher metastatic rates than others. Subcutaneous hemangiosarcoma, synovial cell sarcoma, and rhabdomyosarcoma are three

soft tissue sarcomas reported to possess higher biologic aggressiveness with the formation of distant metastasis in a majority of affected canine patients. Histologic grading of soft tissue sarcomas can also be useful for predicting metastatic behavior. The assignment of histologic grade depends on several histologic features including degree of morphologic differentiation and mitotic index. Tumors may be categorized as being high-, intermediate-, or low-grade. The high-grade tumors are most likely to be metastatic, while low-grade tumors tend to be locally confined.

7. What additional diagnostic tests should be recommended once a diagnosis of soft tissue sarcoma has been reached?

Performing additional diagnostic tests on cancer patients is called clinical staging, and the purpose is to determine the extent of neoplastic involvement. The thoroughness of clinical staging is often dictated by the predicted biologic behavior of the tumor. In the case of benign soft tissue sarcomas, the likelihood of distant metastasis is low; therefore attention should be focused primarily on local disease control. For the successful management of local disease, accurately assessing the extent of local tumor involvement is paramount for thorough surgical planning. Routine radiographs as well as advanced imaging techniques such as computed tomography and magnetic resonance imaging may be required to determine the feasibility of complete surgical resection (Figure 53-3). Patients diagnosed with malignant, high-grade soft tissue sarcomas should be thoroughly staged with a complete blood cell count, serum chemistry panel, urinalysis, thoracic radiographs, and abdominal ultrasound.

Figure 53-3 The rapid and aggressive development of a large, invasive soft tissue sarcoma in a cat affecting the interscapular region after vaccination.

8. When performing surgery on soft tissue sarcomas, is there a better chance of long-term control with a single, aggressive surgery or with multiple, conservative resections?

As a rule of thumb, soft tissue sarcomas are best managed by a single, well-planned, aggressive surgical resection. Given the rapidly infiltrative nature of many malignant soft tissue sarcomas, it is not the best therapeutic option to perform several conservative cytoreductive surgeries. Each successive surgical attempt results in the potential for "seeding" of remnant neoplastic cells along the entire incision line, ultimately favoring the spreading of local disease.

9. What types of therapeutic modalities are available for the long-term management of soft tissue sarcomas in dogs and cats if surgical resection fails to be curative?

Unfortunately, because soft tissue sarcomas may arise from virtually any anatomic portion of the body, some tumors are not amenable to complete resection. Tumors involving the cranium, nasal passages, caudal mandible or maxilla may be particularly difficult to achieve curative surgical margins. In situations where surgery provides reduction of original tumor volume to microscopic disease, the adjunctive use of curative radiation therapy should be recommended to maximize long-term local disease control. For large soft tissue sarcomas that are not amenable to any surgical options, the use of radiation therapy in a palliative setting should be offered as a therapeutic modality that may minimize rapid local tumor growth and associated discomfort.

10. For dogs and cats with malignant soft tissue sarcomas that have metastasized to distant sites, are there other treatment options that should be recommended in addition to surgery and adjunctive radiation therapy?

Management of metastatic disease requires systemic chemotherapy. In human beings, several chemotherapeutic agents are effective for the management of macroscopic soft tissue sarcoma burden including doxorubicin (Adriamycin), dacarbazine, and ifosfamide. Currently, Adriamycin-based protocols are recommended for the treatment of both dogs and cats with metastatic soft tissue sarcomas. Mitoxantrone has been demonstrated to possess some therapeutic efficacy for the treatment of soft tissue sarcomas in both dogs and cats. The use of dacarbazine for the treatment of soft tissue sarcomas has not been described in the veterinary literature. Ifosfamide can be safely administered to both dogs and cats, although its efficacy for the management of soft tissue sarcomas requires further investigation.

11. In the cat, what type of tumors may form secondary to vaccination, and how common is this undesirable complication?

Histologically, vaccine-induced sarcomas may arise from any tissue type normally found within the subcutaneous space, including fibrous connective tissue and striated muscle. Classically, tumors developing within the interscapular space arise from fibrous connective tissue and develop into locally aggressive fibrosarcomas (Figure 53-4). Other tumor types that may develop at the site of injections include poorly differentiated sarcomas and rhabdomyosarcomas. Although these soft tissue sarcomas tend to be difficult to cure with even aggressive multimodality therapy including surgery, radiation therapy, and systemic chemotherapy, their overall incidence remains relatively low. Estimated frequency for vaccine-induced sarcoma formation has been reported to range from three to ten cats affected for every 10,000 cats vaccinated.

12. Are there certain types of vaccines that have been more heavily incriminated in the development of vaccine-associated sarcomas in the cat?

Analysis of various risk factors thought to contribute to the development of vaccine-associated sarcomas has been investigated. A greater relative risk for tumor formation has been ascribed to the administration of rabies and feline leukemia virus vaccines compared to other vaccination types. Although certain vaccines have been associated with greater risks for sarcoma development, it should be emphasized that the steps in tumorigenesis are likely attributed to

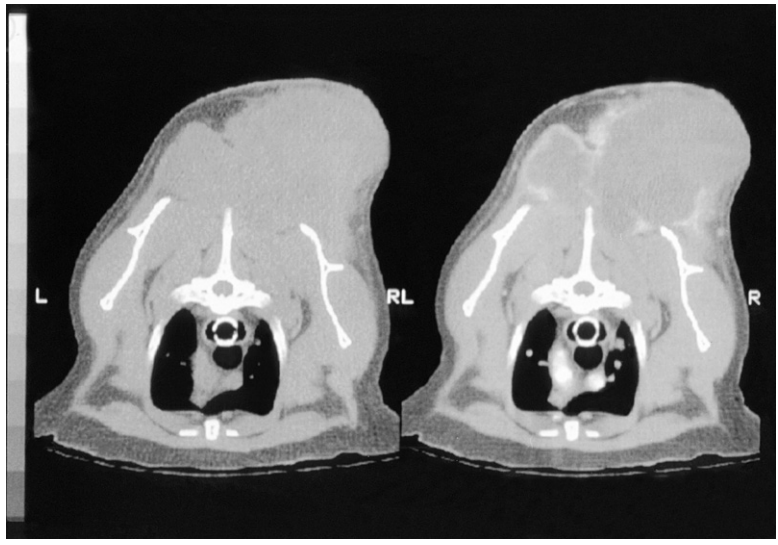

Figure 53-4 A transverse image acquired by computed tomography of a vaccine-associated sarcoma in a cat permits accurate assessment of tumor invasiveness.

multiple factors inclusive of not only vaccination type, but also other more important factors such as host immune response, local inflammatory reaction, and individual genetic composition.

13. What is the biologic behavior of feline vaccine–associated soft tissue sarcomas?

These soft tissue sarcomas are locally aggressive. A cure is rarely achievable with marginal surgical resections. Rapid tumor regrowth is common. The metastatic rate for vaccine-associated sarcomas has been reported to be 15-25%. Multimodality therapy with surgery, curative radiation therapy, and systemic chemotherapy offers the greatest survival times. Adriamycin in conjunction with cyclophosphamide or carboplatin-based protocols have demonstrated efficacy for the management of vaccine-associated sarcomas in cats. Although systemic chemotherapy appears to possess biologic activity against macroscopic tumor burden, the duration of medical cytoreduction is generally short-lived.

14. Hemangiopericytoma is a common malignant soft tissue sarcoma that affects the distal extremities of older dogs. What is the cell of origin for this common tumor type and what is its metastatic potential?

Hemangiopericytomas arise from adventitial pericytes of small vessels. Histologically, these tumors have a characteristic whirling pattern. Hemangiopericytomas are quite common in the elderly dog. Local recurrence is common following conservative surgical resection. However, these tumors have an extremely low metastatic rate (<5%) and usually are cured with radical excision. If complete surgical resection is not possible, curative radiation therapy for microscopic residual disease affords long-term management.

15. How biologically aggressive are cutaneous and subcutaneous hemangiosarcomas compared to hemangiosarcomas arising from the spleen?

Splenic hemangiosarcomas are considered highly aggressive. The vast majority of dogs with splenic hemangiosarcoma have evidence of macroscopic metastatic disease at time of diagnosis. Hemangiosarcoma confined to the skin or dermis possesses a low metastatic potential, with

radical surgical resection often being curative. On the contrary, hemangiosarcoma involving the subcutaneous tissues or deeper structures is similar to splenic hemangiosarcomas with respect to biologic aggressiveness. Subcutaneous hemangiosarcomas often are highly metastatic and require the use of systemic chemotherapy to maximize overall survival times.

16. Are there differences between soft tissue sarcomas that arise from muscle cells?

Tumors that develop from muscle may arise from either smooth or striated muscle. Both types of muscle tumors can adopt either benign or malignant phenotypes. Smooth muscle tumors include leiomyomas (benign) and leiomyosarcomas (malignant). Often these smooth muscle tumors involve the gastrointestinal tract, retroperitoneal space, or visceral organ linings. Striated muscle tumors include rhabdomyomas (benign) and rhabdomyosarcomas (malignant). Rhabdomyosarcomas tend to affect young dogs and have a relatively high metastatic rate.

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54. CUTANEOUS MAST CELL NEOPLASIA IN THE DOG AND CAT

Timothy M. *Fan*, DVM, DACVIM

1. Where are mast cells found, and what are their normal functions?

Mast cells arise from the bone marrow as multipotential hematopoietic stem cells, migrating to and maturing in connective and mucosal tissues. High concentrations of mast cells are found in parts of the body that interface with the environment, allowing them to orchestrate immunologic responses to invading pathogens. Mast cell activation results in the release of several inflammatory mediators that enhance capillary membrane permeability and allow for the efficient recruitment of additional host defense cells including macrophages, neutrophils, and lymphocytes to sites of infection and inflammation. Mast cells play a critical role in many inflammatory diseases including asthma, rhinitis, atopic dermatitis, urticaria, anaphylaxis, and food allergies.

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2. How are mast cells activated, and what types of mediators are they capable of releasing?

When mast cells are activated, they release cytoplasmic granules containing various inflammatory mediators in a process called degranulation. Mast cells can be degranulated either via immunologic or non-immunologic mechanisms. An example of immunologic activation is the type I hypersensitivity reaction where mast cells release preformed and newly synthesized inflammatory mediators in response to antigen cross-linking of receptor-bound IgE. Mast cell degranulation can also be initiated by non-immunologic mechanisms including changes in temperature and pressure, as well as by simple physical manipulation. Mast cell secretory granules contain many preformed substances including histamine, heparin, chymase, tryptase, chondroitin sulfate, and several other vasoactive amines. In addition to the release of preformed mediators, mast cells are capable of de novo synthesis of inflammatory cytokines such as tumor necrosis factor and several interleukins that amplify the adaptive immune response.

3. What causes a normal mast cell to undergo a malignant change that may result in the development of a mast cell tumor?

Several genetic factors appear to be involved in the development of mast cell tumors. One of the most recently identified mutations in the dog is a growth factor receptor called *c-kit*. Mutations in *c-kit* result in a continuous proliferative signal, allowing for the transformation of an individual mast cell into a neoplastic population. In some investigations, mutations in *c-kit* were identified in approximately 50% of cutaneous canine mast cell tumors. The underlying mechanism for malignant transformation in cats remains poorly defined due to the failure to identify *c-kit* mutations in feline mast cell tumors.

4. Have any breed predispositions been reported for the development of cutaneous mast cell tumors in dogs and cats?

Cutaneous mast cell tumors can occur in any breed of dog or cat, however some breeds are more commonly affected. In the dog, mast cell neoplasia appears to be over-represented in Boxers, Boston Terriers, Labrador Retrievers, Beagles, and Schnauzers. Furthermore, mast cell neoplasia affecting the Chinese Shar Pei breed tends to manifest with a highly aggressive phenotype. Chinese Shar Peis commonly present with extensive cutaneous tumor burden with early metastasis to local and distant sites (Figure 54-1). In the cat, cutaneous mast cell tumors can be characterized as being either mastocytic or histiocytic. As a breed, the Siamese appears to be over-represented for the development of both mastocytic and histiocytic cutaneous mast cell tumors.

5. What does a cutaneous mast cell tumor look like?

The majority of canine and feline mast cell tumors arise from the dermis and subcutaneous tissues. Dogs and cats are generally presented for the evaluation of a cutaneous mass that may rapidly change in size and coloration subsequent to intermittent mast cell degranulation. It is important to remember that cutaneous mast cell tumors can manifest with a wide spectrum of physical characteristics. Most commonly, cutaneous mast cell tumors will appear as raised skin lesions, which may rapidly increase in size and develop a vasodilatory blush (Darrier's sign) when physically manipulated (Figure 54-2). Cutaneous mast cell tumors usually arise as solitary lesions; however, it is not uncommon for patients, especially young cats, to manifest with multiple tumors at the same time.

6. Anatomically, where are the most common sites of cutaneous involvement in the dog and cat?

In the dog, cutaneous mast cell tumors are most commonly identified on the trunk and distal extremities. Biologic aggressiveness of canine cutaneous mast cell tumors appears to be influenced by the anatomic site of involvement. Canine cutaneous mast cell tumors arising from the claw bed, oral cavity, and other mucocutaneous sites such as the prepuce, vulva, and perianal

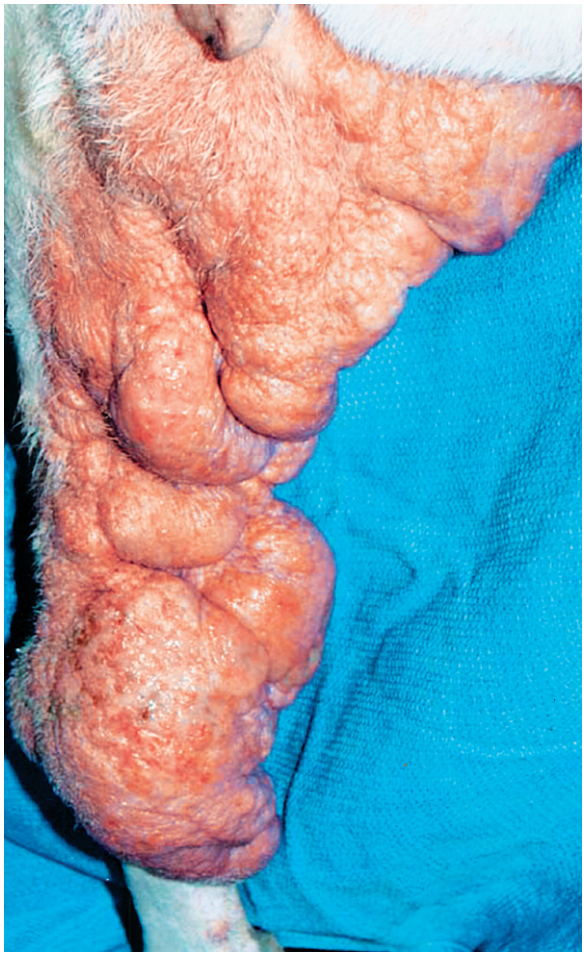

Figure 54-1 Extensive and aggressive cutaneous mast cell neoplasia infiltration in a Chinese Shar Pei.

regions have anecdotally been reported to possess more aggressive biologic behavior characterized by early local metastasis. In the cat, cutaneous mast cell tumors most commonly involve the head and neck regions (Figure 54-3); however, they can affect the trunk and extremities as well. Unlike their dog counterpart, the biologic behavior of most feline cutaneous mast cell tumors is benign with rare metastasis to local or distant sites.

7. How are cutaneous mast cell tumors diagnosed?

The diagnosis of a mast cell tumor is not difficult and can be achieved by either cytology or histopathology. A sample obtained by fine-needle aspiration is often cellular enough to make a definitive diagnosis. Cytologically, mast cells are characterized as discrete round cells with abundant cytoplasmic granules (Figure 54-4). The classic metachromatic staining pattern observed is due to the presence of negatively charged proteoglycans such as heparin that bind avidly to cationic dyes. Poorly differentiated mast cell tumors may lack characteristic metachromatic

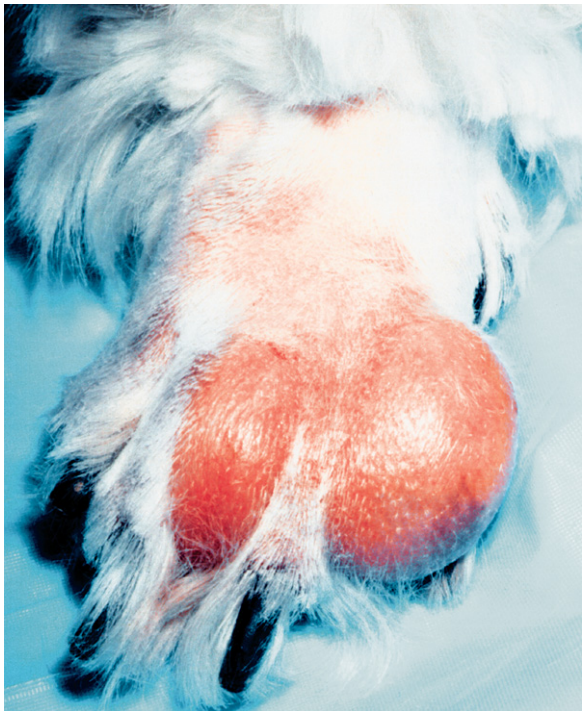

Figure 54-2 Darrier's sign: significant inflammation and swelling of an interdigital mast cell tumor in a dog subsequent to mast cell degranulation.

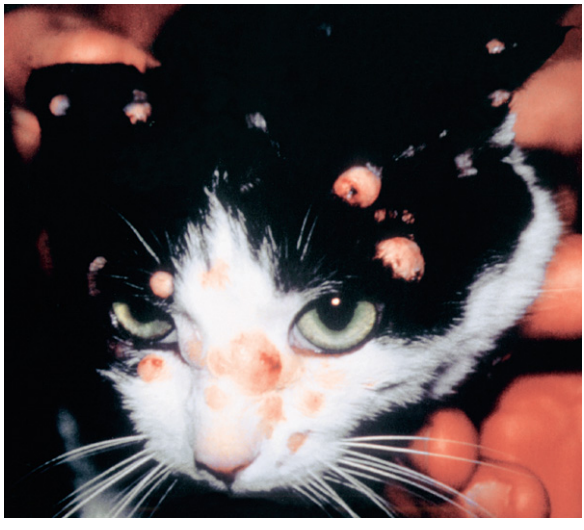

Figure 54-3 Multiple independent primary mast cell tumors affecting the face of a cat.

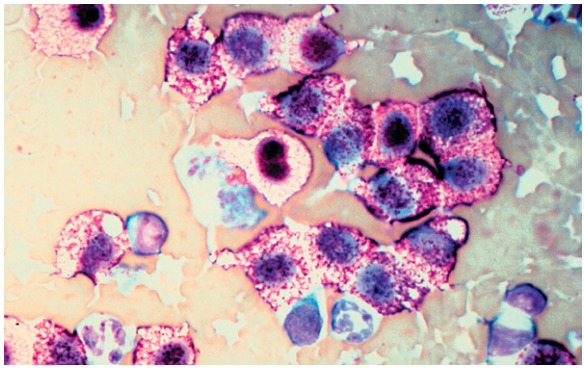

Figure 54-4 Cytologic appearance of a mast cell tumor specimen acquired by routine fine-needle aspiration (Wright stain, ×1000). Note the monomorphic round cell population with discrete cytoplasmic granules.

granules and require more specialized immunohistochemical staining techniques to determine the exact cell origin.

8. Is there an advantage of cytology versus histology for the diagnosis of mast cell tumors?

Cytology is easy and allows for a rapid diagnosis; however, standard cytologic evaluation has not been demonstrated to accurately predict the biologic behavior of cutaneous mast cell tumors. Histologic evaluation of canine mast cell neoplasia classifies tumors into three distinct histologic grades (I, II, and III) and provides a relatively accurate method of predicting biologic aggressiveness. Grade I mast cell tumors tend to be locally confined to the skin and non-metastatic. Grade II mast cell tumors are generally localized; however, some can be aggressive with regional lymph node and distant organ metastasis. Grade III mast cell tumors tend to be biologically aggressive with high metastatic rates to systemic sites. Unfortunately, the established histologic grading scale does not seem to apply well to cutaneous feline mast cell tumors.

9. What additional diagnostic tests should be recommended once a diagnosis of cutaneous mast cell tumor has been reached?

Performing additional diagnostic tests on a cancer patient is called clinical staging, and the purpose is to determine the extent of neoplastic involvement. The thoroughness of clinical staging should be dictated by the predicted biologic behavior of the tumor. Even with the implementation of the established histologic grading scheme, predicting biologic behavior can sometimes be difficult and inaccurate. For this reason, most dogs and cats diagnosed with cutaneous mast cell tumors are routinely clinically staged with a complete blood cell count, serum chemistry panel, urinalysis, and imaging studies (thoracic radiographs and abdominal ultrasound). As clinically indicated, lymph nodes draining the primary mast cell tumor should be cytologically evaluated.

10. What type of systemic clinical signs can be observed in a dog or cat manifesting with a cutaneous mast cell tumor?

Systemic manifestations from primary cutaneous mast cell tumors are rare. However, if the primary tumor is biologically aggressive, regional or distant metastasis may be present at the time of initial presentation. In dogs, neoplastic infiltration to the local draining lymph node is the most common metastatic site for mast cell tumors. Distant visceral organ involvement may occur with aggressive and advanced disease, manifesting in some dogs as vomiting, diarrhea, and melena secondary to excessive histamine release from mast cell degranulation. In the cat, primary

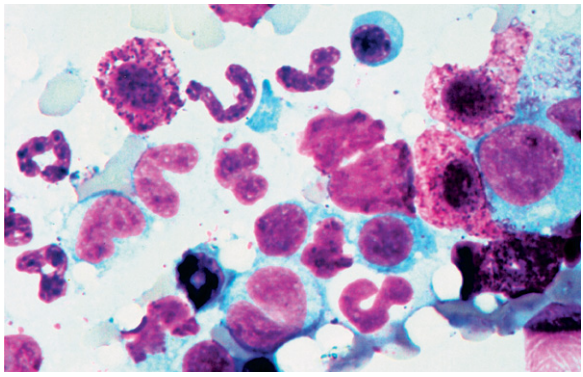

Figure 54-5 Cytologic appearance of a bone marrow aspirate specimen from a cat affected with advanced and disseminated visceral mastocytosis (Wright stain, ×1000). Note the presence of well-granulated mast cells mixed among normal bone marrow precursor cells.

cutaneous mast cell tumors tend not to cause systemic illness due to their overall benign biologic behavior. Some cats will manifest with visceral mast cell neoplasia, which can cause significant morbidity and mortality due to extensive organ infiltration including the spleen, liver, intestines, and bone marrow (Figure 54-5). Clinical signs observed in cats with visceral mastocytosis tend to be nonspecific, such as weight loss, anorexia, vomition, diarrhea, and lethargy. Despite commonality of neoplastic mast cells, it remains unclear if feline cutaneous and visceral mastocytosis are distinct disease processes or simply a continuum of one type of cancer.

11. What factors should be considered when outlining the optimal treatment path for a dog or cat diagnosed with a cutaneous mast cell tumor?

Treatment options available for either curing or managing mast cell tumors include surgery, radiation therapy, and systemic chemotherapy. Implementation of these therapeutic options alone or in combination with one another is dependent upon several factors including clinical stage, tumor location, histologic grade, and owner financial commitment. For localized tumors, surgery or surgery plus radiation therapy usually provides excellent cure rates of greater than 95%. Mast cell tumors that are metastatic may also be managed successfully with multimodality therapy, but are rarely cured. The addition of systemic chemotherapy is strongly recommended for the treatment of aggressive metastatic mast cell neoplasia to minimize the speed of tumor progression.

12. For surgical resection of cutaneous mast cell tumors, what are the recommended surgical margins?

With locally confined mast cell tumors, complete surgical excision has proven to be the most curative therapeutic modality. All surgical margins should be histologically evaluated for completeness of surgical excision. If histologic evaluation reveals an incomplete excision or excision with a narrow margin, additional treatment modalities should be implemented to maximize local tumor control. In amenable anatomic regions such as the trunk or flank, a second more aggressive surgical resection should be attempted. In regions that preclude additional surgical resections, including the distal extremities and head/neck areas, adjunctive curative radiation therapy provides excellent local tumor control rates of greater than 95%.

13. When is it appropriate to recommend the use of systemic chemotherapy?

The use of antineoplastic agents should be reserved for the management of disseminated mast cell neoplasia. Dogs with metastatic cutaneous mast cell tumors or cats affected with

visceral mastocytosis should be considered as candidates for systemic chemotherapy. Several chemotherapeutic agents have been identified as possessing efficacy against mast cell neoplasia in the dog and include combination protocols using prednisone, vinblastine, cyclophosphamide, and lomustine (Table 54-1).

Table 54-1 ***Systemic Chemotherapy for Macroscopic Mast Cell Tumor Burden***

DRUG PROTOCOL	STUDY SIZE	SURVIVAL TIME	RESPONSE RATES
21-day cycle (Elmslie, 1996)			
1a Cyclophosphamide: 250-300 mg/m^2 PO over 4 days, on day 8, 9, 10, and 11 *1b Vinblastine:* 2-3 mg/m^2 IV on day 1 *1c Prednisone:* 1 mg/kg PO SID	14 dogs	150 days	11/14 partial remission Overall response rate: 78%
(Thamm et al., 1999)			
2a Vinblastine: 2 mg/m^2 IV every 7-14 days *2b Prednisone:* 2 mg/kg PO SID 4 weekly treatments, followed by 4 biweekly treatments	15 dogs	154 days	5/15 complete remission 2/15 partial remission Overall response rate: 47%
(Rassnick et al., 1999)			
3a Lomustine: 90 mg/m^2 PO every 21 days	19 dogs	Not reported	1/19 complete remission 7/19 partial remission Overall response rate: 42%

IV, Intravenously; *PO,* orally; *SID,* once a day.

14. In addition to chemotherapy for the management of systemic disease, are there other drugs that can be used to provide symptomatic relief from advanced metastatic mast cell neoplasia?

Advanced mast cell neoplasia is capable of causing systemic illness as a direct consequence of vital organ infiltration. Additionally, mast cell degranulation with the liberation of inflammatory cytokines and histamine can lead to clinical signs of disease. The effects of massive histamine release can result in profound hypotension due to histamine type I (H1) receptor activation in vascular endothelium. Furthermore, histamine can lead to excessive hydrochloric acid production by the gastric parietal cell with subsequent gastric ulceration due to histamine type II (H2) receptor activation. Blockade of H1 receptors with diphenhydramine (2-4 mg/kg orally thrice daily) may be implemented to prevent sudden hypotension associated with histamine-induced vasodilation. Blockade of gastric H2 receptors with cimetidine (Tagamet; 5-10 mg/kg orally every 6-8 hours), ranitidine (Zantac; 1-4 mg/kg orally every 8-12 hours), or famotidine (Pepcid A/C; 0.3-0.6 mg/kg orally every 8-12 hours) should be implemented to minimize gastric irritation from excessive parietal cell hydrochloric acid secretion.

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55. LYMPHOHISTIOCYTIC NEOPLASMS

John C. *Angus*, DVM, DACVD
Louis-Philippe de Lorimier, DVM, DACVM

1. What is a histiocyte?

The term "histiocyte" is used to describe three populations of cells derived from a common bone-marrow precursor: (1) peripheral blood monocytes, (2) tissue macrophages, and (3) myeloid dendritic cells. With use of light microscopy, macrophages and dendritic cells appear to be virtually identical; moreover, other leukocytes and non-leukocytic cells can have morphologic features similar to histiocytes. Therefore, additional phenotyping by immunohistochemistry or flow cytometry is required to differentiate the true origins of "histiocytic" cells seen on cytologic or histologic studies.

2. Which specific cell type causes the solitary cutaneous histiocytoma of young dogs?

Canine cutaneous histiocytomas have been demonstrated to be a "tumor" of Langerhans cell origin. Langerhans cells are tissue dendritic cells of the skin and are essential for induction of normal immune responses. Langerhans cells function as the principal antigen-sampling, antigen-processing, and antigen-presenting cells of the skin. Their main function is to educate naive T cells during induction of the primary immune response and to serve as sentinels for recognition of antigen, activating antigen-specific T cells during the secondary immune response upon subsequent exposure.

Most likely, the solitary cutaneous histiocytomas of young dogs are abnormal proliferations of reactive Langerhans cells, rather than true neoplasms. Researchers studying this condition have suggested that the term "epidermotropic Langerhans cell histiocytosis" be used instead of "histiocytoma."

3. What are the clinical characteristics of the canine cutaneous histiocytoma?

Canine cutaneous histiocytoma is a common benign dermal growth, most often seen in dogs younger than 3 years of age. Affected dogs typically develop a single, solitary mass on the head, pinnae, distal limb, or scrotum; the majority of lesions occur on the cranial half of the body. The

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Figure 55-1 Ulcerated, solitary histiocytoma on the digit of a dog. (Courtesy Dr. Carlos Souza.)

nodule is usually small (less than 2 cm), erythematous, firm, well-circumscribed, hairless, occasionally ulcerated, and freely movable over underlying tissues (Figures 55-1 and 55-2).

Early growth of the lesion is often rapid, reaching maximal size in 1-4 weeks. This stage is followed by spontaneous regression over 1-3 months. In exceptionally uncommon cases, regional lymph node involvement may be seen. In these rare cases, lymphadenopathy typically resolves as the primary lesion regresses.

4. **Describe the cytologic findings of a fine-needle aspirate specimen from a canine cutaneous histiocytoma.**

Cytologic samples obtained from a cutaneous histiocytoma typically contain a pleomorphic population of mononuclear round cells. Cytoplasm may be pale to basophilic. Nuclei are round or indented, with rare nucleoli; chromatin appears finely granular (Figure 55-3). Binucleated cells and mitotic figures can be observed, especially during the rapid growth phase. Lymphocytes become more prominent in cytologic samples as the lesion ages and regresses.

5. **Besides histiocytoma, name seven other differential diagnoses for dermal tumors of dogs that exfoliate predominantly mononuclear, epithelioid round cells on fine-needle aspirate specimen. In other words, give seven additional differential diagnoses for "discrete cell" neoplasia.**
   - Mast cell tumor
   - Plasmacytoma (Figure 55-4)
   - Cutaneous lymphoma (Figure 55-5)
   - Transmissible venereal tumor
   - Melanoma
   - Basal cell tumor
   - Merkel cell tumor (a rare, neuroendocrine neoplasm)

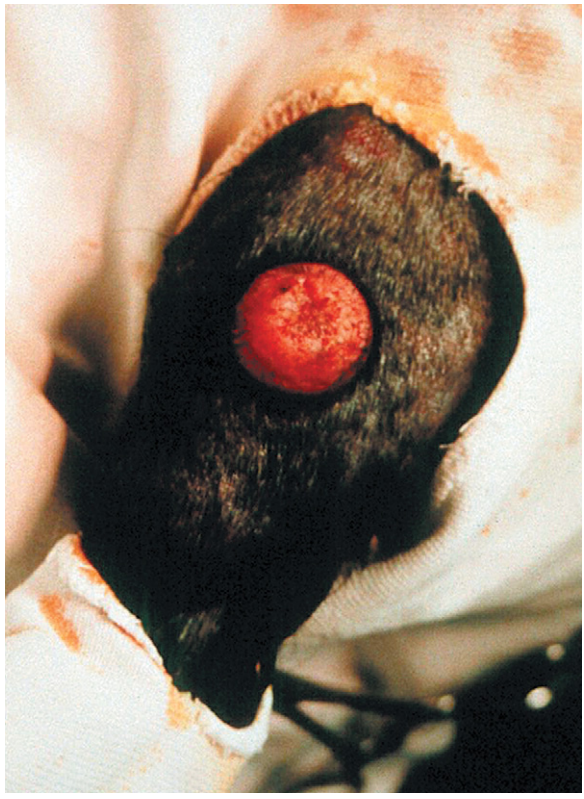

Figure 55-2 Solitary histiocytoma on the hind leg of a dog. Note the classic, sharply demarcated, raised, erythematous, alopecic appearance. (Courtesy Dr. Carlos Souza.)

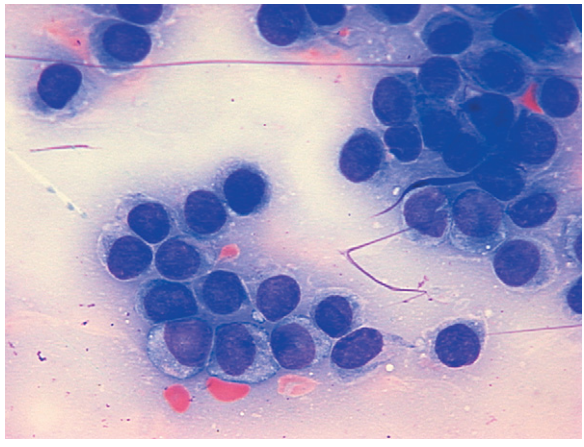

Figure 55-3 Photomicrograph of a cytologic sample obtained by fine-needle aspiration of a solitary cutaneous histiocytoma from a dog. (Courtesy Dr. Anne Barger.)

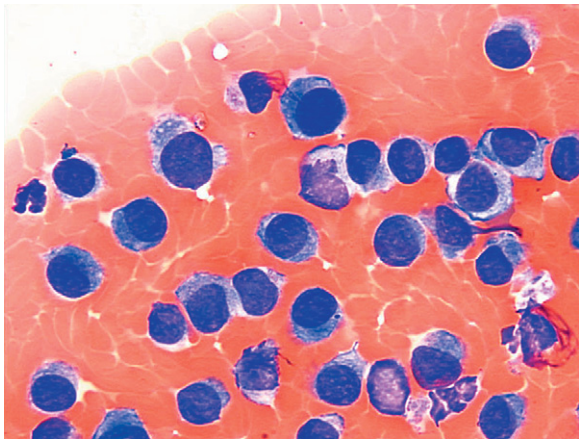

Figure 55-4 Photomicrograph of a cytologic sample obtained by fine-needle aspiration of an extramedullary plasmacytoma from a dog.

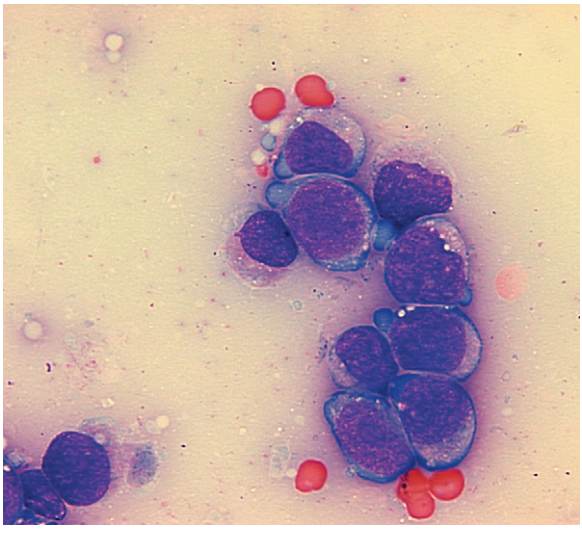

Figure 55-5 Photomicrograph of a cytologic sample obtained by fine-needle aspiration of an epitheliotropic cutaneous T cell lymphoma nodule. (Courtesy Dr. Anne Barger.)

6. Does the biologic behavior of canine cutaneous histiocytomas differ between young dogs (<3 years) and older dogs (>5 years)?

As mentioned in Question 3, histiocytomas of young dogs tend to be solitary, do not usually involve regional lymph nodes, and typically regress spontaneously in 1-3 months. While histiocytomas of older dogs may behave in the same benign fashion, there is an increased risk for development of multiple histiocytomas and migration of Langerhans cells to regional lymph nodes. Furthermore, cutaneous histiocytomas of older dogs are more likely to persist rather than regress. Over time, these reactive lesions may convert to malignant neoplasia with metastatic

potential. Therefore all suspected histiocytomas of older dogs should be completely excised, analyzed by histopathology, and monitored for recurrence.

Because of the fallibility of definitive cytologic diagnosis under light microscopy, all specimens should be submitted for histopathologic diagnosis. Immunophenotyping may be necessary to differentiate benign histiocytoma from malignant histiocytic neoplasia or other histiocytic diseases with aggressive biologic behavior (see Question 15).

7. What is the histologic appearance of solitary cutaneous histiocytoma? Does the appearance change with evolution of the lesion?

During the early growth phase histiocytomas appear as unencapsulated, but circumscribed, dermal nodules, consisting primarily of monomorphic sheets or cords of large, histiocytic cells. Typically the nodule is "top heavy," with a broad presence in the superficial epidermis that narrows like a wedge toward the base in the deeper dermis. Classically, cords of histiocytic cells are described as streaming down from the dermal-epidermal junction. Clusters of histiocytic cells may also be present in the epidermis. In advanced lesions, the epidermis may be ulcerated. Hair follicles and adnexa are usually obliterated within the tumor. The tumor may contain numerous binucleated cells and mitotic figures.

During regression, the tumor becomes infiltrated with lymphocytes (T cells), usually beginning at the deep and lateral margins, gradually becoming scattered throughout the nodule. As the lesion involutes, lymphocytes may outnumber histiocytes, occasionally making definitive diagnosis difficult. Neutrophils may be seen near the ulcerated surface. Plasma cells, eosinophils, and mast cells are less common.

8. How should a solitary cutaneous histiocytoma be treated?

Because the majority of nodules in young dogs regress spontaneously, a common treatment is purposeful benign neglect. If desired, therapeutic intervention may include surgical excision, cryotherapy, electrosurgery, laser ablation, or topical corticosteroid in DMSO. As mentioned in Question 6, older dogs with cutaneous histiocytoma are less likely to experience spontaneous regression of the tumor and have a higher risk for complications; therefore, cutaneous histiocytomas of older dogs should be completely excised.

9. What is the typical signalment of dogs affected by systemic histiocytosis?

Systemic histiocytosis is a non-neoplastic disease of reactive or proliferative histiocytes. Typical age of onset is 2-8 years. Male dogs are over-represented. The condition is most commonly seen in Bernese Mountain Dogs, Rottweilers, Irish Wolfhounds, and Golden Retrievers. The condition has a strong familial tendency, suggesting a genetic predisposition. Although not clearly identified, the mode of inheritance is not autosomal recessive, autosomal dominant, or sex-linked, suggesting a complex multiple gene contribution to inheritance.

10. Describe the lesions of canine systemic histiocytosis.

Dermal nodules are similar in appearance to those of solitary cutaneous histiocytomas, with a similar body site predilection of head, pinna, limbs, and scrotum; however, systemic histiocytosis may also target subcutaneous tissue, lymph nodes, spleen, ocular tissue (conjunctiva and sclera), nasal mucosa, and the lungs (Figures 55-6 and 55-7). Some cases of systemic histiocytosis present with only internal organ involvement, particularly pulmonary histiocytosis; these cases may represent reactive dysregulation of interstitial dendritic cells, rather than dissemination of aberrant Langerhans cells from the epidermis. The clinical course may be waxing and waning, but rarely resolves spontaneously without future recurrence.

11. What is the typical histologic appearance of canine systemic histiocytosis?

Unlike solitary cutaneous histiocytomas, which tend to occur in the superficial dermis, the histopathology of systemic histiocytosis is characterized by multicentric, diffuse, nodular

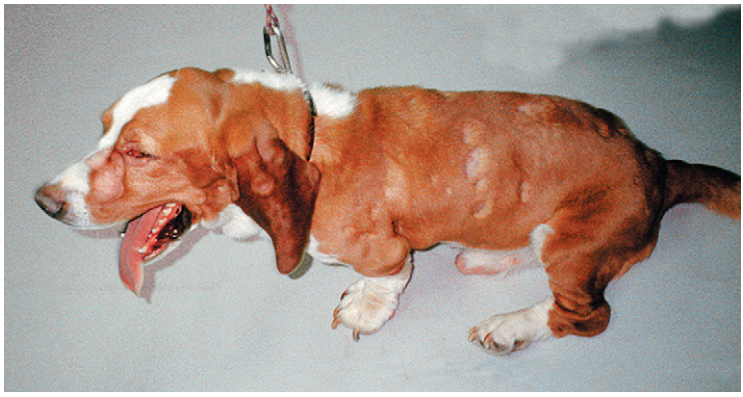

Figure 55-6 Systemic histiocytosis in a Basset Hound. Note the pronounced multicentric subcutaneous nodules. (Courtesy Dr. Karen Campbell.)

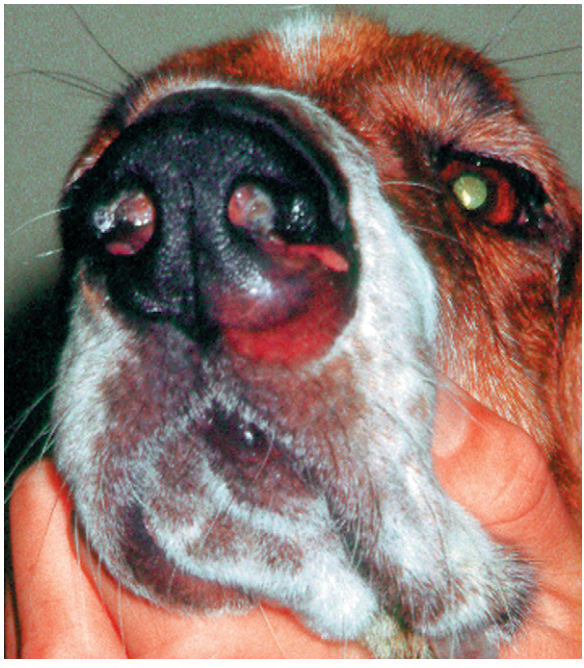

Figure 55-7 Close-up of systemic histiocytosis lesion affecting the nasal planum in the same dog as shown in Figure 55-6. (Courtesy Dr. Karen Campbell.)

accumulations of histiocytic cells in the deep dermis and panniculus. Lymphocytes and neutrophils frequently infiltrate the nodules. To a lesser extent, plasma cells and eosinophils may also be present. Nodules may compress or displace follicles, adnexa, and adipose tissue. Invasion of blood vessels has also been described, which occasionally results in thrombosis and ischemic necrosis.

12. Explain the treatment options available for management of systemic histiocytosis in dogs.

Treatment with glucocorticoids and immunosuppressive, cytotoxic drugs is not generally considered to be completely effective, except in the mildest cases. Leflunomide was described as effective in anecdotal case reports. Oral cyclosporine may also be useful. Treatment of ocular lesions with cyclosporine ophthalmic ointment (Optimmune) may be palliative.

13. How does systemic histiocytosis differ from malignant histiocytosis (synonym: canine disseminated histiocytic sarcoma)?

Unlike systemic histiocytosis, which is likely a phenomenon of dysregulation of dendritic cells, malignant histiocytosis is a true sarcoma of myeloid dendritic cells. Canine disseminated histiocytic sarcoma begins as a solitary invasive tumor of the deep dermis, subcutis, synovial tissue, or internal organs, which metastasizes to regional lymph nodes and disseminates throughout the body. Most histiocytic sarcomas are believed to arise from interstitial dendritic cells, but malignant transformation of migrating dendritic cells in the lymph nodes is also suspected to occur.

14. Why is the term "malignant fibrous histiocytoma" no longer considered correct in describing the morphology of sarcomas with histiocytic characteristics on light microscopy?

"Malignant fibrous histiocytoma" is a descriptive term used for sarcomas of indeterminate origin with a histiocytic morphologic appearance. Unfortunately, this description results in a clustering of tumors with distinctly different biological behavior and prognosis under a single umbrella term. Immunophenotyping of tumors previously described as malignant fibrous histiocytomas revealed a variety of different cellular origins, including fibrosarcoma, leiomyosarcoma, rhabdomyosarcoma, liposarcoma, synovial cell sarcoma, and histiocytic sarcoma. Identification of cellular origin is beneficial to clinicians seeking to improve accuracy of prognosis, selection of appropriate therapy, and advancement of future research.

15. How can immunohistochemical markers assist pathologists in the differentiation of so many different diseases that appear to be "histiocytic" on light microscopy, but vary tremendously in biologic behavior and prognosis?

Advances in immunophenotyping with canine cell-surface molecules permit more accurate, specific identification of cellular phenotypes of the various histiocytic diseases. As with differentiating sarcomas with similar morphologic appearance, a better understanding of cellular phenotype of different dendritic cell diseases improves accuracy of diagnosis, prognosis, therapy, and knowledge of these conditions. Table 55-1 shows the phenotypic characteristics of cells isolated from different canine histiocytic diseases.

16. Should cutaneous histiocytoma or histiocytosis be a differential diagnosis for cutaneous nodular disease in cats?

Yes. The veterinary literature contains limited reports of cutaneous histiocytic disease in cats. A small number of feline cases with multiple cutaneous nodules on the head and neck have been described. Histopathology of the lesions shows a proliferation of histiocytic round cells with epidermal tropism; immunophenotyping suggests a dendritic cell origin. Two cases of dermal accumulations of dendritic cells with an angiocentric distribution, rather than epitheliotropism, have been reported. Solitary and disseminated histiocytic sarcomas have also occasionally been observed in cats.

17. What is mycosis fungoides?

Mycosis fungoides (MF) is the archetypal epitheliotropic T cell lymphoma (epitheliotropic CTCL), first described in humans in 1806. The name, "mycosis fungoides," was coined by an

Table 55-1 *Cell Surface Phenotype of Canine Histiocytes in Normal and Diseased States*

MOLECULE	NORMAL LANGERHANS CELLS	NORMAL DERMAL DENDRITIC CELL	SOLITARY CUTANEOUS HISTIO-CYTOMA	SYSTEMIC HISTIO-CYTOSIS	MALIGNANT HISTIO-CYTOSIS (SARCOMA)
CD1	+	+	+	+	+
CD4	+/–*	+/–*	–	+	–
CD11	+	+	+	+	+
CD80/86	+/–*	+/–*	+/–†	+	not reported
CD90	-	+	–	+	–
MHC II	+	+	+	+	+
ICAM-1	+/–*	+	+/–†	+	+
E-cadherin	+	–	+	–	–

Data from Affolter VK, Moore PF: Histiocytes in skin disease. In Thoday KL, Foil CS, Bond R (eds): *Advances in veterinary dermatology*, ed 4, Oxford, 2002, Blackwell Science, pp 111-130; and Baines SJ, et al. Maturation states of dendritic cells in canine cutaneous histiocytoma. In Thoday KL, Foil CS, Bond R (eds): *Advances in veterinary dermatology*, ed 4, Oxford, 2002, Blackwell Science, pp 131-141.
*Expression depends on the maturation state of the cell. CD4, CD80, CD86, and ICAM-1 are up-regulated in antigen-presenting states.
†During tumor regression cells express CD80, CD86 and ICAM-1; these molecules are absent during the early stage of tumor development.

early observer describing the mushroom-like appearance of the nodular stage of the disease. The term is retained in the human literature, but is now used to specifically describe epitheliotropic CTCL with a CD4+ T cell phenotype affecting the skin or oral cavity. In veterinary literature, the term mycosis fungoides has been applied to all forms of cutaneous or oral epitheliotropic CTCL of all veterinary species regardless of specific cellular phenotype.

18. Define epitheliotropism.

Epitheliotropism refers to the movement of neoplastic cells toward and into an epithelial layer. In the case of mycosis fungoides, the neoplastic T lymphocytes are seen on histopathology to invade the epidermis (epidermotropism) or the follicular infundibulum. Non-epitheliotropic cutaneous lymphoma also exists.

19. Describe the progression of clinical lesions for mycosis fungoides in humans.

Clinical signs of MF can be highly variable between individuals, as well as within the same individual over time. However, some commonalties and generalizations have been made to categorize the behavior of this tumor type. In 1870, Bazin described a natural progression of clinical lesions, which continues to be used today with minor modifications. Affected individuals progress from a "pre-mycotic" patch stage, followed by formation of slightly raised plaques, then to a nodular or tumor stage, and finally to a fourth stage of disseminated disease, representing metastasis to lymph nodes and viscera.

Progression from the patch stage to the plaque stage and beyond is highly unpredictable; many patients remain in the patch stage with limited morbidity and no mortality for decades before progression. Other patients suffer rapid progression from patch to plaque, to nodule, to disseminated disease.

A folliculotropic variant of the disease is characterized by follicular papules, comedones or cyst-like lesions, rather than patches and plaques. Bullous or pustular patterns may also occur, but

these lesions likely represent a secondary epithelial disorder superimposed on MF lesions, rather than a distinctive variant.

20. Describe in detail the clinical appearance of the four stages of progression as outlined in Question 19.

The early patch stage is characterized by well-demarcated erythematous macules, which may be slightly scaly. The degree of redness is highly variable. Hypopigmentation may also be observed in more highly pigmented individuals, as melanocytes drop out of the stratum basale in lesional skin. The lesions are primarily distributed on the trunk and proximal extremities. At this stage, the malignant T cell population is easily suppressed by ultraviolet radiation; therefore patches are most noticeable in areas covered by clothing.

The plaque stage describes development of sharply demarcated red to reddish-brown raised lesions. These plaques may have a serpiginous or annular morphology, ulcerate, or have adherent scale (Figure 55-8).

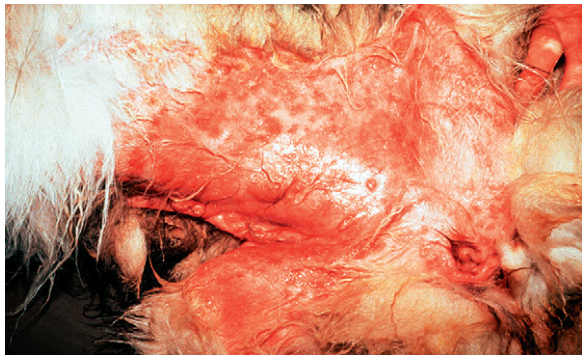

Figure 55-8 Abdomen of a Shetland Sheepdog with epitheliotropic cutaneous T cell lymphoma. Note the generalized erythematous macules and ulcerated plaques. (Courtesy Dr. Karen Campbell.)

The third stage of progression describes the development of nodular lesions or tumors on the surface of the skin. In most cases, the nodules coexist with residual patches and plaques.

Development of disseminated extracutaneous neoplasia during mycosis fungoides differs from other types of lymphomas. Typically with lymphomas, such as Hodgkin's disease, extension progresses predictably from the local site to regional lymph nodes to other tissues. In mycosis fungoides, malignant T cells are not delayed by local lymph nodes; instead, true metastasis appears to be rapid and generalized once the malignancy extends beyond the dermis. Dissemination of malignant epitheliotropic CTCL lymphocytes is believed to be by the hematogenous rather than lymphatic route.

21. Define the term "erythroderma" and describe the application of this term to mycosis fungoides.

Erythroderma is a term used to describe lesions characterized by pruritus, exfoliation, and erythema (Figures 55-9 and 55-10). Erythroderma in mycosis fungoides may occur as the sole clinical sign, or can appear concurrently with any stage of the disease. Generalized erythroderma is categorized as a T4 tumor stage, when using the TNM classification scheme for predicting prognosis (Table 55-2).

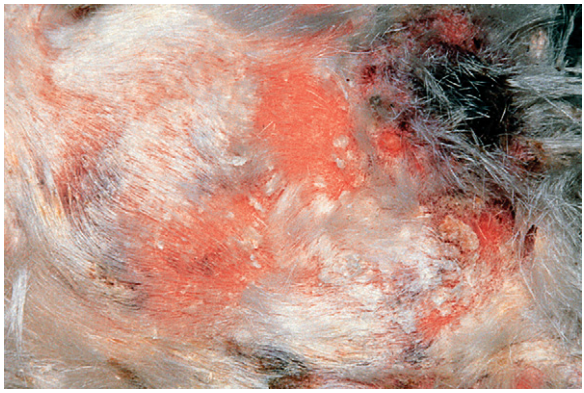

Figure 55-9 Exfoliative erythroderma on the lateral thorax of a dog with epitheliotropic cutaneous T cell lymphoma. (Courtesy Dr. Karen Campbell.)

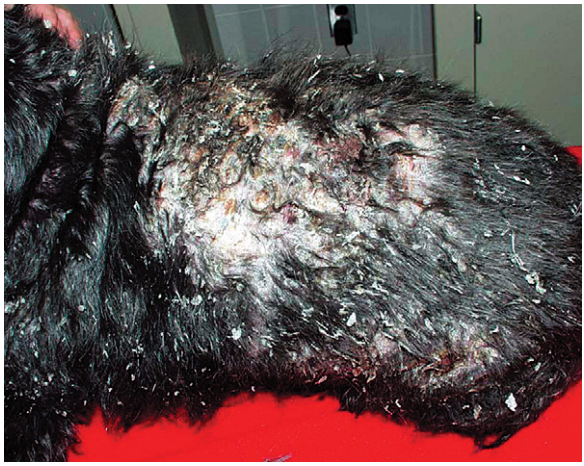

Figure 55-10 Generalized scale on the trunk of a Scottish Terrier with epitheliotropic cutaneous T cell lymphoma.

22. What is the "d'emblée" variant of mycosis fungoides in humans?

In most cases of mycosis fungoides the cutaneous tumor progresses from a patch or plaque stage to a nodular stage. The "d'emblée" variant refers to an unusual clinical presentation in which the nodules develop without a pre-existing patch or plaque stage. This may represent a distinct form of epitheliotropic T cell lymphoma rather than a variant of mycosis fungoides.

23. What are Sézary cells?

The term "Sézary cells" is used to describe small, 8-20 µm, malignant lymphocytes present in circulation of a patient with mycosis fungoides. Classically, Sézary cells have a highly convoluted, "cerebriform" nucleus. Sézary syndrome describes the leukemic form of mycosis fungoides: cutaneous lesions with Sézary cells identified on peripheral blood cytology.

Table 55-2 *TNM Classification System for Mycosis Fungoides in Humans*

DESIGNATION	CLINICAL OR LABORATORY FINDING
	Skin
T1	Patch or plaque covering less than 10% of body surface
T2	Patch or plaque covering greater than 10% of body surface
T3	Nodule or tumor present
T4	Generalized exfoliative erythroderma
	Lymph Node
N0	Lymph node not clinically involved
N1	Lymph node enlarged, but histologically clear
N2	Neoplastic lymphocytes present, non-effacing architecture
N3	Clusters of neoplastic lymphocytes
N4	Effacement of architecture by neoplastic lymphocytes
	Viscera
M0	No visceral involvement
M1	Visceral metastasis
	Blood
B0	No circulating neoplastic lymphocytes or less than 5% of total
B1	Circulating neoplastic lymphocytes greater than 5% of total

Data from LeBoit PE, McCalmont TH: Cutaneous lymphomas and leukemias. In Elder D, Elenitsas R, Jaworsky C, Johnson B (eds): *Lever's histopathology of the skin,* ed 8. Philadelphia, 1997, Lippincott Raven, pp 805-847.

24. How does pagetoid reticulosis differ from other forms of epitheliotropic CTCL?

Pagetoid reticulosis is a clinical variant of epitheliotropic CTCL described in humans and dogs. This variant typically exhibits extreme epidermotropism by malignant T lymphocytes with minimal to absent dermal involvement. The malignant cells are often characterized by pericellular halos within the epidermis. To early authors, the malignant cells of pagetoid reticulosis were reminiscent of the histopathologic appearance of haloed malignant cells seen in Paget's disease, a carcinoma of the breast seen in women.

Two subtypes of pagetoid reticulosis occur: (1) a localized form (Woringer-Kolopp), which can be cured completely by surgical excision if removed early in the disease progression; and (2) a generalized form (Ketron-Goodman), which has a clinical course similar to mycosis fungoides.

25. How common is epitheliotropic CTCL in dogs and cats?

In veterinary oncology, malignant lymphomas are common, accounting for 7-24% of all neoplasia in DOGS, and 33% of all neoplastic diseases in cats. However, the majority of these are of B cell origin and infrequently involve cutaneous sites. Epitheliotropic CTCL represents only 3-8% of all canine lymphomas, and as few as 2% of all feline lymphoma cases.

26. Describe the clinical presentation and progression of epitheliotropic CTCL in dogs.

In dogs, the clinical presentation and course is similar to that described in humans. Like mycosis fungoides in humans, canine epitheliotropic CTCL is highly variable between individuals.

The most common clinical sign in dogs is erythema, followed by varying degrees of scale, pruritus, alopecia, papules, plaques, nodules, ulceration, and depigmentation (Table 55-3). Muco-

Table 55-3 ***Cutaneous Signs of Epitheliotropic Cutaneous T Cell Lymphoma in the Canine***

MORPHOLOGIC PRESENTATION	PERCENTAGE SEEN (N=26)
Erythema	80.8
Pruritus	38.5
Scaling	61.5
Crusting	38.5
Papules	15.4
Plaques	61.5
Nodules	57.7
Ulceration	42.3
Mucosal lesions	38.5

Adapted from Beale KM, Bolon B: Canine cutaneous lymphosarcoma: epitheliotropic and non-epitheliotropic, a retrospective study. In Ihrke PJ, Mason IS, White SD (eds): *Advances in veterinary dermatology,* vol 2. New York, 1993, Pergamon, pp 273-284.

cutaneous ulceration and depigmentation, as well as infiltrative or ulcerative oral disease, are also common. Foot pads, when they are involved, may appear depigmented, hyperkeratotic, or ulcerated.

The early stages of solitary, erythematous patches are frequently missed under the thick coat of many dogs; therefore, the disease is usually not recognized until more noticeable signs, such as multifocal plaques or nodules, severe scaling, or pruritus, are present.

27. How does epitheliotropic CTCL present in cats?

In cats, sharply demarcated, annular areas of alopecia, erythema, scaling on the trunk or exfoliative erythroderma of the head and neck are common initial signs. Some cats are presented with eruptions easily confused with miliary dermatitis. Plaques, nodules, and oral lesions are observed less commonly in cats than in dogs and humans.

28. What are the principal differential diagnoses for cutaneous epitheliotropic T cell lymphoma in dogs? In cats?

The order of most likely differential diagnoses will vary tremendously depending on the clinical signs present at the time (Table 55-4). Since epitheliotropic CTCL may mimic clinical signs or lesions of so many other diseases, veterinarians should consider CTCL as a differential for patients that fail to respond to appropriate therapy for more common conditions. Failure to consider the possibility of epitheliotropic CTCL during management of other exfoliative, pruritic, or ulcerative diseases may delay biopsy, diagnosis, and appropriate therapy, potentially altering the outcome of the case.

29. Is cutaneous lymphoma in cats associated with the feline leukemia virus (FeLV)?

Maybe. Most cats with epitheliotropic or non-epitheliotropic cutaneous lymphoma are seronegative for FeLV. However, one study demonstrated the presence of FeLV antigen in 40% of the malignant cells isolated from cats with non-epitheliotropic CTCL. A separate study reported the extraction of proviral DNA from the tumor cell DNA of a cat with epitheliotropic CTCL.

Table 55-4 ***Important Differential Diagnoses for Epitheliotropic Cutaneous T Cell Lymphoma***

PREDOMINANT CLINICAL SIGN	DOGS	CATS
Exfoliative erythroderma	Atopic dermatitis	Miliary dermatitis
	Adverse food reaction	Atopy
	Flea allergy dermatitis	Adverse food reaction
	Pyoderma	Pyoderma
	Malassezia dermatitis	Dermatophytosis
	Dermatophytosis	Demodicosis
	Demodicosis	*Demodex gatoi* (short form)
	Sarcoptes	*Notoedres*
	Cheyletiella	*Otodectes*
	Seborrhea	*Cheyletiella*
	Sebaceous adenitis	Lupus erythematosus
Papular dermatitis	Pyoderma	Pyoderma
	Dermatophytosis	Dermatophytosis
	Demodicosis	Miliary dermatitis
	Pemphigus foliaceus	Pemphigus foliaceus
	Comedones	Many others
Nasal depigmentation	Discoid lupus erythematosus	Actinic dermatitis
	Systemic lupus erythematosus	Squamous cell carcinoma
	Uveodermatologic syndrome	Immune-mediated diseases
	Erythema multiforme	Cutaneous drug eruption
	Vitiligo	
Erythematous macules and plaques	Erythema multiforme	Eosinophilic granuloma complex
	Calcinosis cutis	Erythema multiforme
	Granulomatous inflammation	Granulomatous inflammation
	Other depositional disorders	Xanthomatosis
	Other neoplasia	Other depositional disorders
		Other neoplasia
Oral or mucocutaneous ulceration	Pemphigus vulgaris	Eosinophilic granuloma complex
	Bullous pemphigoid	Stomatitis
	Lupus erythematosus	Lupus erythematosus
	Drug eruption	Pemphigus vulgaris
	Stomatitis	Drug eruption
	Uremic ulceration	Viral
All clinical signs simultaneously	Systemic lupus erythematosus	Systemic lupus erythematosus
	Pemphigus diseases	Pemphigus diseases
	Uveodermatologic syndrome	Drug eruption
	Erythema multiforme	Combination of diseases
	Cutaneous drug eruption	

This list is not intended to be exhaustive.

30. Do dogs with epitheliotropic CTCL commonly develop hypercalcemia?

No. Hypercalcemia frequently associated with other T cell lymphomas is not a common feature of epitheliotropic CTCL. Hypercalcemia of malignancy seen in veterinary lymphoma cases usually results from production and release of parathyroid hormone–related peptide (PTHrp).

31. Describe the histologic characteristics of cutaneous epitheliotropic T cell lymphoma.

Histologic findings can be as varied as the clinical presentation. In general the classic histologic findings are characterized by (1) epitheliotropism—malignant lymphocytes present in the stratum basale, stratum spinosum, or follicular infundibulum; (2) Pautrier's microabscesses—clear lacunae within the epidermis occupied by an accumulation of two or more neoplastic lymphocytes; (3) mycosis cells—large, hyperchromatic lymphocytes with nuclear atypia characterized by hyperchromatic, indented nuclei, cerebriform convolutions, or finger-like projections; and (4) a lichenoid band of pleomorphic lymphoid cells in the superficial dermis. Pigmentary incontinence, melanocytes dropping out of the stratum basale into the superficial dermis, may be observed in specimens taken from recently depigmented lesions.

Histopathologic progression mirrors clinical evolution. In the early patch stage, only a small number of lymphocytes may be present in a linear arrangement on the epidermal side of the dermal-epidermal interface; this "string of pearls" configuration in the basal layer of the epidermis may be subtle and easily missed. Pautrier's microabscesses can be uncommon at the patch stage. Neoplastic cells should appear slightly larger and have nuclear hyperchromasia and increased nuclear convolution relative to normal lymphocytes present in the dermis. Immunohistochemical staining with CD3 and CD79a may be useful in differentiating lymphocytes and highlighting epitheliotropic arrangement; T cells should be CD3+ and CD79a–.

As lesions progress to the plaque stage, increased epidermal hyperplasia coupled with a dense, band-like infiltration of the superficial dermis develops. This dermal infiltrate, or lichenoid band, parallels the dermal-epidermal junction. This stage may be difficult to differentiate from other diseases that result in an interface dermatitis, such as lupus erythematosus, uveodermatologic syndrome, erythema multiforme, severe pyoderma, or ectoparasitism.

The nodule stage is characterized by dense neoplastic infiltrate extending into the deep dermis and panniculitis. Hair follicles and adnexa may be effaced, leaving only the glassy membrane to indicate the presence of the former follicle.

32. When selecting sites for biopsy from a patient with multiple lesion types, which lesion(s) are most likely to yield diagnostic histopathologic pattern? Which lesion(s) is least valuable to biopsy?

If present, nodular lesions are the preferred specimens for biopsy, followed by non-ulcerated plaques, and recently depigmented regions on the nasal planum or lips. Recently depigmented areas may be erythematous or have a gray appearance (Figure 55-11).

If there are no nodules, plaques, or recently depigmented areas, then erythematous macules or the erythematous region adjacent to ulcers should be selected. Taking multiple biopsy samples from various different-appearing lesions will maximize the probability of obtaining a diagnostic sample for the pathologist.

Ulcers are the least valuable lesions to biopsy, as the epidermis, and therefore evidence of epitheliotropism, will be absent. In addition, ulcers are rapidly colonized by bacterial organisms, resulting in an extensive dermal inflammatory infiltrate that will mask evidence of the primary cause of the ulceration.

33. How do the immunohistochemistry characteristics of canine epitheliotropic CTCL differ from the human disease?

In humans, malignant T cells observed in epitheliotropic CTCL are most frequently CD4+/CD8-, occasionally dual negative, and rarely CD4-/CD8+. In dogs, epitheliotropic CTCL

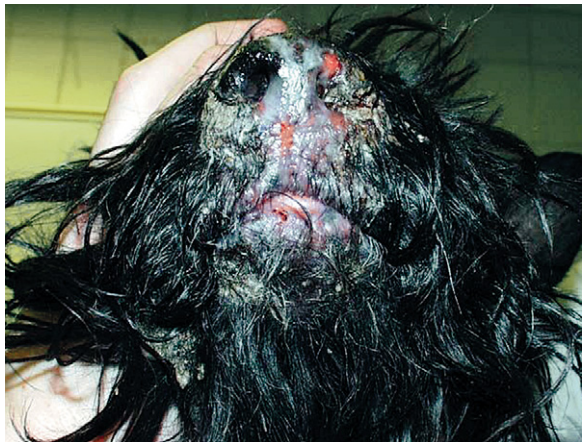

Figure 55-11 Depigmentation on nasal planum and mucocutaneous junctions of the same dog as shown in Figure 55-10.

is most often found to be caused by CD4-/CD8+ malignant T cells. Additionally, the majority of canine epitheliotropic CTCL T cells express γδ T cell receptor (TCR), rather than TCR-αβ.

34. What is the prognosis for a patient affected by epitheliotropic CTCL?

Because of the unpredictable clinical progression, discussing prognosis can be confusing for clinicians, human patients, and pet owners. Since surgical excision is often not feasible and T cell lymphomas are less responsive to chemotherapy, achieving a durable complete remission or cure is rare. For this reason, many texts report the prognosis for epitheliotropic CTCL to be grave. On the other hand, patients may remain in the patch or scaling stage of the disease for a long time, with limited morbidity and no mortality; therefore, patients in the early stages may be considered to have a fair prognosis. In fact, human patients with patch-only disease do not have significantly different survival rates compared with age-matched control populations. Similarly patients with solitary nodules or localized disease may be cured by surgical excision or local radiation therapy, if the lesion is treated before dissemination. Unfortunately, many patients are not caught during the early stages or their disease progresses rapidly from patches to multicentric advanced lesions to systemic metastasis after only a short course. In general terms, the more advanced the lesions, the worse the prognosis.

In veterinary patients, euthanasia due to perceived poor quality of life determines survival more often than death due to organ failure. Before systemic involvement, the degree of pruritus, ulceration, oral lesions, and secondary infections have the largest impact on quality of life. Many dogs with generalized alopecia, erythema, depigmentation, plaques, and nodules continue to behave normally with no signs of systemic illness. As long as the owners accept the cosmetic changes to their pet, prognosis may be considered fair. Therefore, survival times for epitheliotropic CTCL, in dogs and cats, may depend as much on the clinician's ability to control pruritus as the response of the malignancy to chemotherapy.

35. Discuss the treatment options available for management of epitheliotropic CTCL.

Therapy for epitheliotropic CTCL can be divided into two areas: chemotherapy aimed at killing or inhibiting malignant cells and therapy designed to palliate quality of life factors, such as pruritus and secondary infections.

In humans, one of the most common treatments during the patch stage is topical application of the alkylating agent mechlorethamine hydrochloride, a form of nitrogen mustard. Humans in prolonged contact may develop severe irritant dermatitis, urticaria, hyperpigmentation, bullous eruptions, and secondary neoplasia. Because of the carcinogenic potential and other adverse skin reactions to long-term exposure by the owner during application to the pet, topical mechlorethamine hydrochloride is not commonly used in veterinary patients.

Other therapies used in human oncology during the cutaneous stages include topical carmustine (BCNU), oral lomustine (CCNU), topical and oral corticosteroids, topical or oral retinoids, interferon-α2a, psoralen with UVA radiation, and total skin electron beam radiation. A recently available option is denileukin diftitox, an immunoconjugate that specifically targets T lymphocytes expressing IL-2 receptors.

BCNU has fewer adverse side effects than mechlorethamine, but is still not commonly used in veterinary patients because of the extensive haircoat that prevents thorough application.

Once extracutaneous involvement has occurred, single agent or combination systemic chemotherapy is used. Oral corticosteroids are palliative in animals, and may be used alone (if no other therapy is intended) or in combination with chemotherapy protocols, such as cyclophosphamide, vincristine (Oncovin) and prednisone (COP), L-asparaginase plus COP, or doxorubicin plus COP. Unfortunately these protocols have not been shown to be successful in prolonging survival times in canine patients. Newer protocols utilizing CCNU are anecdotally useful, but large prospective studies have not been published.

Additional therapy includes topical and systemic high-dose omega-3 and omega-6 fatty acids, synthetic retinoids, cyclosporin, interferon, and dacarbazine.

36. Are synthetic retinoids useful in management of epitheliotropic CTCL in veterinary patients?

The effects and outcome in canine patients treated with retinoids are not well described. The veterinary literature contains only short case studies and anecdotal reports regarding the clinical efficacy of synthetic retinoids. In these accounts, oral retinoids are reported to be palliative in some canine and feline cases. Retinoids alter replication, keratinization, and metabolism of epidermal keratinocytes, normalizing the state of cells surrounding the malignant T cells, palliating clinical signs of the disease. Theoretically, retinoids are most useful in cases associated with exfoliative erythroderma rather than nodular or ulcerative disease. Malignant T cells do have receptors for retinoids and may be directly affected as well. Bexarotene, a second-generation RXR-specific retinoid, has been shown to induce apoptosis of malignant T cells. In human clinical trials using bexarotene, response rates of previously treated CTCL cases exceeded 50%.

Publications on the use of retinoids in cats are fewer still. Cats have increased sensitivity to vitamin A toxicity than dogs, and theoretically could experience greater adverse side effects to synthetic retinoid therapy.

37. Are all cutaneous lymphomas derived from T cells?

No. While, epitheliotropic cutaneous lymphoma is always derived from T lymphocytes, non-epitheliotropic cutaneous lymphoma may be T cell, B cell, natural killer (NK) cells, or other null cells (non-T, non-B). Put another way, cutaneous T cell lymphoma may be either epitheliotropic or non-epitheliotropic, but cutaneous B cell lymphoma is always non-epitheliotropic (Figure 55-12).

38. How does non-epitheliotropic cutaneous lymphoma differ from epitheliotropic CTCL in dogs and cats?

Not all cutaneous lesions caused by neoplastic lymphocytes are epitheliotropic. In fact, non-epitheliotropic cutaneous lymphoma is more common in cats than the epitheliotropic variety. Clinically, non-epitheliotropic lymphoma may be solitary or multicentric. While nodules are

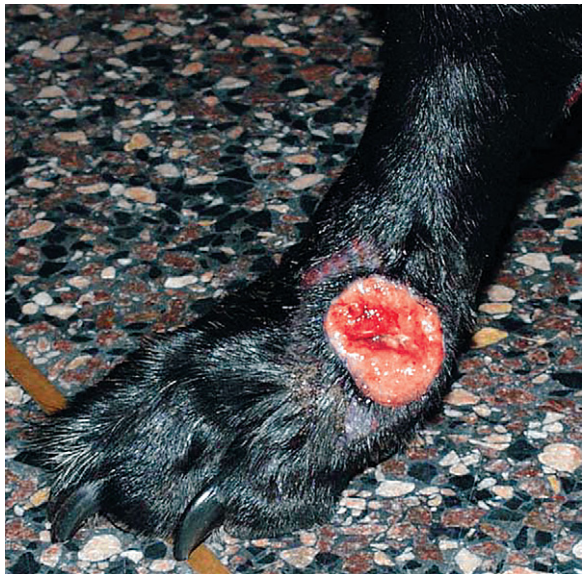

Figure 55-12 Cutaneous B cell lymphoma on the hind limb of a Labrador Retriever.

almost invariably present with this neoplasia, the nodular lesions may be accompanied by generalized erythroderma, pruritus, oral ulcerations, or bizarre, arciform, serpiginous plaques.

Histologically, the tumor consists of malignant lymphocytes distributed in nodular to diffuse pattern in the dermis and subcutis, without the marked epidermotropism that characterizes mycosis fungoides and its variants. In most cases, the uppermost dermis is typically spared, leaving an observable "Grenz zone," defined as an area of unaffected dermis between the epidermis and the dermal lesion. Less commonly, the infiltrate can extend up to the dermal-epidermal junction. On rare occasions there is upward migration into the epidermis. Adnexa are usually obliterated, but the follicular epithelium is normally left intact. Immunophenotyping studies have demonstrated that the majority of these cases are T lymphocyte tumors, although, as mentioned in Question 36, some varieties may be B cell, NK cell, or other null-cell.

If the lesions are solitary, surgical excision may result in cure or long-term remission. Radiation therapy is often palliative for non-resectable solitary tumors. Multicentric tumors can be treated with similar systemic protocols as described for epitheliotropic CTCL. Survival times in dogs range from 4 to 8 months, from onset of clinical disease to euthanasia or death.

39. What are the clinical features of cutaneous plasmacytomas in dogs and cats?

Cutaneous extramedullary plasmacytoma (EMP) is typically a solitary tumor of older dogs. There is no reported gender predilection. Cocker Spaniels are believed to be over-represented. EMPs are usually small (1 to 2 cm), well-circumscribed, raised, smooth, and erythematous nodules. Occasionally larger tumors may develop. Multiple tumors and ulcerative changes can also occur. There is a strong body site predilection for special sites such as digits, lips, and the external ear canal (Figure 55-13). The tumor does not commonly arise on normal haired skin far from mucocutaneous junctions. Metastasis is rare, so surgical excision is usually curative. For non-resectable or incompletely resected tumors, radiation therapy should be considered because EMPs tend to be highly sensitive to radiation.

Although EMP is a relatively common dermal neoplasia of dogs, the condition has rarely been reported in cats.

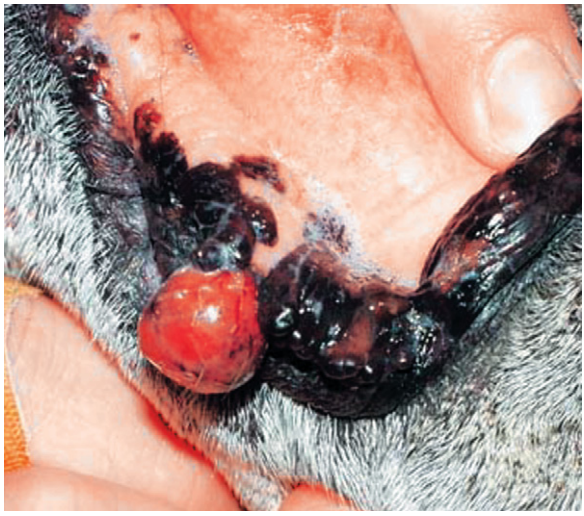

Figure 55-13 Extramedullary plasmacytoma on the lip of a Boxer.

40. Describe the cytologic and histiologic characteristics of a plasmacytoma.

Plasmacytomas typically exfoliate well on fine needle aspiration, revealing large numbers of well-differentiated, round to oval cells with an eccentric single nucleus and a zone of perinuclear clearing (see Figure 55-4). On histopathology, the tumor is made up of sheets, cords, or packets of variably differentiated, monomorphic or pleomorphic malignant plasma cells. Approximately 10% of tumors contain amyloid; although EMP is rarely associated with multiple myeloma.

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56. MELANOCYTIC NEOPLASMS

Laura B. Stokking, PhD, DVM

1. What are the differences between melanocytomas, melanomas, cutaneous melanomas, malignant melanomas, and nevi?

All of these terms refer to proliferations of melanocytes. Normally, melanocytes are restricted to the basal layer of the epidermis. The cells transfer melanosomes, melanin-containing vesicles, to keratinocytes in the overlying spinous layer. A melanocytoma is a neoplastic proliferation of melanocytes; the suffix "-cytoma" indicates that the neoplasm is benign. The use of the terms "melanoma" and "cutaneous melanoma" to describe both benign and malignant proliferations of melanocytes has produced some confusion. No misinterpretation exists if the term "malignant melanoma" is employed: the tumor described has aggressive biologic behavior and a strong likelihood of metastasis.

In humans, a "nevus" is basically a birthmark: a congenital, abnormal proliferation of one or more components of skin. In human dermatology, "nevus" is used to describe a plethora of benign congenital or acquired proliferation or deficiency of any cell type present in the dermis or epidermis (such as melanocytomas, hemangiomas, fibromas, lipomas, or proliferations of adnexal components). The term "cutaneous hamartoma," synonymous with nevus, is used more commonly in veterinary medicine; a hamartoma is a benign proliferation of cells within the tissue or organ in which the cells would normally occur. Several common nevi in humans are pigmented; the cells comprising them were thus originally named "nevus cells." Study of nevus cells in culture demonstrated them to be melanocytes. The lesions formerly described as pigmented epidermal nevi, renamed pigmented epidermal plaques, are discussed in Chapter 51.

2. What are the signalments of dogs and cats most commonly diagnosed with melanocytoma and malignant melanoma?

Signalments and common locations of melanocytoma and malignant melanoma in dogs are compared in Table 56-1. Clinical appearance alone should not be used to distinguish benign melanocytomas from malignant melanomas.

Cats have no breed or gender predispositions for melanocytic neoplasms. Ages of cats with cutaneous melanocytic neoplasms (benign and malignant) range from 6 months to 19 years, with a median of about 10-12 years.

3. List differential diagnoses for melanocytic neoplasms in dogs and cats.

See Table 56-2.

4. Histopathologic descriptions of canine and feline melanocytomas and malignant melanomas often include descriptors such as "junctional," "compound," "dermal," "signet-ring," "balloon cell, "or "clear cell." What is the meaning and prognostic significance of these terms?

The terms "junctional," "compound," and "dermal" refer to the location of the melanocytic neoplasm within the skin section. The tumor arises at the dermal-epidermal junction in junctional neoplasms and within the dermis in dermal tumors. Compound neoplasms contain clusters of melanocytes within the epidermis, the dermis, or the epithelium of hair follicles. Junctional tumors have not been reported in dogs. Tumor location within the skin section carries no prognostic information.

Table 56-1 ***Signalments and Common Locations of Melanocytomas and Malignant Melanomas in Dogs***

TYPE	SIGNALMENT	LOCATION
Melanocytoma	*Average age*: 9 yr *Breed predisposition:* Cocker Spaniels, Scottish Terriers, Airedales, Boston Terriers, Springer Spaniels, Boxers, Golden Retrievers, Miniature Schnauzers, Irish Setters, Irish Terriers, Chow Chows, Chihuahuas, Doberman Pinschers *Gender predisposition:* None proved	Head (eyelid, muzzle) Trunk Paws (interdigital)
Malignant melanoma	*Age:* 9-11 yr, can be as young as 3 *Breed:* Heavily pigmented Cocker Spaniels, Scottish Terriers, Airedales, Boston Terriers, Standard and Miniature Schnauzers, Gordon Setters, Irish Setters, and Golden Retrievers *Gender predisposition:* None proved	Eyelids Digits Nailbeds Trunk Oral cavity

Melanocytes are neuroectodermal in origin; thus can develop into either round, epithelioid, or spindled cells. Cells within the neoplasms can be pleomorphic; one morphology may predominate, several might be present within a single tumor. The predominant cell type does not appear to predict biologic behavior. Balloon cells, also called clear cells, are large and either round or polygonal. The nucleus is central or eccentric and can itself be pleomorphic. A single nucleolus is usually present. The cytoplasm is clear and finely granular, with abundant vacuoles produced by abnormal melanosome formation, lipids, or glycogen. Balloon cell malignant melanomas are relatively common in cats, but rare in dogs.

Signet-ring melanocytic neoplasms are more common in cats than in dogs. The nucleus in signet-ring cells is pushed into a crescent shape at the edge of the cell by cytoplasmic intermediate filaments (vimentin). Intracytoplasmic accumulations of many substances can create a similar cytologic morphology; signet-ring melanocytic neoplasms may be amelanotic or only faintly pigmented. Several differential diagnoses should be considered, including lymphoma, plasmacytoma, or other lymphoid tumors; adenocarcinomas of any origin; carcinomas (mammary, gastric, intestinal); lipoma or liposarcoma; smooth muscle tumors; and other mesenchymal tumors.

5. What are risk factors for malignant melanoma in dogs and cats?

Risk factors for malignant melanoma in humans include light complexions, exposure to ultraviolet radiation, a family history of malignant melanoma, multiple atypical or large congenital melanocytic nevi, mutated or abnormal tumor suppressor genes, and exposure to chemical carcinogens such as certain insecticides. The causes of benign or malignant melanocytic tumors in dogs and cats are not fully known. Chemical mutagens may be involved: topical application of tar extracts resulted in malignant melanoma in dogs. Increased prevalence in certain canine breeds suggests a role of genetic predisposition to both melanocytoma and malignant melanoma (see Table 56-1). Associations with aberrant function of tumor suppressor genes, such as *p53*, retinoblastoma-1 (*Rb-1*), and the cyclin-dependent kinase inhibitor family, have been demonstrated in malignant melanoma from several species.

Table 56-2 *Differential Diagnoses for Melanocytic Neoplasms in Dogs and Cats*

PIGMENTED	UNPIGMENTED	CLAW BED
Melanocytoma	Melanocytoma (amelanotic)	Melanocytoma
Malignant melanoma	Malignant melanoma (amelanotic)	Malignant melanoma
Pigmented hamartoma	Hamartoma	Squamous cell carcinoma
Basal cell tumor (cats only)	Basal cell tumor (cats only)	Keratoacanthoma
Basal cell carcinoma and maturational or adnexal variants	Basal cell carcinoma and maturational or adnexal variants	Mast cell tumor
Lentigo	Other adnexal tumors	Osteosarcoma
Macular melanosis (dogs only)	Infundibular keratinizing acanthoma	Fibrosarcoma
Pigmented epidermal plaques (dogs only)	Squamous cell carcinoma	Epitheliotropic lymphoma
Squamous cell carcinoma	Epitheliotropic lymphoma	Hemangioma, hemangiosarcoma
Hemangioma (cutaneous)	Mast cell tumor	Myxosarcoma
	Hemangioma, hemangiosarcoma	Neurofibroma
	Plasmacytoma	Metastases from other sites (usually carcinoma)
	Fibroma/fibrosarcoma	Inverted squamous papilloma
	Undifferentiated sarcomas	Osteomyelitis
	Undifferentiated carcinomas	Paronychia (bacterial or fungal)
	Granuloma (bacterial or fungal)	

6. What clinical features can be used to distinguish melanocytoma from malignant melanoma in dogs?

The distinction between a benign melanocytoma and a malignant melanoma in both species should made on the basis of histopathologic criteria rather than clinical signs.

Signalment and site are the best clinical indicators of malignant potential in dogs, although neither should be considered sufficient to diagnose a pigmented tumor as innocuous. Pigmented masses on the haired skin of dogs are typically benign, whereas those within the mucous membranes of the oral cavity, other mucocutaneous junctions, and the nailbeds should be considered malignant until proven otherwise. Lesions should be biopsied carefully so that the exact site of origin of the tumor can be determined. Distinctions must be made between tumors arising from the oral mucous membranes versus haired skin of the lip, from conjunctiva versus palpebral haired skin, and from subungual epithelium versus interdigital haired skin. Pigmented tumors within haired skin at any site on Scottish Terriers are probably malignant. Standard and Miniature Schnauzers are predisposed to benign melanocytoma as well as to malignant melanoma of the haired skin; thus lymph nodes and lungs should be evaluated for evidence of metastases at the time of initial presentation. Male Miniature Schnauzers are more likely than females to have malignant melanomas on the haired skin, particularly that of the forelimbs. In general, malignant melanoma is more likely in older patients.

Tumor color, size, or ulceration should never be used to assess biological behavior. Although the probability of metastasis, thus malignancy, is greater in larger tumors, small masses can be extremely aggressive, whereas large melanocytic neoplasms may prove benign.

7. What clinical features can be used to distinguish a benign melanocytoma from malignant melanoma in cats?

The distinction between a benign melanocytoma and a malignant melanoma in cats as in dogs should made on the basis of histopathologic criteria rather than clinical signs. Approximately 50% of feline melanocytic neoplasms are malignant. The likelihood of malignancy increases for pigmented tumors on the eyelid. Although the probability of metastasis, thus malignancy, is greater in larger tumors, small masses can be extremely aggressive biologically, whereas large melanocytic neoplasms may prove benign. The presence of ulceration or tumor necrosis fails to predict biologic behavior. Studies disagree on malignant potential of amelanotic versus heavily pigmented neoplasms.

8. What histologic features are most useful in distinguishing benign from malignant melanocytic tumors in dogs?

See Table 56-3.

Table 56-3 *Benign vs. Malignant Disease*

BENIGN	MALIGNANT
Tissue architecture is symmetric	Neoplastic cells extend above dermal-epidermal junction or deep into underlying tissues.
Margins well-defined	Neoplastic cells invade tumor margins
Uniform nuclei	Nuclear atypia, anisokaryosis, hyperchromasia
Mitotic index* (MI) ≤2	MI ≥3
Uniform cells	Anisocytosis, cellular pleomorphism
Diploid DNA	Aneuploid DNA

*Total number of mitotic figures per ten high-power fields.

9. Can the histologic criteria of malignancy used for canine melanocytic neoplasms be applied to feline tumors?

Characteristics of malignancy such as invasiveness and nuclear atypia are indeed predictive of biologic behavior in feline melanocytic tumors. The significance of mitotic index, however, is not as clear in neoplasms of cats as in those of dogs. Restriction of neoplastic cells to the dermal-epidermal junction implies that the tumor is benign, whereas the presence of dermal inflammation suggests malignancy. One study found that the presence of epithelioid melanocytes, characterized by a large oval nucleus and abundant cytoplasm with melanin granules, indicated malignancy; a later study failed to corroborate that correlation.

10. How are amelanotic melanomas or melanocytomas identified?

The paucity of melanin in poorly pigmented tumors makes identification of amelanotic melanocytic neoplasms difficult (Figure 56-1) (see Table 56-2 for differential diagnoses). Both benign and malignant tumors can lack pigment; abundance of melanin has no prognostic significance. Many of the classic stains for melanocytic neoplasms, such as acid orcein–Giemsa, Gomori's or Wilder's reticulin, and Fontana ammoniacal silver nitrate, require the presence of melanin pigment, so will not identify amelanotic neoplasms of melanocytic origin. The DOPA reaction tests the ability of a cell to produce pigment and is useful in identifying weakly

Figure 56-1 Amelanotic melanoma on the muzzle of a 13-year-old male castrated Boston Terrier.

melanotic neoplasms; however, poorly differentiated melanocytic neoplasms incapable of pigment production might fail to react. Likewise, tyrosinase may be absent or abnormal in unpigmented tumors. Monoclonal antibodies capable of detecting minute amounts of tumor-related antigens are available for immunohistochemical analysis of formalin-fixed sections. Dermatopathologists commonly use a panel of several immunohistochemical markers when an amelanotic melanocytic neoplasm is suspected. These include the following:

- S100: S100 is a calcium-binding protein found within cells of vertebral neuroectodermal origin. S100 reactions are positive in most human, canine, and feline melanocytic neoplasms. Not only neural tissue and melanocytes react with anti-S100 antibodies; however. Schwann cells, myoepithelial cells, skeletal muscle cells, Langerhans cells, sustentacular cells, cartilage, and various adenocarcinomas and carcinomas may also be S100 positive. Thus, anti-S100 antibodies are sensitive, but not specific, melanocytic markers.
- Neuron-specific enolase (NSE): NSE is a glycolytic enzyme present in cells of neuroectodermal origin. Anti-NSE antibody reactions are generally positive in melanocytes and this marker is included in several immunohistochemical panels when melanocytic neoplasms are suspected.
- Vimentin: Both neuroectodermal and mesenchymal cells contain the intermediate filament vimentin. Anti-vimentin antibodies react positively with pigmented and unpigmented melanocytic tumors, which then can be distinguished from mesenchymal neoplasms by other methods.
- Melan-A (MART-1): Melan-A is a melanoma-specific antigen recognized by T cells (MART); the function of this protein is not known. In humans, this marker is both highly sensitive and highly specific for melanocytic tumors. Amelanotic melanocytic tumors in both cats and dogs can be Melan-A negative. In cats, this marker consistently distinguished melanocytic neoplasms from pigmented basal cell tumors. Melan-A is more specific but less sensitive than S100.

11. Do benign melanocytomas neoplastically transform to malignant melanoma?

Neoplastic transformation of benign pigmented hamartomas to malignant melanoma in dogs is rare; most canine malignant melanomas are biologically aggressive at the outset. Nevertheless,

recurrence of a pigmented mass previously classified by histopathologic criteria as benign should prompt further biopsy and re-examination by a dermatopathologist.

12. Describe the clinical evaluation and staging of a dog or cat with a cutaneous melanocytic neoplasm.

- Chart tumor location and size.
- Biopsy the mass and submit tissue to a dermatopathologist so that histopathologic criteria of malignancy can be assessed.
- Evaluate local and regional lymph nodes for metastases by fine-needle aspiration cytology or lymph node biopsies.
- Evaluate the general health of the patient: complete blood cell count, general chemistry panel with electrolytes, urinalysis, thyroxine measurement in cats. The existence of concurrent disease worsens the patient's prognosis, suitability for radical surgical excision of a malignant tumor, and ability to tolerate radiation therapy or chemotherapy.
- Metastasis of malignant melanoma usually occurs by lymphatic routes, although hematogenous dissemination is possible as well. Tumor cells spread first to regional lymph nodes, then to the lungs. More distant metastases affect the central nervous system, heart, liver, kidney, and spleen. Check for metastases to lungs by performing radiography of the thorax. Three views (ventrodorsal, left lateral, and right lateral) are required to detect gross metastases. Any cardiac, hepatic, or renal abnormalities detected by physical examination and diagnostic tests should prompt further evaluation using cardiac and/or abdominal ultrasonography.

Tumor Staging

Classification of tumor stages in companion animals follows guidelines established by the World Health Organization (WHO). Three factors are evaluated: the size and invasiveness of the primary tumor (T), involvement of regional lymph nodes (N), and the existence of distant metastases (M). Stage is then assigned based on combinations of T, N, and M results:

T (Primary tumor)

Tis: Pre-invasive (in situ)
T0: No evidence of tumor
T1: Diameter <2 cm
T2: Diameter 2-5 cm OR
Minimal invasion (any tumor size)
T3: Diameter >5 cm OR
Invasion of subcutaneous tissue (any tumor size)
T4: Invasion of fascia, muscle, bone, cartilage (any tumor size)

N (Regional lymph nodes)

N0: No evidence of involvement of regional lymph nodes
N1: Ipsilateral nodes are movable
N1a: Nodes contain no histologic evidence of tumor
N1b: Nodes contain histologic evidence of tumor
N2: Contralateral or bilateral nodes are movable
N2a: Nodes contain no histologic evidence of tumor
N2b: Nodes contain histologic evidence of tumor
N3: Nodes are immovable, fixed

M (Distant metastasis)

M0: No evidence of distant metastasis
M1: Presence of distant metastasis (including distant lymph nodes)

Stages (modified from stage groupings used in canine oral melanocytic tumors):

	T	N	M
Stage 0:	Tis, T0	N0, N1a, N2a	M0
Stage I:	T0, T1	N0, N1a, N2a	M0
Stage II:	T2	N0, N1a, N2a	M0
Stage III:	T3, T4	N0, N1a, N2a	M0
	Any T	N1b	M0
Stage IV:	Any T	Any N2b or N3	M0
	Any T	Any N	M1

13. What is the most effective treatment for melanocytic neoplasms?

Radical surgical excision is the optimum therapy for benign and malignant tumors in both dogs and cats; surgical margins should be at least 2 cm wide. The probability of recurrence and metastases of malignant neoplasms correlates roughly with the degree of tumor invasiveness and size. Approximately one third of subungual malignant melanomas have metastasized by the time of initial diagnosis. For malignant neoplasms at other sites, postoperative median survival times range from 4 months in dogs with large tumors to 12 months in those with smaller masses. In cats, postoperative median survival times average only 4.5 months.

14. How effective is radiation in therapy for malignant melanoma?

Radiation-induced cytotoxicity depends on the production of free radicals by interactions between ionizing radiation and water within the cells. These unstable radicals react with and break chemical bonds within tissue molecules. If bonds within DNA molecules are destroyed, the cell is more likely to die at its next mitosis. Because neoplastic cells cycle more rapidly than most normal tissues, neoplastic cells have less time to repair these DNA breaks before the next mitosis, so are more likely to die from the effects of ionizing radiation. Malignant melanoma in all species is considered resistant to radiation therapy. This radioresistance has been suggested to reflect an inherent ability of melanocytes to repair sublethal DNA damage. Resistance to radiation is now attributed, at least in part, to tumor hypoxia. Hypoxia increases the resistance to a single dose of radiation therapy by a factor of three. Decreased oxygen levels within a solid tumor result from increased consumption of oxygen by the rapidly growing and actively metabolizing tumor cells in conjunction with decreased delivery of oxygen to the tumor cells. Most patients with malignant neoplasia have concurrent anemia, either from chronic disease or from the effects of chemotherapy or radiation therapy on erythrogenesis. Low levels of hemoglobin lead to decreased oxygen delivery. Solid tumors can outgrow their vascular supply; areas within the tumor then necrose, further limiting oxygen delivery. In addition, as the neoplastic cells proliferate away from the tumor's blood supply, the distance through which oxygen must diffuse increases. This is exacerbated by abnormalities in tumor vasculature because of faulty angiogenesis. Low oxygen levels exert selection pressure that favors biologically aggressive cells and their clones. Radiation resistance is linked to the mutagenic potential of hypoxia and subsequent mechanisms by which surviving cells escape apoptosis and death. To minimize toxicity, the total radiation dose a patient receives is divided into fractions, typically administered on a weekly basis. The resulting cycles of hypoxia followed by reoxygenation are mutagenic; free radical production is enhanced, but not always to lethal levels. Time between administration of radiation fractions allows cells with sublethal damage to self-repair before their next mitosis, thus enhancing the probability that sublethal mutations, including mutations in p53 tumor suppressor genes, will be preserved.

Treatments to overcome the effects of hypoxia tried in human medicine include increasing the partial pressure of oxygen in the tissues using hyperbaric oxygen therapy or inhalation of carbogen, a gas containing 5% carbon dioxide and 95% oxygen; increasing tissue perfusion, with

niacinamide, for example; correcting anemia with blood transfusions or administration of erythropoietin; and the use of hypoxic cell sensitizers such as mitomycin C.

In humans, radiation therapy for malignant melanoma depends on several factors: tumor volume, oxygenation status of the mass, total radiation dose, and dose administered per treatment session (dose per fraction). Studies of radiation therapy for malignant melanoma have focused on dogs with malignant melanoma in the oral cavity. In these patients, radiation therapy can be an adjunct to mandibulectomy or maxillectomy. This modality is also used to debulk large masses pre-operatively or as a palliative measure in tumors whose location or size make surgical excision unfeasible. In humans and canines, remission rates improve when dose per fraction increases. Doses ≥8 Gray (Gy) per fraction led to substantial increases in response rates for humans with malignant melanoma. Administration of 9 Gy weekly for 4 weeks resulted in complete remission in 69% of dogs with oral malignant melanoma and partial remission in 25%. Adverse effects at the radiation site were limited to superficial cutaneous or mucocutaneous reactions. Treatment with 4 Gy fractions every other day, to deliver a total of 48 Gy, resulted in fistula formation or osteonecrosis in over 7% of canine patients.

15. How effective is chemotherapy in malignant melanoma?

Chemotherapy can be used as an adjunct to surgical excision or radiation therapy, but is not considered to increase survival times for individuals of any species with malignant melanoma. Nevertheless, encouraging results have been reported in canine patients treated systemically with carboplatin and intralesionally with cisplatin, methotrexate, or carmustine. Carboplatin induced partial or complete remission in seven of 25 patients with aggressive malignant melanoma; another study reported a response rate of <25%. Results of therapy with dacarbazine, melphalan, and doxorubicin were disappointing.

Implantation within malignant melanoma of a gel containing epinephrine as a vasoactive agent and either cisplatin, methotrexate, or carmustine in a protein carrier resulted in complete remission in 11 of 30 dogs and partial remission in 14 of 30. An additional advantage of this technique was decreased systemic adverse effects of the chemotherapeutic agents.

16. What new treatment modalities in humans may become available to veterinary patients in the future?

Malignant melanoma cells contain several proteins that are highly antigenic, thus can be targets of cell-mediated or humoral immunity. As a result, much current research on therapy for malignant melanoma in humans focuses on identification and targeting of melanoma antigens and stimulation of cytotoxic antineoplastic effector cells.

In general, immunotherapy influences tumor growth by stimulating or inhibiting cytokine-secreting immune cells. Endogenous immune cells can either be activated or suppressed. Exogenous cytokines or immune cells may be administered exogenously to activate or suppress effector cells. In adoptive cellular therapy, the patient receives sensitized anti-tumor cytotoxic cells, such as CTLs, NK cells, tumor-infiltrating cells, and macrophages. Therapeutic use of cytokines has focused on interferon-α (discussed in Chapter 51) and IL-2.

Current research in human oncology involves gene therapy that targets control of the cell cycle and activation of cytotoxic cells. Other areas of study focus on enhancement of antigen presentation to cytotoxic effector cells. Mechanisms used by malignant cells to escape recognition and destruction can be bypassed or overcome by exogenous administration of cytokines that enhance the function of the patient's effector cells and optimize the patient's own cell-mediated immunity. Tumor vaccines stimulate active specific immunity and are discussed in the answer to Question 18.

T cell–associated cytokines with activities against malignant melanoma have been studied in several species, including dogs. The different subtypes of helper T cells, Th1 and Th2, produce cytokines that either enhance or inhibit tumor survival and proliferation. Cytokines produced by Th1 cells include IL-2, IL-12, and IFN-γ, whereas those produced by Th2 cells include IL-4, IL-5,

IL-6, IL-9, and IL-10. In general, Th1 activity favors the actions of cytotoxic T lymphocytes (CTLs). Th2-associated cytokines IL-4 and IL-10 suppress Th1 activity, thus also inhibit CTL activity.

IL-2, a Th1-associated cytokine, has been studied extensively. Its primary antineoplastic function is induction of NK cells, which are potent cytotoxic effector cells. IL-2 is toxic when administered exogenously as a single agent. To receive the immunologic benefits of IL-2 but bypass its toxic systemic effects, neoplastic cells taken from a melanoma are incubated in vitro for several weeks with IL-2 and tumor-derived lymphocytes. The resulting "hyperactivated" tumor-infiltrating effector cells are then reinjected into the patient and specifically target the patient's tumor and its clones. One experimental protocol uses IL-2 by inserting into the melanoma genetically modified cells that secrete high levels of IL-2 within the tumor itself. IL-2, as well as granulocyte macrophage colony stimulating factor (GM-CSF) and interferon, act on melanoma cells to enhance their antigenicity, thereby making them more accessible to antigen-presenting cells and more vulnerable to the cytotoxic activities of effector cells.

In several human cancers, including malignant melanoma and osteosarcoma, significant anti-tumor effects are induced by post-operative intravenous injection of liposome–encapsulated muramyl tripeptide-phosphatidylethanolamine (L-MTP-PE). Results of clinical trials of this agent in dogs with oral malignant melanoma were encouraging for stage I disease. In the trials, L-MTP-PE was injected either singly or in conjunction with recombinant GM-CSF. Macrophages activated by these agents then secrete tumor necrosis factor-α and interferon, both of which further stimulate antineoplastic cytotoxic activity. GM-CSF induces hematopoietic progenitor cells to differentiate into dendritic cells, which are highly effective at antigen presentation. Additional antineoplastic effects of GM-CSF are activation of eosinophils and neutrophils, enhancement of antibody-dependent cellular cytotoxicity, and increased cytotoxicity of circulating lymphocytes. Administration of LT-MTP-PE significantly increased survival time in dogs with stage I disease; 80% survived at least 2 years postoperatively, whereas only 25% of control dogs survived for a similar amount of time. When administered with recombinant GM-CSF, pulmonary alveolar macrophages were also activated; these have the potential to inhibit the growth or development of pulmonary metastases. Results of this protocol were stage dependent: no significant anti-neoplastic benefit was reported for dogs with advanced disease.

17. What is the role of antihistamines in therapy for melanocytic neoplasia?

The role of antihistamines as a chemotherapeutic or immunomodulatory adjunct in the treatment of malignant melanoma in dogs and cats is unclear. The most commonly used antineoplastic antihistamine in companion animals is cimetidine. This drug antagonizes type 2 histamine receptors (H2), which are expressed by suppressor T cells. When the receptors are blocked, the suppressive effects of these T cells on cell-mediated immunity are inhibited, thus the patient's cell-mediated, anti-tumor responses can be expressed. In human medicine, cimetidine is commonly used as adjunctive therapy for gastrointestinal tumors. However, mixed results have been reported from the use of cimetidine in equine melanomas, and antihistamines have not gained favor as antineoplastic agents in therapy for canine and feline melanomas. Nevertheless, recent research in human oncology has expanded the understanding of the role of histamine and may identify future uses of H2 antagonists in veterinary medicine. Although best known for its activities in allergy, inflammation, and gastric acid secretion, histamine functions in neurotransmission, wound repair, hematopoiesis, embryogenesis, and suppression of cutaneous immunity. Histamine exerts both direct and indirect effects on the growth of melanocytic neoplasms in mice and in humans. Melanoma cells express growth factors and cytokines not expressed by normal melanocytes; these factors both promote tumor growth and assist the escape of neoplastic clones from immune-mediated tumor control. Furthermore, malignant melanoma cells express histidine decarboxylase, giving them the ability to synthesize histamine, a capability normal melanocytes lack. The functions of histamine in tumor growth are not fully understood and reflect a complex interplay between the different actions of histamine on H1 or H2 receptors expressed by normal immune cells and by neoplastic melanoma cells. Additional differences in histaminergic effects

reflect changes in the local cytokine microenvironment. Histamine exerts both direct and indirect effects on malignant melanoma cells. When bound to H1 receptors, histamine inhibits cell proliferation. In contrast, histamine bound to H2 receptors on the same cells enhances cell proliferation. Which of the two effects the tumor manifests depends not only upon the balance between the absolute numbers of H1 and H2 receptors, but also on their availability for histamine binding. This is one point at which selective H2-blocking antihistamines, such as cimetidine, might exert their effect.

When the indirect effects of histamine are considered, however, the outcomes are less straightforward. Histaminergic responses of immune cells can be either pro-neoplastic or anti-neoplastic. Activities that promote tumor growth thus could be targets of antihistamine therapy, including H2-receptor-mediated inhibition of natural killer cells and suppression of the production of several anti-neoplastic cytokines: IL-1β, IL-2, IL-12, tumor necrosis factor (TNF)-α, and IFNγ. The cytotoxic capability of macrophages is impaired by the action of histamine on H2 receptors, which causes decreased production of oxygen-free radicals. In contrast, in certain cytokine settings, histamine inhibits the growth of neoplastic cells. Stage IV malignant melanoma in humans regressed after histamine was administered with IL-2 or IFN-α, both of which stimulate natural killer cells. Tumors at that stage generally fail to respond to IL-2 or IFN-α alone. Histamine also shifts the helper T cell response from one dominated by type 1 to type 2 cells; Th1-associated cytokines inhibit tumor proliferation, whereas Th2-associated cytokines facilitate tumor growth and survival.

IL-6, a Th2-associated cytokine, influences the H1-H2 receptor balance on melanoma cells, favoring H1. The effect of IL-6 on melanoma cell proliferation is concentration-dependent: high levels of IL-6 inhibit cell proliferation via H1 receptors, whereas low levels facilitate cell growth via H2 receptors. IL-6 stimulates the activity of histidine decarboxylase, the enzyme responsible for histamine synthesis. Effectiveness of IL-6 activity against the malignant melanoma depends on tumor stage: early melanoma activity is inhibited by IL-6, whereas metastatic cells in advanced stages are stimulated by that cytokine.

18. How effective are tumor vaccines against malignant melanoma?

Tumor vaccines are injections of immunogenic components administered to stimulate active immunity against a specific antigenic target. The presence of multiple antigenic moieties in malignant melanoma cells makes them vulnerable to active specific immunity. Melanocyte- or neuroendocrine-specific epitopes include tyrosinase, Melan-A, gp75, and gp100. Vaccines can also target moieties found on several different types of neoplasms, including melanoma (tumor-associated antigens). Vaccines may be univalent, containing a single antigenic moiety, or polyvalent, with several separate antigenic epitopes. Univalent vaccines consist of purified antigen or specific peptide epitopes, such as gp100 or tyrosinase. The most specific antigens result from mutations in peptide moieties. Polyvalent vaccines contain whole cells, cell lysate, or mixtures of incompletely purified antigens. Neoplastic cells are extracted from the patient's melanoma to create autologous vaccines; production of these vaccines requires a large tumor volume to yield sufficient cells. Vaccines of this type have been used to treat equine melanomatosis. Cells derived from malignant melanoma from an individual of the same species, but different major histocompatibility complex (MHC) class I, are used to make allogeneic vaccines. Cell lysates from allogeneic melanomas contain tumor particles that are engulfed by macrophages. This enhances the presentation of tumor epitopes to cytotoxic effector cells. Research in murine and human melanoma cell lines has produced genetically modified vaccines that induce expression of cytokines and costimulatory molecules, including GM-CSF, IFNs, IL-2, and IL-6.

Antigenicity does not always correlate with immunogenicity. Immunogenicity may be optimized by including haptens or adjuvants. GM-CSF is an example of a stimulatory cytokine included in some autologous melanoma vaccines. Despite mixed responses to preliminary clinical trials in humans and canines, tumor vaccines may prove to be beneficial therapeutic adjuncts, especially in prevention or therapy for metastatic disease.

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57. MISCELLANEOUS CUTANEOUS NEOPLASMS

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1. **What is a naturally occurring allograft?**
   - Transmission occurring by transplantation of viable neoplastic cells to a susceptible host.
   - Clinical example: transmissible venereal tumor (TVT)
   - Immunohistochemical studies support a histiocytic origin for TVTs.
   - TVT tumor cells contain 59 chromosomes as compared with the normal canine complement of 78.
   - Possible viral etiology; however, tumor has not been successfully transplanted with particle-free tissue grafts.

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57. MISCELLANEOUS CUTANEOUS NEOPLASMS

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1. **What is a naturally occurring allograft?**
   - Transmission occurring by transplantation of viable neoplastic cells to a susceptible host.
   - Clinical example: transmissible venereal tumor (TVT)
   - Immunohistochemical studies support a histiocytic origin for TVTs.
   - TVT tumor cells contain 59 chromosomes as compared with the normal canine complement of 78.
   - Possible viral etiology; however, tumor has not been successfully transplanted with particle-free tissue grafts.

2. **What is the typical signalment of a dog affected with TVT?**
   - Intact male and female dogs
   - Spread primarily horizontal (by sexual contact)
   - More common in regions where dog less domesticated, "no leash laws"

3. **What are the most common locations of the lesions of TVT?**
   - External genitalia (Figure 57-1)
   - Oral cavity
   - Nasal cavity
   - Skin (less common), face and limbs

4. **How is the diagnosis of TVT made in most cases?**
   - TVT is usually easily diagnosed by exfoliate cytology
   - Tissue is friable and bleeds easily
   - Obtain samples by aspiration/scraping/impression
   - Round cell neoplasia, moderate amounts of cytoplasm (Figure 57-2)
   - Cytoplasm contains small vacuoles
   - Mitotic figures common

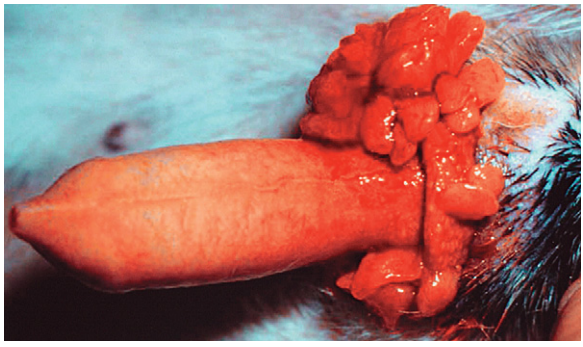

Figure 57-1 Transmissible venereal tumor involving the penis of a dog.

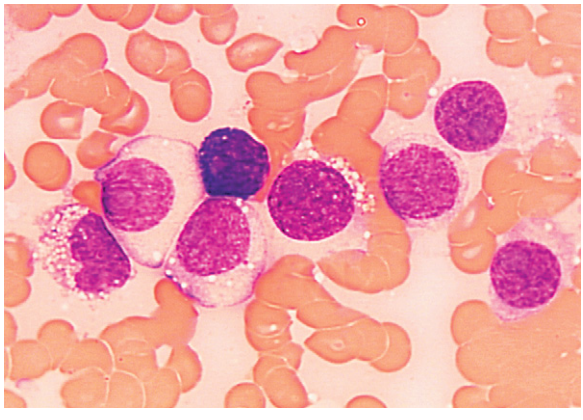

Figure 57-2 Impressions smear of a transmissible venereal tumor. Note that the round cells of this tumor have abundant cytoplasm containing many vacuoles (×100).

5. What are differential diagnoses to consider when evaluating a pink fleshy mass on a dog's penis?
- Transmissible venereal tumor
- Transitional cell tumor (originating from penile urethra mucosa)
- Papilloma
- Squamous cell carcinoma
- Fibrosarcoma
- Histiocytic reticulocytoma
- Lymphoma
- Non-neoplastic conditions such as leishmaniasis, pythiosis, or granulation tissue

6. What is the biologic behavior of TVT?
- Metastasis uncommon, but may occur in approximately 17% of cases.
- Metastases are most common to local lymph nodes, skin, eyes, liver, and brain. In some cases, spreading between the skin oral and nasal cavities is due to autotransplantation.
- Evaluate draining lymph nodes by fine-needle aspiration (FNA) and radiography of the thoracic cavity and abdomen (ultrasonography) to screen for metastases.
- Some TVTs may synthesize and secrete erythropoietin and some affected animals may have a paraneoplastic polycythemia.

7. Is there any relationship between the hormonal status of a dog and the progression of TVT?
- Some veterinarians report that TVTs are usually benign in male dogs while metastasis to regional lymph nodes is common in intact female dogs.
- This activity may suggest that TVT is hormone dependent.
- Ovariectomy was reported to cause rapid reduction in size of TVT in intact females.
- Other veterinarians report that males are more susceptible to metastatic disease.

8. What is the therapy of choice for TVT?
- Vincristine (0.5-0.7 mg/m^2 intravenously weekly for 4-6 weeks) results in complete cure in 90-95% of afflicted animals.
- Surgery effective for small localized tumors. However, in many cases surgery as a monotherapy leads to a high rate of recurrence (20-60%).
- External beam radiation therapy is also curative in most cases, but its use is usually not necessary due to efficacy of chemotherapy.
- Other chemotherapeutic agents used for TVT include cyclophosphamide, doxorubicin, methotrexate, as well as certain biologic response modifiers (BCG and *Staphylococcus* protein A). Although the chemotherapy agents are efficacious there have only been inconsistent results noted with use of the immunomodulatory agents, and their use is not recommended at this time.

9. Does the presence of metastases change the response to chemotherapy?
- In most cases, no
- The presence of metastasis does not affect efficacy of chemotherapy and dogs often have a complete cure even in the presence of metastatic lesions.

10. Merkel's cells are found associated with the following sense organs:
- Tylotrich pad: Each tylotrich follicle (as opposed to sinus hair follicle [whisker]), is associated with a tylotrich pad (Haarscheibe, touch corpuscle, touch dome, hair disk, Pinkus corpuscle, Eimer's organ, Iggo dome, etc.).
- Tylotrich pads are composed of thickened epidermis underlayered by a fine connective tissue (convex), which is highly innervated and vascularized.
- Merkel's cells serve as slow-adapting touch receptors.

11. Tumors of neuroendocrine origin in dogs clinically present
- In solitary lesions
- In dogs older than 8 years of age
- In lips, ears, digits, oral cavity

12. What is the biologic behavior of neuroendocrine tumors?
- Malignant with metastases

Or
- Benign

13. Histologic diagnosis of tumors of neuroendocrine origin may require:
- Histopathology: uniformly round tumor cells with abundant cytoplasm, high mitotic index, giant/multinucleate tumor cells, hyperchromatic/vesicular nuclei
- Electron microscopic examination: cytoplasmic dense-core membrane bound granules and perinuclear whorl of intermediate filaments, neurosecretory granules are often lost in formalin-fixed routine histopathologic sections
- Immunohistochemistry: cytokeratin and chromogranin A

14. List the important characteristics of cutaneous plasmacytoma in the dog and cat (cutaneous extramedullary plasmacytoma).
- Common in the dog, extremely rare in the cat
- Occur at a later age, average 10 years old in the dog
- Cocker Spaniels may be predisposed
- Usually solitary
- Perhaps associated with cutaneous areas of chronic inflammation/infection/irritation

15. Are any cutaneous areas predisposed to develop plasmacytomas?
- Digits
- Lips
- Chin
- Ears (especially external ear canal)

16. List some of the histologic/immunohistochemical markers reported in cutaneous plasmacytoma?
- Immunoglobulin G: heavy and light chains
- Vimentin
- Thioflavin T
- CD 79a
- CD 3 T cells
- CD 18 dendritic cells
- Ki-67 antigen

17. Are histologic grading systems of great benefit in assessing malignancy potential in canine cutaneous plasmacytoma?
- No
- These neoplasms typically exhibit benign biologic behavior despite histologic malignant appearance (Figure 57-3).
- Treatment of choice is surgical excision.

18. What is cutaneous angiomatosis?
- An uncommon condition involving a progressively invasive, non-malignant lesion composed of proliferation of vascular tissue within the dermis or subcutis.
- Reported in several veterinary species, including the dog and cat

19. What is the preferred mode of therapy for these lesions?

Wide surgical excision or amputation is often recommended for control of the lesions because of the recurrent nature of the disease and the afflicted regions (most commonly the distal

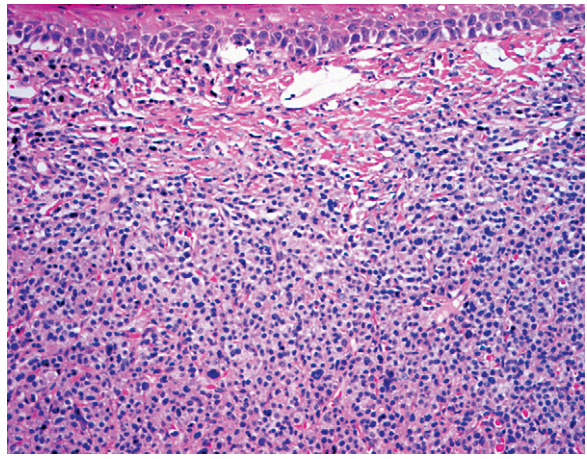

Figure 57-3 Photomicrograph of a canine cutaneous plasmacytoma. Note the multinucleated nucleoli (×100).

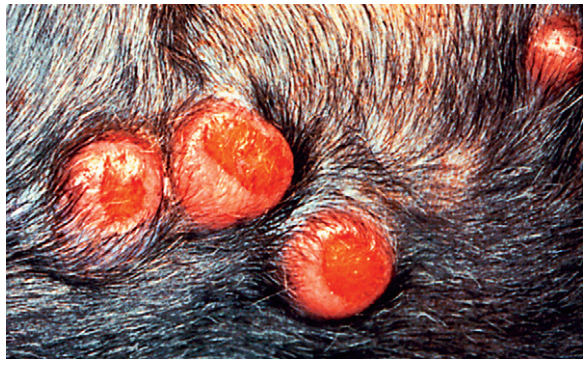

Figure 57-4 Metastatic anaplastic sarcoma in a dog.

limb in the cat). However, laser photocoagulation using a neodymium:yttrium-aluminum-garnet laser has replaced surgical excision as the recommended therapy for humans with highly vascular dermal lesions. Animals treated with this modality have required multiple treatments and have reported a good functional and cosmetic outcome in most cases.

20. What are the broad categories of neoplasia involving the skin?

- *Primary tumors:* those tumors that arise primarily within the dermis, subcutis, or alveolar tissue. A myriad of tumors occur in this region and can be benign or malignant.
- *Secondary tumors:* those tumors that develop at a distant site and metastasize to the skin. By definition these tumors are part of a malignant neoplastic process.

21. What is a rarely reported iatrogenic cause for metastatic spread to the integument?

Surgical transplantation of a neoplasm (tumor seeding) is rarely reported in dogs or cats (Figure 57-4). If they occur, lesions appear most commonly in the healed surgical incision through which the primary neoplasm was removed. Most cases reported involved urinary tract carcinomas.

22. What are some multicentric-type tumors that may involve the skin as a secondary, metastatic site?

- Systemic histiocytosis
- Lymphoma
- Hemangiosarcoma
- Transmissible venereal tumors
- Various carcinoma/adenocarcinoma
- Mast cell tumor

In some cases, especially lymphoma and MCT, it is difficult to clinically differentiate where the neoplasia originated.

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